Supporting Information

Amino and Hydroxyl Functionalization of Nucleosides via Resonant Acoustic Mixing

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S1 General Information

S 1.1 Reagents and instrumentation

Non-Anhydrous dichloromethane (DCM), ethanol (EtOH), methanol (MeOH), ethyl acetate (EtOAc) and toluene were purchased from Fisher Scientific or SigmaAldrich and underwent no further drying. Pyridine obtained from Sigma-Adrich was dried over 5Å molecular sieves. Nucleosides, nucleotides, 2-cyanoethyl N, N-diisorpoylchlorophosphoramidite, and dimethoxytrityl chloride were purchased from ChemGenes Corporation. All other chemicals (Acetic Anhydride, tert-Butyldimethylsilyl chloride, etc…) were purchased from Sigma Aldrich, Fisher Scientific, or TCI. RAM reactions were performed on the LabRAM I instrument from Resodyn. Isolated yields refer to chromatographically and spectroscopically (^{1}H NMR and ^{31}P NMR) homogeneous material. RAM reactions were performed in 2.5mL polypropylene vials, 4mL clear glass vials supplied by Sigma Aldrich, and 5mL, 20mL, and 50mL PTFE jars supplied by Cole-Parmer Canada. Glass and polypropylene vials were capped with 13-425 thread melamine caps with PTFE liners. Polypropylene and glass vials had dimensions of 15 mm x 45 mm x 8 mm (outer diameter, height, inner diameter, respectively). Thin-layer chromatography (TLC) was performed on 0.15-0.2 mm pre-coated silica gel (10-40 µm) plates obtained from SiliCycle Inc. using UV light, iodine vapour, and heat as visualizing agents. NMR spectra were recorded on a Bruker-500 or 400 MHz spectrometer and were calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$ ^{1}H NMR δ = 7.26 ppm) and ^{31}P NMR spectra were measured from 85% H_3PO_4 as an external standard. ^{31}P NMR shifts were proton-decoupled referenced to solvent.

S2 Methodology

S 2.1 Vessel choice and setup

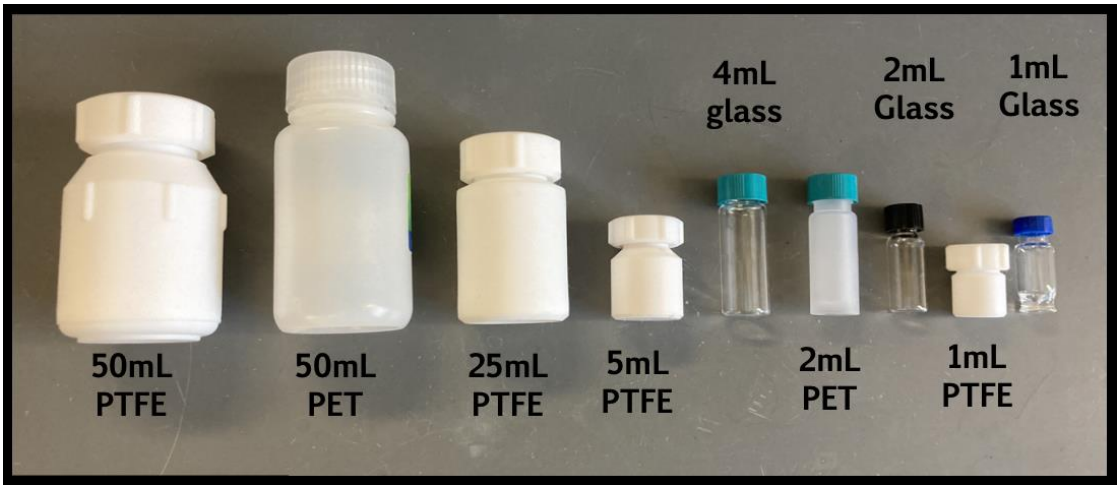


Figure S1: Vessel options compatible with RAM, labels indicate volume and material. All reported experiments were performed in directly clamped PTFE bottles, ensuring proper resonance mixing.

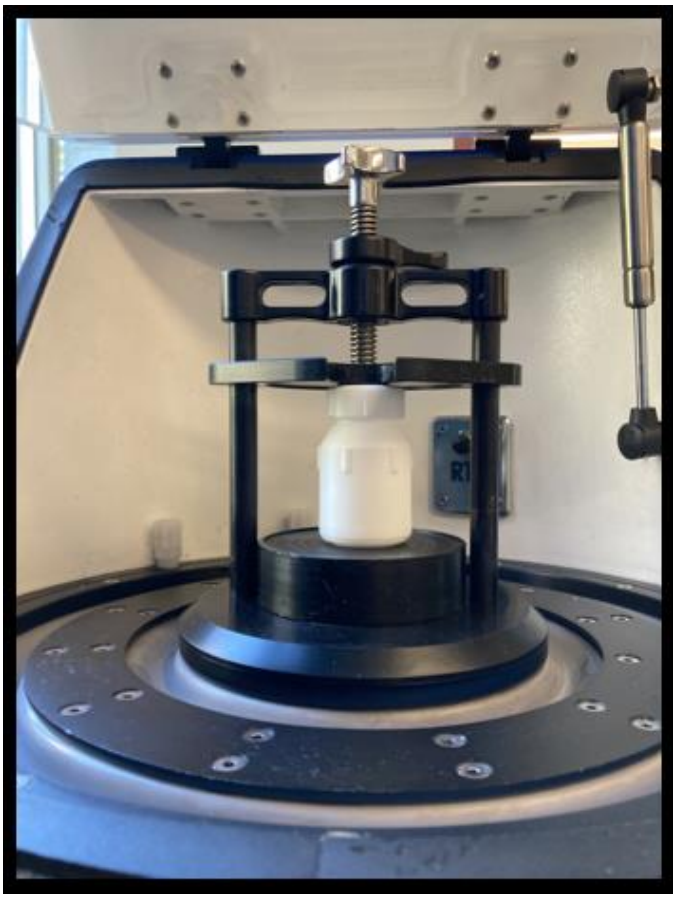


Figure S2: Setup for 100 mL Teflon bottle, secured with clamp and plastic spacer

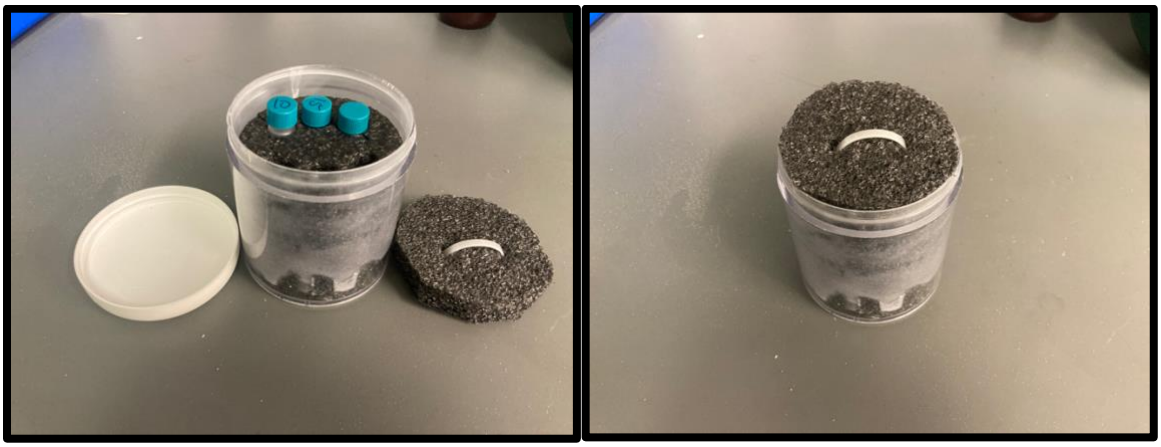


Figure S3: Custom formed closed cell polyethylene foam holder, allowing for simultaneous screening of six reactions. Enclosed vessel and tight fit of vessels is important to stabilize vials. Setup was used exclusively for screening conditions. Due to the possibility of vial movement, all experiments were validated and reported in PTFE bottles.

S 2.2 Empirical Observations

Throughout our studies, we consistently observed several very consistent trends which we thought important to communicate for those replicating this work, as well as investigating future related reactions.

S 2.2.1 Vessel fill level

The fill level of the vessel, and therefore the choice of vessel volume for a specific reaction was key in ensuring proper mixing and therefore reaction. While this was not explicitly investigated, we found reactions to have most favorable outcomes when vessels were filled between 1/3 and 2/3 in volume. Lower volumes resulting in adhesion forces between the vessel walls and reaction mixture overcoming mixing forces, leading to heterogeneous mixtures and lack of mass transfer. Higher volumes resulted in poor mixing. Due to our reactions remaining in a free-flowing slurry, the results within this range were consistent. A basic explanation for this phenomenon is that a uniform single fluid does not experience significant mass transfer when subjected to vertical acceleration forces. However, introduction of a second fluid of differing density, in this case air, allows for transfer of inertia from the vessel to the denser fluid, permitting it to displace the air volume and effectively mix. Future studies into resonant acoustic mixing in conjunction with experts in fluid dynamics may allow for the design of vessels which maximize mixing for a given reaction mixture and vessel, and we encourage further research into this topic.

S 2.2.2 Vessel material

We found quickly that the vessel material has a profound impact on reaction outcomes. Adhesion forces between vessel walls and slurry reaction mixtures reduced mixing efficiency and homogeneity of the bulk material. At small scale this effect was particularly severe, as the ratio between the surface area of the reaction vessel and the volume of material was larger. Glass was found to be detrimental for our relatively polar reaction mixtures, while polypropylene and PTFE provided visibly improved mixing.

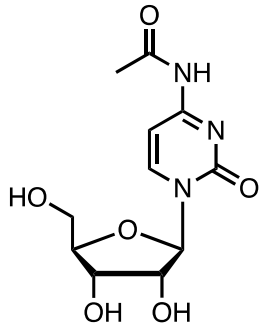
S 2.2.3 Vessel Sources

Teflon bottles: **https://www.coleparmer.ca/p/cole-parmer-wide-mouth-bottles-ptfe/57772**
Glass 4mL vials: **https://www.sigmaaldrich.com/CA/en/product/supelco/854190**
Melamine PTFE lined caps: **https://www.sigmaaldrich.com/CA/en/product/supelco/27141**
Polypropylene 2.5mL vials: **https://www.sigmaaldrich.com/CA/en/product/supelco/27435**

S 2.2.4 Slurries vs. wet powders

One additional finding was that nucleoside substrates tended to produce sticky viscous mixtures, particularly at low eta values. Polar solvents resulted in partial dissolution of materials, resulting in aggregated portions of material. We found this detrimental to consistent mixing and generation of a consistent slurry, inhibiting the progression of reactions. We observed that the limiting factor for solvent reduction in our polar nucleoside substrates was based around generating homogeneous flowing mixtures as opposed to wetted powders.

S3 Synthetic Procedures for Hydroxyl Protection and Functionalization by Resonant Acoustic Mixing (RAM)



2

Synthesis of **2**

To an oven-dried 5mL PTFE vial was added 1.0 eq. of cytidine (**1**, 4.0 mmol, 973 mg), and 1.2 eq. of acetic anhydride (4.80 mmol, 0.454 mL). This mixture was subjected to RAM for 30 mins at 60 g (9.8 m/s^2), then precipitated in 50mL of EtOAc and filtered, yielding a fine white powder (1.08 g, 94%) then dried under high vacuum. Product was characterized by ^{1}H NMR and ESI-MS.

^{1}H-NMR (400 MHz; D_2O): ^{1}H-NMR (500 MHz; DMSO-d_6): δ 10.87 (s, 1H), 8.42 (d, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 5.79 (d, *J* = 3.0 Hz, 1H, 5.47 (d, *J* = 4.7 Hz, 1H), 5.15 (t, *J* = 5.1 Hz, 1H), 5.04 (t, *J* = 5.1 Hz, 1H), 4.00-3.95 (m, 2H), 3.90 (dt, *J* = 5.8, 2.9 Hz, 1H), 3.74 (ddd, *J* = 12.2, 4.9, 2.9 Hz, 1H), 3.60 (ddd, *J* = 12.2, 4.8, 3.2 Hz, 1H), 2.10 (s, 3H)

HRMS (ESI, m/z): calcd. 308.08531 for $[C_{11}H_{15}N_3O_6+Na]^+$; Found 308.08444

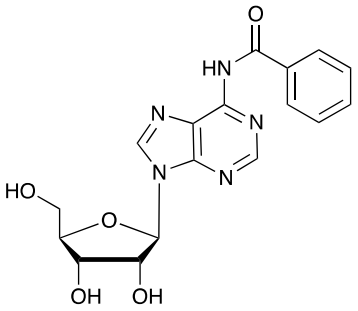
Control solution phase synthesis of **2**

To an oven-dried 20 mL RBF was added 10 mL anhydrous pyridine, 973 mg of cytidine (1.0 eq., 4.0 mmol), and 2.0 eq. of acetic anhydride (6.80 mmol, 0.757 mL). This mixture was stirred for 24 hours at room temperature. Pyridine and excess acetic anhydride was removed under reduced pressure, and the resulting wet powder was taken up in 10 mL of methanol, then precipitated in

200 mL of EtOAc and filtered, yielding a fine white powder (1.13 g, 86%) then dried under high vacuum. Product was characterized by ^{1}H NMR and ESI-MS.

^{1}H-NMR (500 MHz; DMSO-d_6): δ 8.42 (d, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 5.79 (d, *J* = 3.0 Hz, 1H), 5.47 (d, *J* = 4.7 Hz, 1H), 5.15 (t, *J* = 5.1 Hz, 1H), 5.04 (d, *J* = 5.3 Hz, 1H), 3.97 (ddd, *J* = 5.4, 5.3, 3.9 Hz, 2H), 3.90 (dd, *J* = 5.9, 2.9 Hz, 1H), 3.74 (ddd, *J* = 12.2, 4.9, 2.9 Hz, 1H), 3.60 (ddd, *J* = 12.2, 4.8, 3.2 Hz, 1H), 2.51 (dt, *J* = 3.7, 1.8 Hz, 1H), 2.10 (s, 3H).

HRMS (ESI, m/z): calcd. 308.08531 for $[C_{11}H_{15}N_3O_6+Na]^+$; Found 308.08213



4a

Synthesis of **4a**

To an oven dried 25 mL PTFE vial was added 3.00 g of adenosine (**1b**, 11.2 mmol, 1.00 eq), and 9.0 mL of pyridine (111.7 mmol, 10 eq.). This mixture was subjected to RAM for 1 minute at 60 g until the mixture was a homogeneous slurry. To this was added 6.40 mL of trimethylsilyl chloride (TMSCl) (50.4 mmol, 4.5 eq.), and the resulting mixture was subjected to RAM for 30 mins, until TLC analysis (5% MeOH in DCM) showed complete conversion of starting material to a single upper spot representing the 2',3',5'-OH-Trisilylated nucleoside. Next, 41 mg (0.33 mmol, 0.03 eq.) of 4-dimethylaminopyridine and 1.86 mL (14.56 mmol, 1.3 eq.) of benzoyl chloride was added and the resulting slurry was subjected to RAM for a further 3.5 hours at 60 g, until the intermediate spot was no longer present, and a clear upper spot could be observed. Next, the mixture was treated with 20 mL of ammonia in MeOH and 5 mL of deionized (DI) water for 30 minutes, until TLC analysis (7% MeOH in DCM) showed complete removal of TMS groups. Crude product was dried under reduced pressure and resuspended in 50mL of deionized (DI) water, then filtered and dried under reduced pressure resulting in an amorphous white powder (3.62g, 87% yield). Product was characterized by ^{1}H NMR and ESI-MS.

^{1}H-NMR (500 MHz; DMSO-d_6): δ 11.22 (s, 1H), 8.75 (d, *J* = 18.0 Hz, 2H), 8.06 (d, *J* = 7.6 Hz, 2H), 7.65 (d, *J* = 7.2 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 2H), 6.06 (d, *J* = 5.7 Hz, 1H), 5.58 (d, *J* = 6.1 Hz, 1H), 5.27 (d, *J* = 4.9 Hz, 1H), 5.15 (t, *J* = 5.6 Hz, 1H), 4.66 (dt, *J* = 8.6, 4.1 Hz, 1H), 4.21 (q, *J* = 4.1 Hz, 1H), 4.00-3.99 (m, 1H), 3.71 (td, *J* = 8.2, 3.5 Hz, 1H), 3.61-3.58 (m, 1H), 3.36 (d, *J* = 4.4 Hz, 1H).

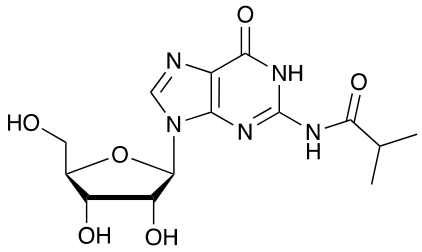
HRMS (ESI, m/z): calcd. 372.13025 for $[C_{17}H_{18}N_5O_5+H]^+$; Found 372.13001

Control solution phase synthesis of **4a**

To an oven dried 200 mL RBF was added 3.00 g of adenosine (**1b**, 11.2 mmol, 1.00 eq), and 75 mL of pyridine. To this was added 6.40 mL of trimethylsilyl chloride (TMSCl) (50.4 mmol, 4.5 eq.), and the resulting mixture was stirred for 30 minutes, until TLC analysis (5% MeOH in DCM) showed complete conversion of starting material to a single upper spot representing the 2',3',5'-O-Trisilylated nucleoside. Next, 41 mg (0.33 mmol, 0.03 eq.) of 4-dimethylaminopyridine and 1.86 mL (14.56 mmol, 1.3 eq.) of benzoyl chloride was added. The mixture was stirred for 5 hours until the intermediate spot was no longer present, and a clear upper spot could be observed. Next, the mixture was treated with 100 mL of aqueous ammonium hydroxide for 30 minutes, until TLC analysis (7% MeOH in DCM) showed complete removal of TMS groups. Crude product was dried under reduced pressure and resuspended in 50mL of deionized (DI) water, then filtered and dried under reduced pressure resulting in an amorphous white powder (3.74g, 90% yield). Product was characterized by ^{1}H NMR and ESI-MS.

^{1}H-NMR (500 MHz; DMSO-d_6): δ 8.77-8.74 (m, 2H), 8.06 (d, *J* = 7.9 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 2H), 6.06 (d, *J* = 5.8 Hz, 1H), 5.66-5.63 (m, 1H), 5.33 (dt, *J* = 8.9, 4.5 Hz, 1H), 5.21 (t, *J* = 5.8 Hz, 1H), 4.66 (q, *J* = 5.5 Hz, 1H), 4.22 (d, *J* = 3.3 Hz, 1H), 4.00 (d, *J* = 3.5 Hz, 1H), 3.70 (td, *J* = 8.2, 3.8 Hz, 1H), 3.59 (ddd, *J* = 11.9, 5.9, 4.2 Hz, 1H), 3.40-3.37 (m, 2H).

HRMS (ESI, m/z): calcd. 394.1109 for $[C_{17}H_{18}N_5O_5+Na]^+$; Found 394.1109



4b

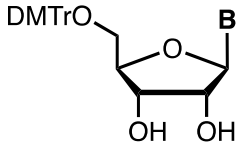
Synthesis of **4b**

To an oven dried 25 mL PTFE vial was added 2.83 g of adenosine (**1b**, 10.0 mmol, 1.00 eq), and 10 mL of pyridine (100 mmol, 10 eq.). This mixture was subjected to RAM for 1 minute at 60 g until the mixture formed a slurry. To this was added 6.90 mL of trimethylsilyl chloride (TMSCl) (60 mmol, 6.0 eq.), and the resulting mixture was subjected to RAM for 30 mins, or until TLC analysis (5% MeOH in DCM) showed complete conversion of starting material to a single upper spot representing the 2',3',5'-OH-Trisilylated nucleoside. Next, 41 mg (0.33 mmol, 0.03 eq.) of 4-dimethylaminopyridine and 1.35 mL (13 mmol, 1.3 eq.) of benzoyl chloride was added and the resulting slurry was subjected to RAM for a further 2.5 hours at 60 g, until the intermediate spot was no longer present, and a clear upper spot could be observed. Next, the mixture was cooled over ice and treated with 20 mL of ammonia in MeOH and 5 mL of deionized (DI) water for 30 minutes, until

TLC analysis (7% MeOH in DCM) showed complete removal of TMS groups. Crude product was dried under reduced pressure and resuspended in 50mL of deionized (DI) water, then filtered and dried under reduced pressure resulting in a crystaline white powder (2.69g, 76% yield). Product was characterized by ^{1}H NMR and ESI-MS.

^{1}H-NMR (400 MHz; DMSO-d_6): δ 12.10 (s, 1H), 11.70 (s, 1H), 5.82 (d, *J* = 5.8 Hz, 1H), 4.44 (t, *J* = 5.3 Hz, 1H), 4.14 (t, *J* = 4.2 Hz, 1H), 3.91 (d, *J* = 3.8 Hz, 1H), 3.67-3.54 (m, 2H), 2.51 (t, *J* = 1.7 Hz, 1H), 1.13 (d, *J* = 6.8 Hz, 6H).

HRMS (ESI, m/z): calcd. 354.14081 for $[C_{14}H_{20}N_5O_6+Na]^+$; Found 354.13934



General procedure **A** for the synthesis of 5'-OH-trityl nucleosides **6a**-**6c**

To an oven-dried 5mL PTFE vial was added 2.0 mmol dry nucleoside, 2.0 eq. EtOAc (4.0 mmol, 390 mL), and 2.0 eq. dry pyridine (4.0 mmol, 526 mL). This mixture was subjected to RAM at 60 *g* for 1 minute until a slurry formed. To this slurry was added 0.35 eq. of DMTrCl (0.70 mmol, 237 mg), then subjected to RAM for 60 g for 5 minutes, or until no remaining DMTrCl was visible by TLC (5% MeOH in DCM). The above procedure is repeated twice more, until a total of 1.05 eq. of DMTrCl (2.10 mmol, 711 mg) had been added. This mixture was then subjected to RAM at 60 g until no starting material was visible at baseline of TLC (5-10 mins). Crude product was diluted with 5 mL of EtOAc, then quenched and washed once with 5 mL 10% $NaHCO_3$ in water, and once with 5mL of saturated brine. The crude mixture was dried with anhydrous sodium sulfate then evaporated under reduced pressure and further subjected to high vacuum to ensure complete removal of pyridine, yielding an orange-yellow foam. Product was purified by silica gel column chromatography (1-3% MeOH in DCM), precipitation in hexanes, or recrystallization from toluene and hexanes. 3',5'-OH-tritylated products were separated by silica gel column chromatography, but were contaminated with unknown impurities. Masses of impure di-tritylated products were used for yield estimates. Products were characterized by ^{1}H NMR and ESI-MS

6a (5'-OH-trityl U)

^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.04 (d, *J* = 8.1 Hz, 1H), 7.43-7.17 (m, 13H), 6.88-6.84 (m, 4H), 5.91 (d, *J* = 2.4 Hz, 1H), 5.39 (d, *J* = 8.1 Hz, 1H), 4.45 (dd, *J* = 7.3, 4.2 Hz, 1H), 4.36 (dd, *J* = 5.1, 2.6 Hz, 1H), 4.22-4.20 (m, 1H), 3.82-3.79 (m, 6H), 3.54 (qd, *J* = 10.6, 2.5 Hz, 2H), 2.38 (s, 2H).

HRMS (ESI, m/z): calcd. for $[C_{30}H_{30}N_2O_8+Na]^+$ 569.1894; Found 569.1903

Yield product: 0.968 g, 85%

Yield mixed non-polar impurities: 77 mg, 8%,

6b (5'-OH-trityl C^{Ac})

1H-NMR (500 MHz; CDCl3): δ 9.25 (s, 1H), 8.27 (d, J = 7.5 Hz, 1H), 7.37-7.25 (m, 10H), 6.85 (dd, J = 9.0, 3.3 Hz, 4H), 5.93 (d, J = 2.9 Hz, 1H), 5.83 (s, 1H), 4.42 (d, J = 2.7 Hz, 2H), 4.38 (s, 1H), 3.81 (s, 7H), 3.50-3.42 (m, 2H), 2.25 (s, 3H).

HRMS (ESI, m/z): calcd. 586.21949 for $[C_{32}H_{33}O_8N_3\text{-}H^+]^-$, Found 586.21780

Yield: 0.926 g, 79%

Yield mixed non-polar impurities: 47 mg, 4%

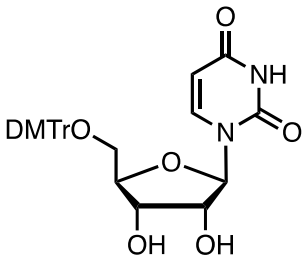
6c (5'-OH-trityl A^{Bz})

^{1}H-NMR (500 MHz; CD_3CN): δ 8.63-8.62 (m, 1H), 8.30 (s, 1H), 8.03-8.02 (m, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.58-7.55 (m, 2H), 7.42 (dd, *J* = 8.6, 1.1 Hz, 2H), 7.31-7.21 (m, 7H), 6.83 (dd, *J* = 8.9, 4.1 Hz, 4H), 6.07 (d, *J* = 4.3 Hz, 1H), 4.85 (dd, *J* = 5.0, 4.5 Hz, 1H), 4.52 (t, *J* = 5.1 Hz, 1H), 4.20-4.17 (m, 1H), 3.77 (d, *J* = 1.0 Hz, 6H), 2.52 (q, *J* = 7.1 Hz, 5H).

HRMS (ESI, m/z): calcd. 696.2399 for $[C_{34}H_{37}N_3O_{13}+H]^+$; Found 696.2414

Yield: 1.02 g, 73%

Yield mixed non-polar impurities: 56 mg, 5%



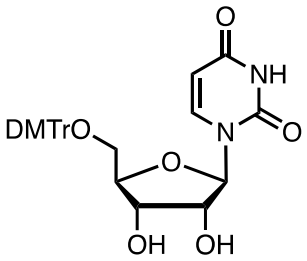
6a

Scale up synthesis of **6a**, 5'-OH-trityluridine by RAM

To an oven-dried 50mL PTFE vial was added 9.77 g of dry uridine (40.00 mmol, 1.0 eq), 7.82 mL EtOAc (80.01 mmol, 2.0 eq.) and 10.53 mL dry pyridine (80.1 mmol, 2.0 eq.). This mixture was subjected to RAM at 60 g for 1 minute until a slurry formed. To this slurry was added 4.97 g of DMTrCl (0.35 eq., 14.3 mmol), then subjected to RAM for at 60 g for 5 minutes, or until no remaining DMTrCl is visible by TLC (5% MeOH in DCM). The above procedure is repeated twice more, until a total of 14.91 g of DMTrCl (44 mmol, 1.1 eq.) had been added, and subjected to RAM at 60 g for a further 10 mins until no starting material was visible by TLC. Crude product was diluted with 20 mL of EtOAc, then quenched and washed once with 104 mL 10% $NaHCO_3$ in water. The crude mixture was dried with 5 g anhydrous sodium sulfate then evaporated under reduced pressure and further subjected to high vacuum to ensure complete removal of pyridine, yielding a light-yellow foam. The resulting foam was dissolved in 240 mL of warm toluene, after which 10 mL of warm hexanes was added dropwise. Product was allowed to recrystallize in the freezer overnight, after which a white crystalline product was filtered and washed with 10 mL cold hexanes then dried under high vacuum, yielding 18.42 g of white crystalline powder (84.5% yield). The resulting material was characterized by ^{1}H NMR and ESI-MS.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.04 (d, *J* = 8.1 Hz, 1H), 7.41 (d, *J* = 7.2 Hz, 2H), 7.32-7.27 (m, 9H), 7.21 (s, 2H), 6.86 (d, *J* = 9.0 Hz, 4H), 5.91 (d, *J* = 2.4 Hz, 1H), 5.39 (d, *J* = 8.1 Hz, 1H), 4.45 (t, *J* = 5.7 Hz, 1H), 4.36 (dd, *J* = 5.1, 2.6 Hz, 1H), 4.21 (dd, *J* = 3.5, 2.8 Hz, 1H), 3.80 (s, 7H), 3.54 (qd, *J* = 10.6, 2.5 Hz, 2H).

RMS (ESI, m/z): calcd. for $[C_{30}H_{30}N_2O_8+Na]^+$ 569.1894; Found 569.1917



6a

Scale up synthesis of **6a**, 5'-OH-dimethoxytrityluridine in solution phase

To an oven-dried 50mL PTFE vial was added 9.77 g of dry uridine (40.0 mmol, 1.0 eq) and 114.2 mL dry pyridine. This mixture was stirred for 5 minutes yielding a suspension. To this was added 9.04 g of DMTrCl (0.66 eq., 26.6 mmol), stirred for 30 minutes. The above procedure is repeated twice more, until a total of 27.10g of DMTrCl (79.9 mmol 2.0 eq.) had been added, and the mixture was stirred for an additional 2.5 hours, or until no baseline starting material was observed by TLC (5% MeOH in DCM). Crude product was diluted with 100 mL of EtOAc, then quenched and washed once with 104 mL 10% $NaHCO_3$ in water. The crude mixture was dried with anhydrous sodium sulfate then evaporated under reduced pressure and further subjected to high vacuum to ensure complete removal of pyridine, yielding a light-yellow foam. The resulting foam was dissolved in a

small volume of warm toluene and recrystallized from 250mL of toluene and hexanes. White crystalline product was filtered and washed with 10mL cold hexanes then dried under high vacuum, yielding 17.05 g of white crystalline powder (78.2% yield). The resulting material was characterized by ^{1}H NMR and MS.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 8.06 (d, *J* = 8.1 Hz, 1H), 7.41-7.28 (m, 9H), 6.86 (d, *J* = 9.0 Hz, 4H), 5.92 (d, *J* = 2.4 Hz, 1H), 5.54 (d, *J* = 4.3 Hz, 1H), 5.37 (dd, *J* = 8.1, 1.3 Hz, 1H), 4.45 (t, *J* = 6.2 Hz, 1H), 4.37 (t, *J* = 3.5 Hz, 1H), 4.21-4.19 (m, 1H), 3.79 (d, *J* = 1.2 Hz, 6H), 3.54 (qd, *J* = 11.1, 2.4 Hz, 2H), 3.39 (d, *J* = 7.5 Hz, 1H).

RMS (ESI, m/z): calcd. for $[C_{30}H_{30}N_2O_8+Na]^+$ 569.1894; Found 569.1983

RAM

Segment	Material	Mass (g)	Sum Mass (g)	Sum PMI
Reaction	Uridine	9.77	42.67	2.32
	Pyridine	7.68		
	Ethyl Acetate	10.31		
	DMTrCl	14.91		
Workup	EtOAc	19.64	128.64	6.98
	10% NaHCO3	104.00		
	Sodium Sulfate	5.00		
Purification	Toluene	208.08	221.30	12.01
	Hexanes (recry)	6.61		
	Hexanes (wash)	6.61		
	Sum	**392.61**		**19.00**

Yield	**18.42**

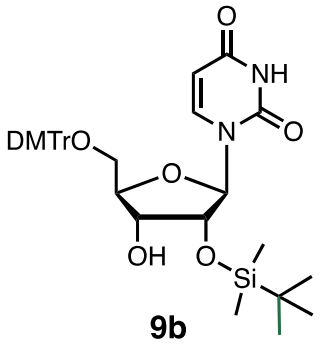
Solution

Segment	Material	Mass (g)	Sum Mass (g)	Sum PMI
Reaction	Uridine	9.77	153.07	8.98
	Pyridine	116.29		
	DMTrCl	27.01		
Workup	EtOAc	100.90	208.90	12.25
	10% NaHCO3	103.00		
	Sodium Sulfate	5.00		
Purification	Toluene	208.08	260.00	15.25
	Hexanes(recry)	6.61		
	Hexanes (wash)	6.61		
	Sum	**583.28**		**36.48**

Yield	**17.05**

$$\frac{PMI\ Sol.\ Phase - PMI\ RAM}{PMI\ Sol.\ Phase} = \frac{36.48-19.00}{36.48} = 48\%\ reduction$$

Figure S4: PMI Analysis and comparison between solution phase and RAM large scale synthesis of **6a**



9b

Synthesis of **9b**

To an oven dried 5 mL PTFE vial was added 1.32 g of 5′-dimethoxytrityl uridine (2.42 mmol, 1.0 eq.), 1.20 mL dimethylformamide (15.48 mmol, 6.4 eq.), and 428 mg of imidazole (6.29 mmol, 2.6 eq.). The mixture was subjected to RAM at 60 g for 5 minutes, forming a slurry. To this mixture was added 437 mg tert-butyldimethylsilyl chloride (2.90 mmol, 1.2 eq.). This mixture was subjected to RAM for 5 minutes at 60 g. TLC showed complete consumption of starting material (3% MeOH in DCM). The crude mixture was taken up in 10 mL EtOAc, then quenched and washed once with 5 mL of 10% $NaHCO_3$ in water and washed once with 10 mL saturated brine. The resulting crude material was dried with anhydrous sodium sulfate and solvent was removed under reduced pressure. The crude material was dried under high vacuum overnight to remove trace solvents. TLC showed two closely spaced spots, consistent with the 2′ and 3′-tert-butyldimethylsilylated products (4% MeOH in DCM). The crude mixture was purified by silica gel column chromatography (1.2-2.8% MeOH in DCM). Two products with differing Rf values, but consistent mass spectra were isolated, and analyzed by ^{1}H and COSY NMR were confirmed to be the desired 5′-dimethoxytrityl-2′-tert-butyldimethylsislyl uridine (**9b**) (898.3 mg, 56.1% yield), and 5′-dimethoxytrityl-3′-tert-butyldimethylsislyl uridine (**9a**) (545.0 mg, 34.1% yield).

Characterization data of **9a,** RAM

^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.24 (s, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.38-7.26 (m, 10H), 6.87 (dd, *J* = 8.9, 1.5 Hz, 4H), 5.99 (d, *J* = 4.2 Hz, 1H), 5.40 (d, *J* = 8.2 Hz, 1H), 4.41 (d, *J* = 5.1 Hz, 1H), 4.20-4.18 (m, 1H), 4.09-4.08 (m, 1H), 3.62 (dd, *J* = 11.0, 2.5 Hz, 1H), 3.35-3.32 (m, 1H), 2.84 (d, *J* = 6.2 Hz, 1H), 0.89-0.86 (m, 9H), 0.03 (d, *J* = 42.3 Hz, 6H).

HRMS (ESI, m/z) calcd. For 683.2759 $[C_{36}H_{44}N_2O_8Si+Na]^+$; Found 683.2773

Characterization data of **9b,** RAM

^{1}H-NMR (500 MHz; $CDCl_3$): δ 8.75 (s, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.39 (d, *J* = 1.2 Hz, 2H), 7.32-7.28 (m, 8H), 6.87 (d, *J* = 8.9 Hz, 4H), 5.97 (d, *J* = 3.0 Hz, 1H), 5.31 (dd, *J* = 8.1, 2.3 Hz, 1H), 4.38-4.37 (m, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.82 (d, *J* = 0.8 Hz, 6H), 3.53 (dd, *J* = 7.4, 2.3 Hz, 2H), 2.60 (d, *J* = 5.9 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 2H), 0.95 (s, 10H), 0.20 (d, *J* = 11.3 Hz, 6H).

HRMS (ESI, m/z): calcd. For 683.2759 $[C_{36}H_{44}N_2O_8Si+Na]^+$; Found 683.2723

Control Synthesis of **9b**

To an oven dried 20 mL RBF was added 1.32 g of 5′-dimethoxytrityl uridine (2.42 mmol, 1.0 eq.), 10 mL dimethylformamide, and 428 mg of imidazole (6.29 mmol, 2.6 eq.). The mixture was stirred for 5 minutes to dissolve starting materials. To this mixture was added 437 mg tert-butyldimethylsilyl chloride (2.90 mmol, 1.2 eq.). This mixture was stirred until TLC indicated complete consumption of 5′-dimethoxytrityl uridine, occurring at 18 hours. The crude mixture

was taken up in 50 mL EtOAc, then quenched and washed once with 50 mL of 10% $NaHCO_3$ in water again once with 50mL saturated brine. The resulting crude material was dried with anhydrous sodium sulfate and solvent was removed under reduced pressure. The crude material was dried under high vacuum overnight to remove trace solvents. TLC showed two closely spaced spots, consistent with the 2′ and 3′-tert-butyldimethylsilylated products. The crude mixture was purified by silica gel column chromatography (1.1-3.0% MeOH in DCM). Two products with differing Rf values, but consistent mass spectra were isolated, and analyzed by ^{1}H and COSY NMR were confirmed to be the desired 5′-dimethoxytrityl-2′-tert-butyldimethylsislyl uridine (**9b**) (803.3 mg, 50.1% yield), and 5′-dimethoxytrityl-3′-tert-butyldimethylsislyl uridine (**9a**) (610.5 mg, 38.2% yield).

Characterization data of **9a,** solution phase

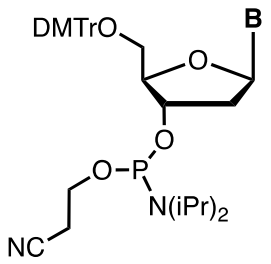
^{1}H-NMR (500 MHz; $CDCl_3$): δ 8.68 (s, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.38-7.27 (m, 10H), 6.88-6.85 (m, 4H), 5.99 (d, *J* = 4.2 Hz, 1H), 5.41 (dd, *J* = 8.1, 1.7 Hz, 1H), 4.41 (d, *J* = 5.1 Hz, 1H), 4.21-4.17 (m, 1H), 4.08 (d, *J* = 4.9 Hz, 1H), 3.81 (s, 6H), 3.62 (dd, *J* = 10.9, 2.5 Hz, 1H), 3.34 (dd, *J* = 11.0, 2.7 Hz, 1H), 2.91-2.87 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 1H), 0.91 (dd, *J* = 33.5, 6.2 Hz, 10H), 0.09-0.08 (m, 3H), -0.01--0.02 (m, 3H).

HRMS (ESI, m/z): calcd. For 683.2759 $[C_{36}H_{44}N_2O_8Si+Na]^+$; Found 683.2753

Characterization data of **9b,** solution phase

1H-NMR (500 MHz; CDCl3): δ 8.14 (s, 1H), 8.04 (s, 1H), 7.96 (d, J = 8.2 Hz, 1H), 7.38-7.28 (m, 10H), 6.87 (d, J = 8.8 Hz, 4H), 5.97 (d, J = 3.2 Hz, 1H), 5.30 (dd, J = 8.1, 2.3 Hz, 1H), 4.38 (d, J = 1.5 Hz, 2H), 4.13 (t, J = 2.2 Hz, 1H), 3.82 (s, 5H), 3.52 (dd, J = 7.8, 2.3 Hz, 2H), 2.98 (s, 3H), 2.91 (s, 3H), 2.61 (s, 1H), 1.60 (s, 2H), 0.95 (s, 8H), 0.18 (s, 5H).

HRMS (ESI, m/z): calcd. For 683.2759 $[C_{36}H_{44}N_2O_8Si+Na]^+$; Found 683.2755



11a, B = Thy
11b, B = Cyt^{Ac}
11c, B = Ade^{Bz}

General procedure for the synthesis of 3’-(2-cyanoethyl)-N,N'-diisopropylphosphoramidite nucleosides **11a-11c**

To an oven dried 5 mL PTFE vial was added 2.0 mmol of N-acyl*-5’-dimethoxytrityl nucleoside (*Ade^{Bz}, Cyt^{Ac}), followed by 1.37 mL diisopropylethylamine (8.0 mmol, 4 eq.) and 947 mL 2-Cyanoethyl N,N-diisopropylcholrophosphoramidite (4.30 mmol, 2.2 eq.). This mixture was subjected to RAM at 60 g for 5-10 minutes or until all starting material was absent by TLC. The mixture was dried under reduced pressure and taken up in a small amount of dichloromethane before silica gel column purification (2-6% MeOH in DCM). Excess solvent was removed under reduced pressure, yielding a white foam.

Phosphitylation control synthesis of **11a**

To an oven dried 20 mL RBF was added 2.0 mmol of 5’-dimethoxytrityl thymidine and 10 mL dry dichloromethane. To this stirred solution as added 1.37 mL diisopropylethylamine (8.0 mmol, 4 eq.) and 947 mL 2-Cyanoethyl N,N-diisopropylcholrophosphoramidite (4.30 mmol, 2.2 eq.). This mixture was stirred for 3.5 hours, or until all starting material was absent by TLC. The mixture was dried under reduced pressure, and taken up in a small amount of dichloromethane before silica gel column purification (2-6% MeOH in DCM). Excess solvent was removed under reduced pressure, yielding a white foam (1.12 g, 73%)

Characterization data for **11a** RAM

^{1}H-NMR (400 MHz; MeOD): δ 8.66 (s, 1H), 8.55 (s, 1H), 8.10 (d, J = 7.2 Hz, 2H), 7.60-7.24 (m, 14H), 6.82 (t, J = 4.4 Hz, 4H), 6.18 (d, J = 4.5 Hz, 1H), 4.99-4.97 (m, 1H), 4.57 (d, J = 4.8 Hz, 1H), 4.28-4.27 (m, 1H), 3.77 (d, J = 1.0 Hz, 6H), 3.45 (dd, J = 2.5, 0.8 Hz, 2H), 3.36-3.31 (m, 6H), 2.72-2.66 (m, 4H), 1.11 (t, J = 7.2 Hz, 6H).

31-P NMR (203 MHz; CD3CN): δ 148.5, δ 148.9

HRMS (ESI, m/z): calcd. 767.31802 for $[C_{41}H_{50}O_8N_5+H]^+$; Found 767.31569

Yield: 1.41 g, 92%

Characterization data for **11a** solution phase

^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.64 (dd, *J* = 23.5, 1.2 Hz, 1H), 7.43 (s, 2H), 7.33-7.28 (m, 7H), 6.87-6.86 (m, 4H), 6.42 (ddd, *J* = 10.3, 7.9, 5.9 Hz, 1H), 4.70-4.66 (m, 1H), 4.21-4.16 (m, 1H), 3.64-3.55 (m, 4H), 3.34 (ddd, *J* = 10.5, 9.1, 2.8 Hz, 1H), 2.64 (t, *J* = 6.3 Hz, 1H), 2.44 (t, *J* = 6.4 Hz, 1H), 1.45 (dd, *J* = 3.3, 1.1 Hz, 3H).

31-P NMR (203 MHz; CDCl3): δ 148.9, 148.5

HRMS (ESI, m/z): calcd. 767.31802 for $[C_{41}H_{50}O_8N_5+H]^+$; Found 767.31923

Characterization data for **11b**

^{1}H-NMR (500 MHz; CD3CN) δ 8.43 (s, 1H), 7.99-7.97 (m, 2H), 7.68-7.64 (m, 1H), 7.57-7.49 (m, 4H), 7.41-7.36 (m, 6H), 7.32-7.30 (m, 1H), 6.95-6.92 (m, 4H), 5.84 (d, *J* = 1.7 Hz, 1H), 4.42 (dd, *J* = 3.6, 2.3 Hz, 1H), 4.35 (td, *J* = 6.4, 2.1 Hz, 2H), 3.74-3.52 (m, 6H), 2.52-2.50 (m, 1H), 1.29 (dd, *J* = 9.0, 6.8 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 1H), 1.16 (dt, *J* = 12.1, 5.8 Hz, 10H), 0.96-0.93 (m, 9H), 0.20 (dd, *J* = 29.2, 7.9 Hz, 7H).

31-P NMR (203 MHz; CD3CN): δ 149.6

HRMS (ESI, m/z): calcd. 794.32892 for $[C_{41}H_{50}O_8N_5+H]^+$; Found 794.32693

Yield: 1.33 g, 84%

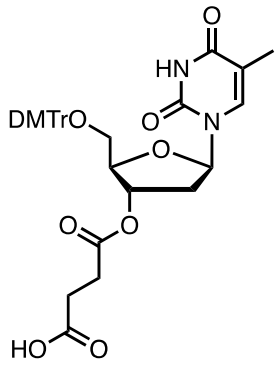
Characterization data for **11c**

^{1}H-NMR (500 MHz; CD3CN): δ 8.54 (d, *J* = 15.9 Hz, 1H), 8.28 (d, *J* = 10.8 Hz, 1H), 7.99 (d, *J* = 7.1 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.52-7.19 (m, 11H), 6.83 (ddd, *J* = 7.8, 5.3, 2.6 Hz, 4H), 5.14-5.10 (m, 1H), 4.51 (dt, *J* = 9.3, 4.9 Hz, 1H), 4.43 (d, *J* = 4.0 Hz,), 4.36 (d, *J* = 3.9 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 1H), 3.93-3.83 (m, 2H), 3.73 (s, 6H), 3.69-3.61 (m, 3H), 3.51 (ddd, *J* = 15.0, 10.8, 4.0 Hz, 1H), 3.38-3.33 (m, 1H), 2.69-2.65 (m, 2H), 2.45 (t, *J* = 6.2 Hz, 1H), 1.18 (q, *J* = 5.7 Hz, 10H), 1.09 (s, 4H), 0.77 (d, *J* = 3.9 Hz, 9H), -0.01 (s, 1H), -0.03 (s, 2H), -0.17 (s, 1H), -0.20 (s, 2H).

31-P NMR (203 MHz; CD3CN): δ 150.0, 148.6

HRMS (ESI, m/z): calcd. 858.37386 for $[C_{47}H_{53}O_7N_7+H]^+$; Found 858.37221

Yield: 1.60 g, 93%



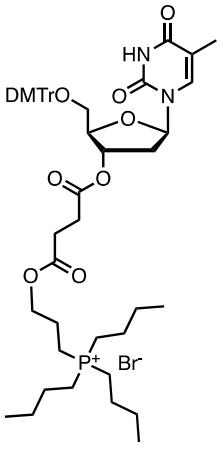
13

Synthesis of **13**

To an oven dried 5 mL PTFE vial was added 1.00 g of 5'-dimethoxytritylthymidine (1.8 mmol, 1.0 eq.), 202 mg of succinic anhydride (2.02 mmol, 1.1 eq.), 112 mg of 4-dimethylaminopyridine (0.92 mmol, 0.5 eq.), and 704 ml of ethyl acetate (11.0 mmol, 6.0 eq.). The resulting mixture was subjected to RAM for 40 minutes at 60 g, or until TLC indicated complete consumption of starting material. The crude mixture was analyzed by ^{1}H NMR and mass spectrometry. Yields calculated from integration of the 3' proton indicating quantitative conversion. Isolated yield reported following silica gel column chromatography (2-4% MeOH in DCM). 1.11 g, 96% yield

^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.42-8.42 (m, 1H), 7.59 (d, *J* = 1.2 Hz, 1H), 7.41 (d, *J* = 7.1 Hz, 2H), 7.32-7.29 (m, 8H), 6.87-6.85 (m, 4H), 6.43 (dd, *J* = 7.6, 6.1 Hz, 1H), 4.59 (t, *J* = 3.0 Hz, 1H), 4.07 (d, *J* = 3.0 Hz, 1H), 3.81 (s, 6H), 3.50 (dd, *J* = 10.5, 3.3 Hz, 1H), 3.39 (dd, *J* = 10.5, 3.0 Hz, 1H), 2.46-2.30 (m, 3H), 1.50 (d, *J* = 1.0 Hz, 3H).

HRMS (ESI, m/z): calcd. 643.2297 for $[C_{35}H_{35}N_2O_1]^-$; Found 643.2295



15

Synthesis of **15**

To an oven dried 5 mL PTFE vial was added 3.00 g of 5'-dimethoxytritylthymidine (5.51 mmol, 1.0 eq.), 605 mg of succinic anhydride (6.06 mmol, 1.1 eq.), 336 mg of 4-dimethylaminopyridine (2.75 mmol, 0.5 eq.), and 3.23 mL of ethyl acetate (33.0 mmol, 6.0 eq.). The resulting mixture was subjected to RAM for 40 minutes at 60 g, or until TLC indicated complete consumption of starting material. To this mixture was added 2.28 g of **14** (6.67 mmol, 1.1 eq.), followed by 739 mg of N,N'-Dicyclohexylcarbodiimide (3.58 mmol, 1.33 eq.). This mixture was subjected to RAM for a further 40 minutes at 60 g, then diluted in 3 mL of EtOAc before being filtered through celite to remove precipitated dicyclohexylurea. Solvent was removed under reduced pressure and dried by high vacuum to remove residual solvent. The crude material was purified by precipitation in hexanes followed by filtration over a bed a celite. Retained material was washed through with minimal ethyl acetate and solvent was removed under reduced pressure and dried under high vacuum to remove residual solvent. Further purification by column chromatography (1-6% MeOH in DCM) provided pure material via ^{1}H NMR. Fraction solvent was removed under reduced pressure, affording a white amorphous solid (3.04 g, 57% yield). The product was characterized by ^{1}H NMR, as well as by ESI mass spectrometry.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 8.42 (s, 1H), 7.62 (s, 1H), 7.38 (s, 2H), 7.28 (q, *J* = 4.3 Hz, 10H), 6.86 (d, *J* = 8.8 Hz, 4H), 6.42-6.39 (m, 1H), 5.49-5.48 (m, 1H), 4.26-4.25 (m, 2H), 4.18 (dd, *J* = 0.8, 0.4 Hz, 1H), 3.81 (s, 6H), 3.51-3.45 (m, 2H), 2.70 (d, *J* = 8.3 Hz, 6H), 2.53-2.45 (m, 7H), 2.00 (d, *J* = 3.0 Hz, 2H), 1.55-1.54 (m, 10H), 1.00 (d, *J* = 6.8 Hz, 8H).

31-P NMR (203 MHz; CDCl3): δ 33.7

HRMS (ESI, m/z): calcd. 887.4593 for $[C_{50}H_{68}N_2O_{10}P]^+$;Found 887.4604

DCC coupling control synthesis of **15**

To an oven dried 50 mL RBF was added 3.55 g 5'-dimethoxytrity-3'-succinyllthymidine (5.51 mmol, 1 eq.) and 19 mL dichloromethane. This mixture was stirred at room temperature until starting material was fully dissolved. To the mixture was added 4.15 g of **14** (12.13 mmol, 2.0 eq.), followed by 2.217 g of N,N'-Dicyclohexylcarbodiimide (10.74 mmol, 4 eq.). The mixture was stirred at room temperature and monitored by TLC twice daily. At 3 days TLC indicated complete absence of starting material. White precipitate (dicyclohexylurea) was filtered through a bed of celite. Retained material was washed with dichloromethane three times, and excess solvent was removed under reduced pressure, yielding a light yellow foam. Purification by column chromatography (1-5% MeOH in DCM) provided spectroscopically pure material. Excess solvent was removed under reduced pressure, yielding a white foam (3.24 g, 61% yield). The product was characterized by ^{1}H NMR as well as by ESI mass spectrometry.

^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.62 (d, *J* = 1.2 Hz, 1H), 7.39-7.30 (m, 4H), 7.30-7.25 (m, 8H), 6.86-6.84 (m, 4H), 6.40 (dd, *J* = 7.9, 6.7 Hz, 1H), 5.48 (t, *J* = 1.9 Hz, 1H), 4.27-4.24 (m, 2H), 4.17 (d, *J* =

1.5 Hz, 1H), 3.51-3.45 (m, 2H), 2.71-2.68 (m, 6H), 2.48-2.45 (m, 8H), 2.03-1.98 (m, 2H), 1.54 (t, *J* = 3.7 Hz, 12H), 1.00-0.99 (m, 9H).

31-P NMR (203 MHz; CDCl3): δ 33.7

HRMS (ESI, m/z): calcd. 887.4593 for $[C_{50}H_{68}N_2O_{10}P]^+$;Found 887.46061

S4 Spectral Data

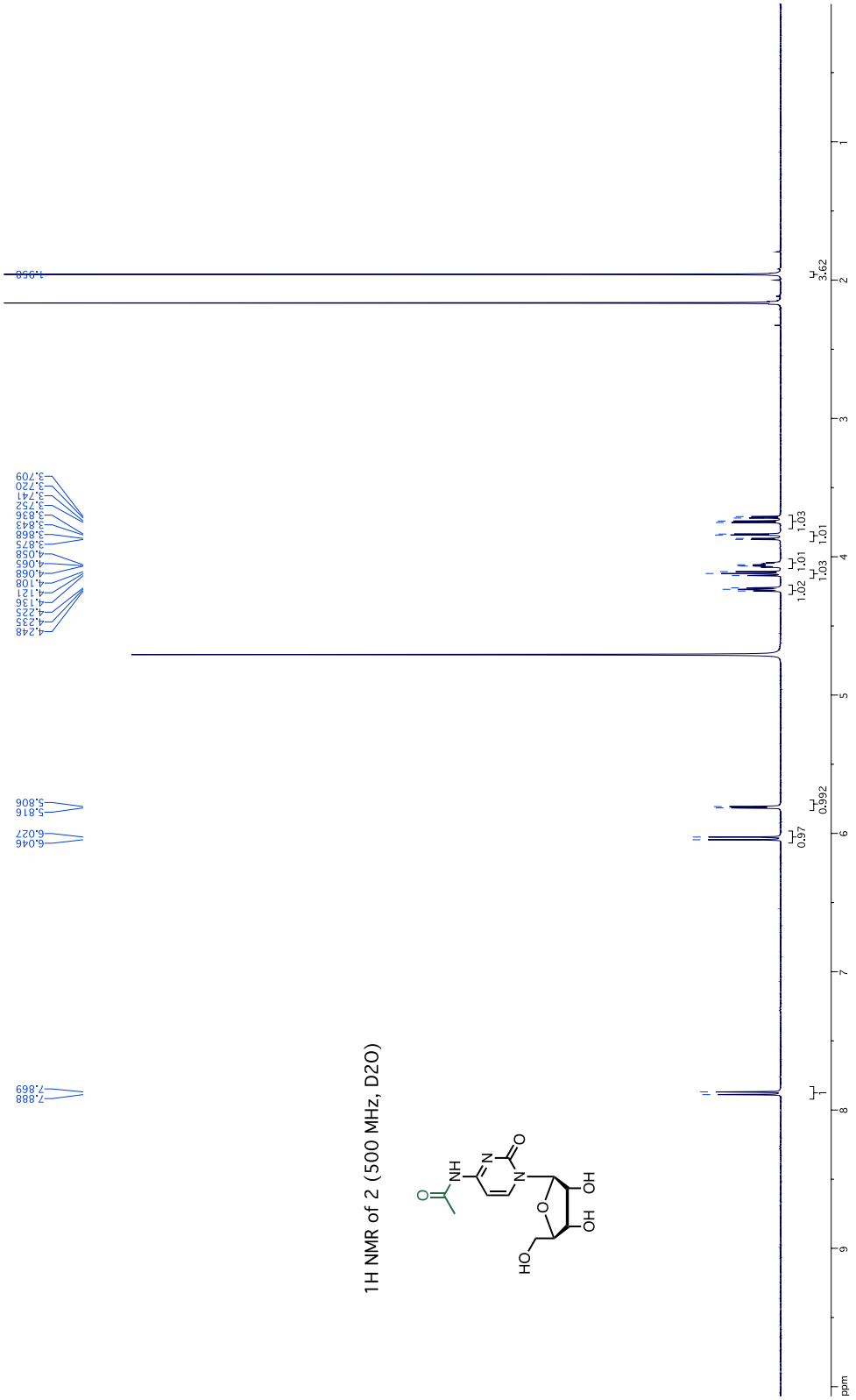
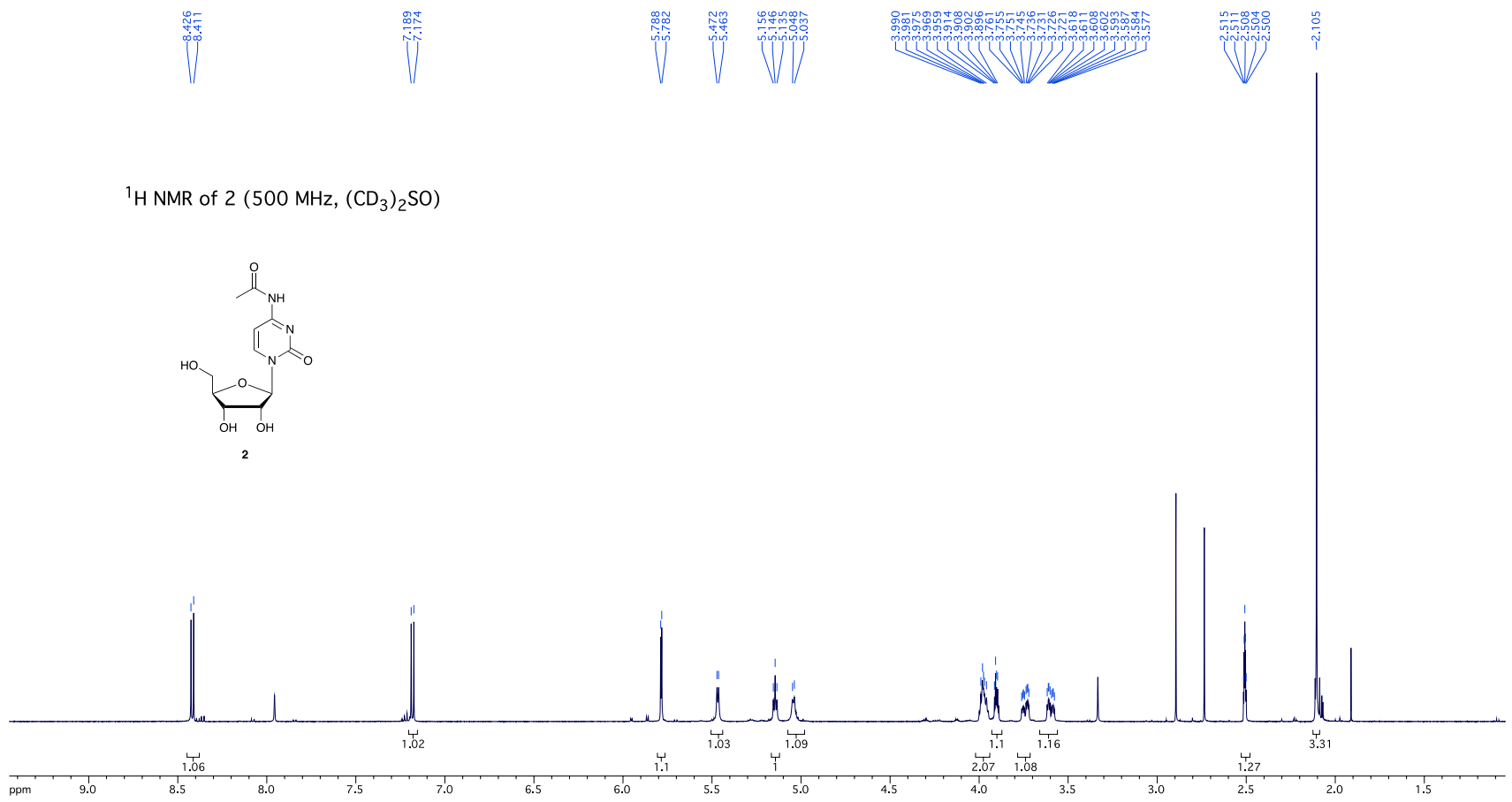


Figure S4-1: ^{1}H NMR Spectrum of **2** synthesized via RAM



^{1}H NMR of 2 (500 MHz, $(CD_3)_2SO$)

2

Figure S4-2: ^{1}H NMR Spectrum of **2** synthesized via RAM

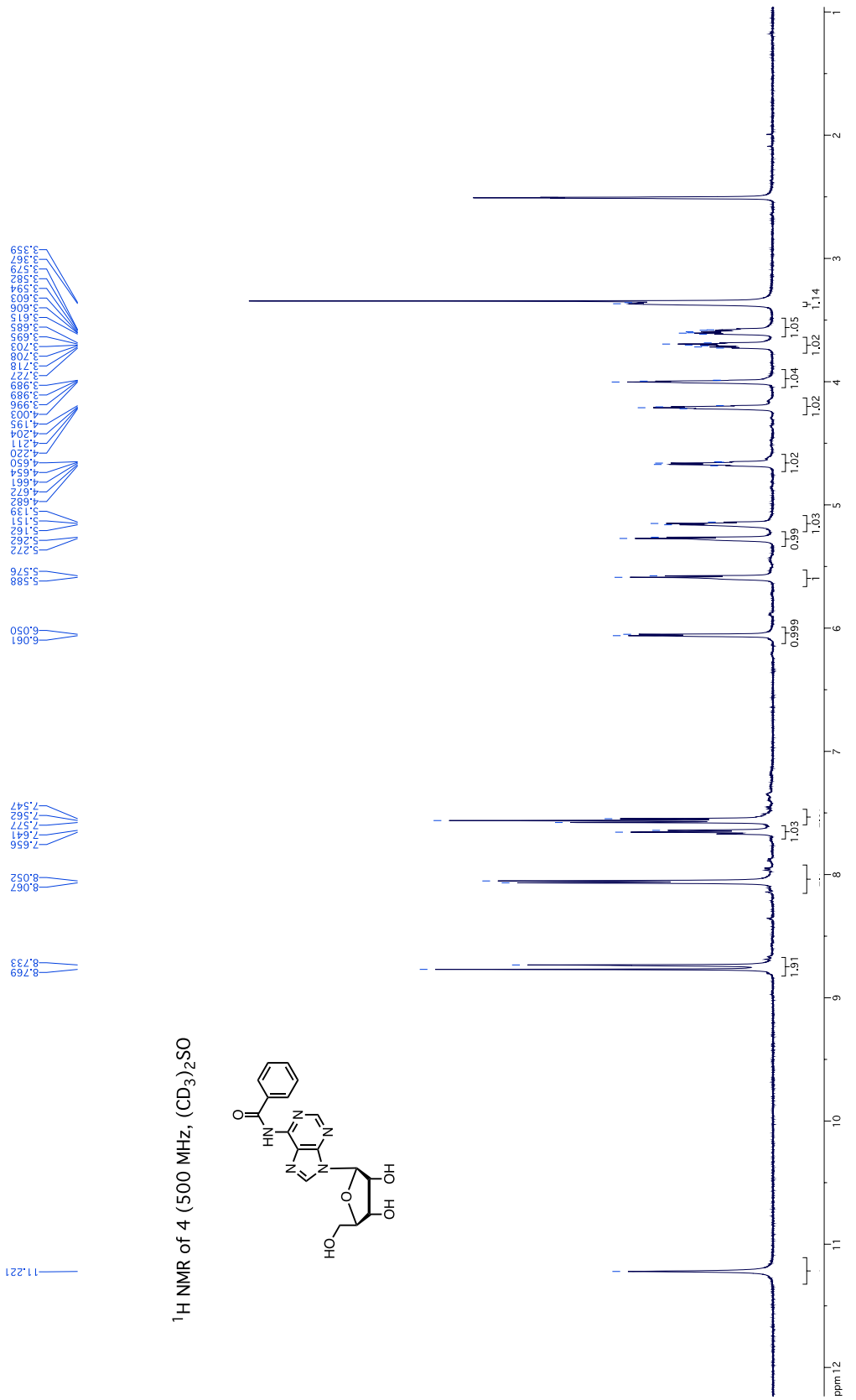


Figure S4-3: ^{1}H NMR Spectrum of **4a** synthesized via RAM

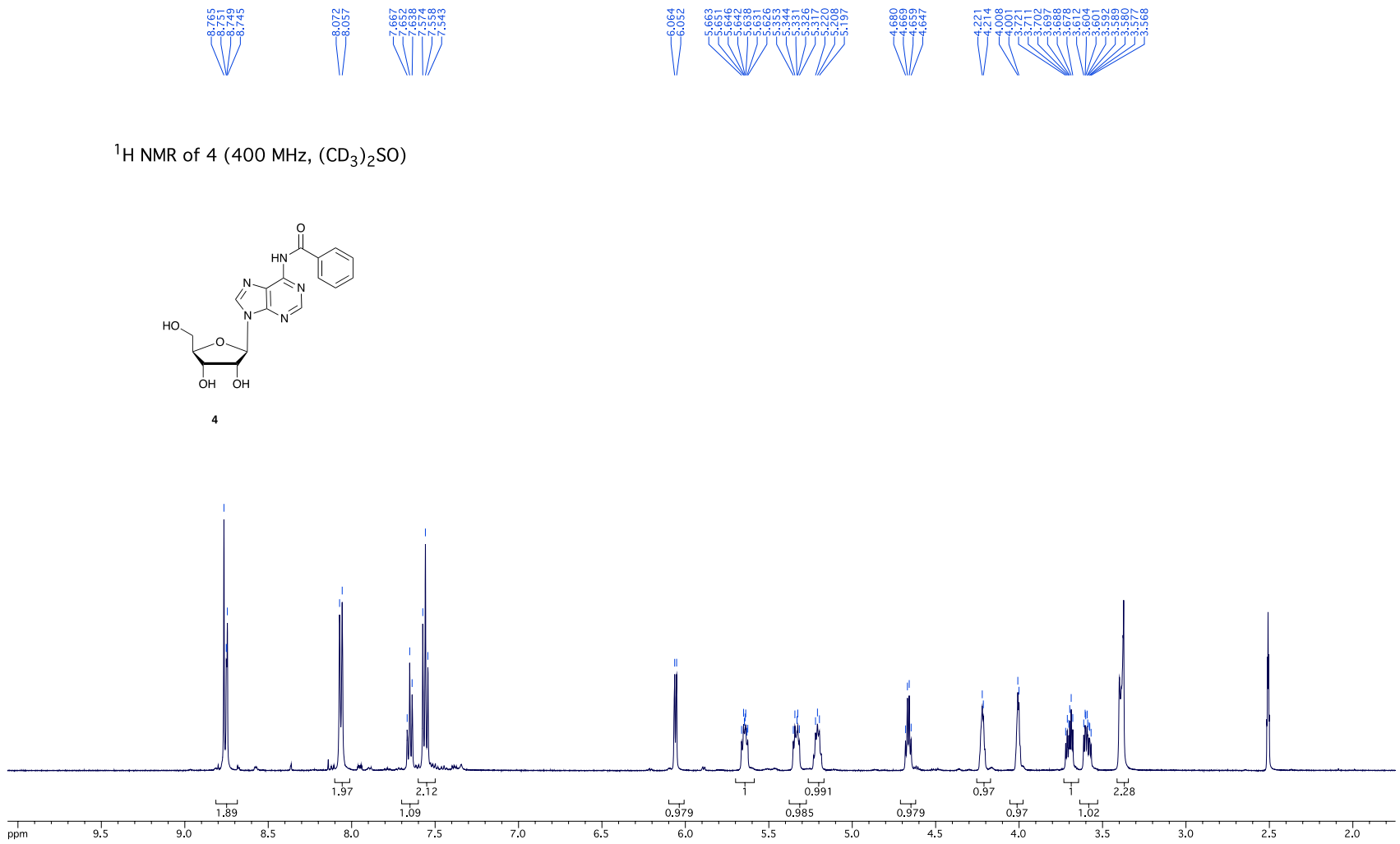


Figure S4-4: [1]H NMR Spectrum of **4a** solution phase control

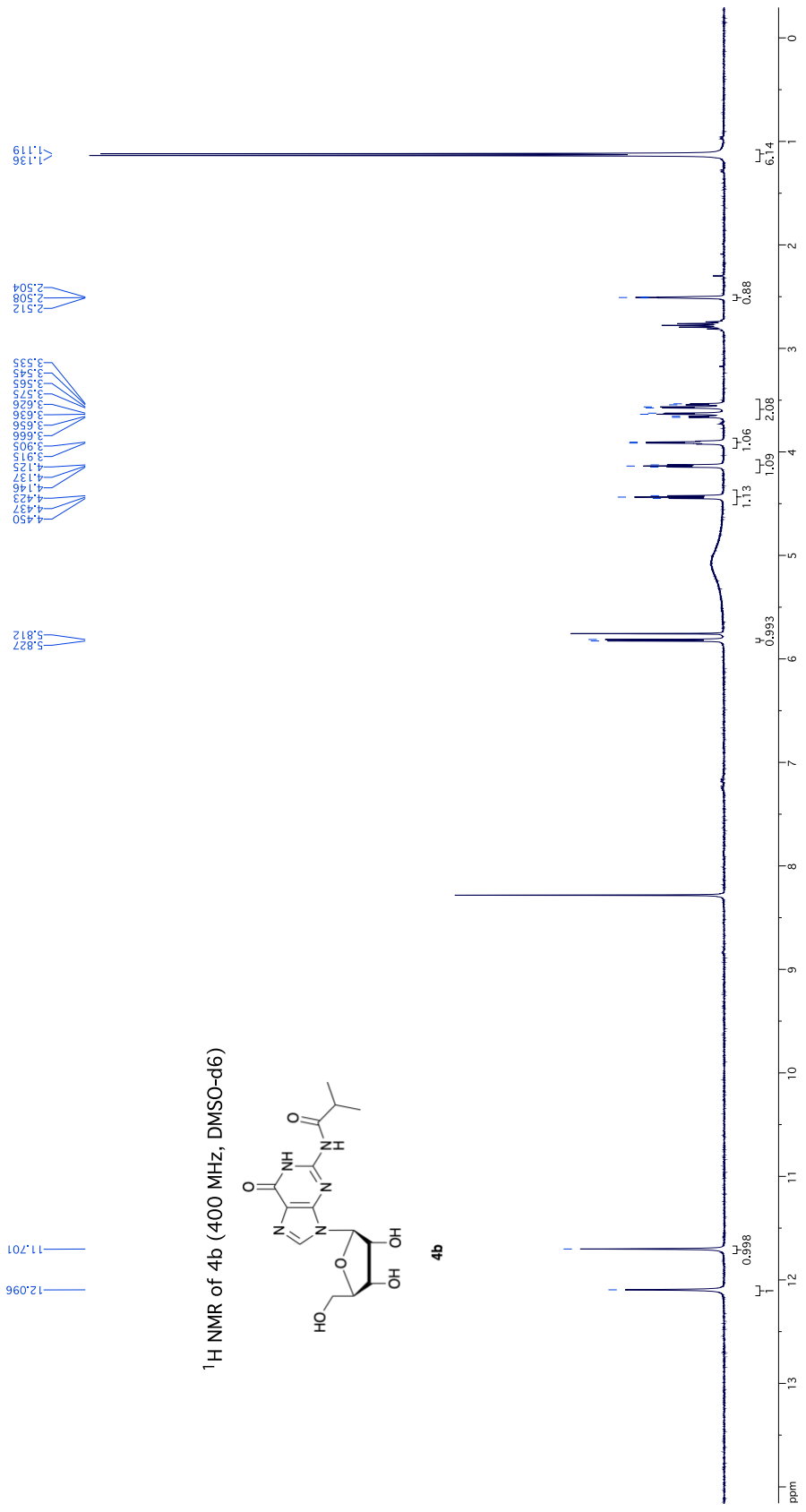


Figure S4-5: ^{1}H NMR Spectrum of **4b** synthesized via RAM

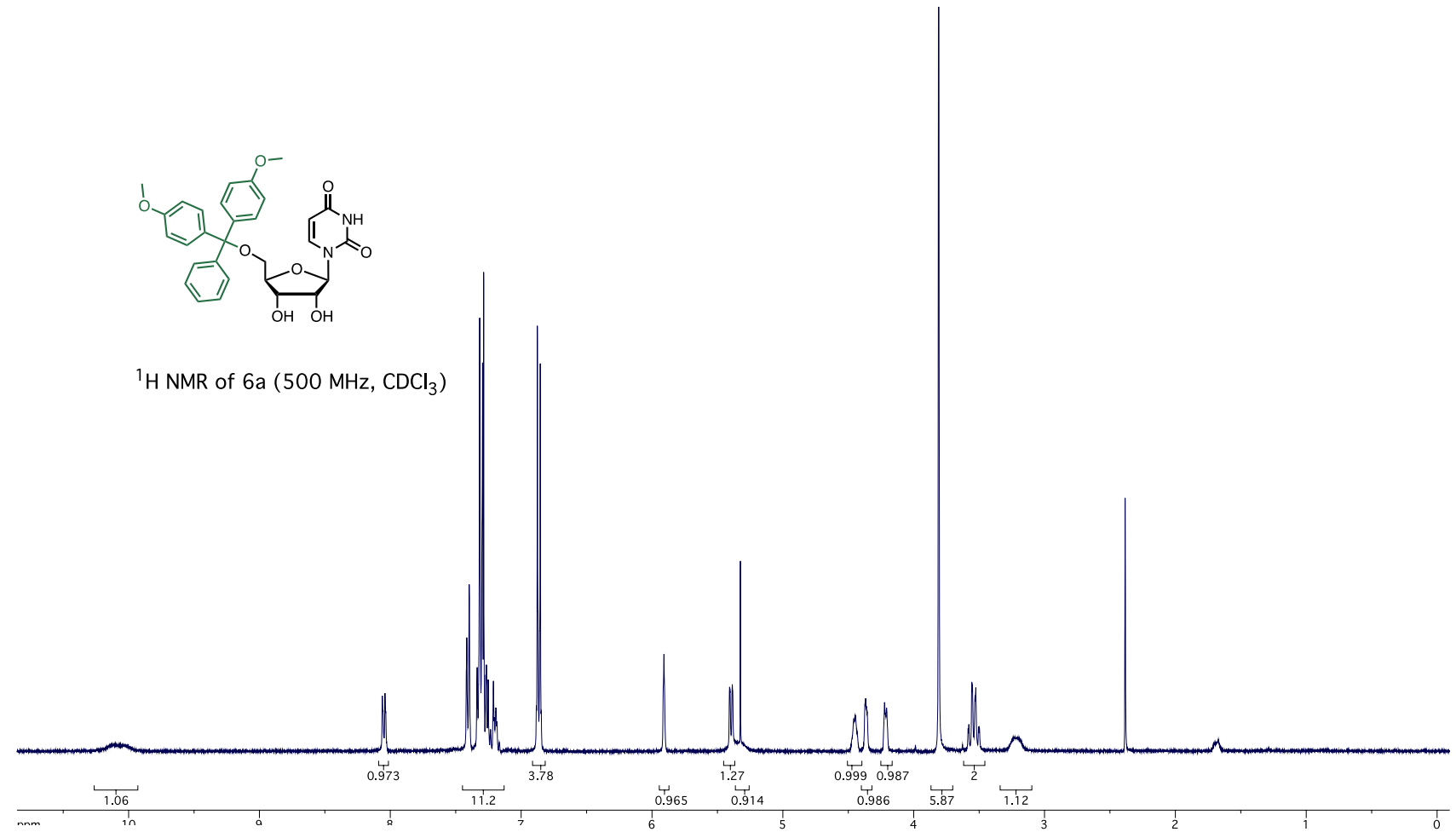


Figure S4-6: ^{1}H NMR Spectrum of **6a** synthesized via RAM

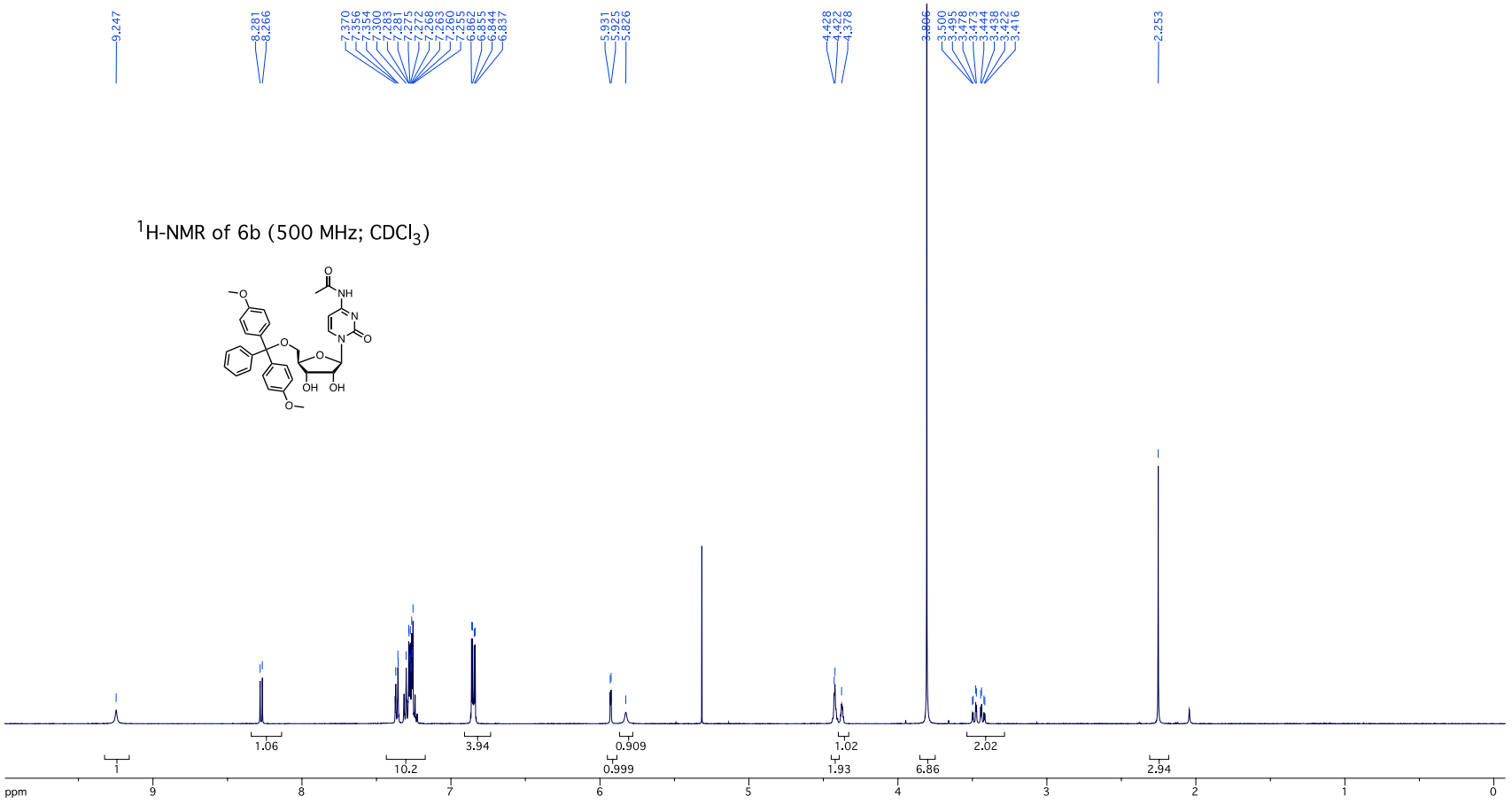


Figure S4-7: ^{1}H NMR Spectrum of **6b** synthesized via RAM

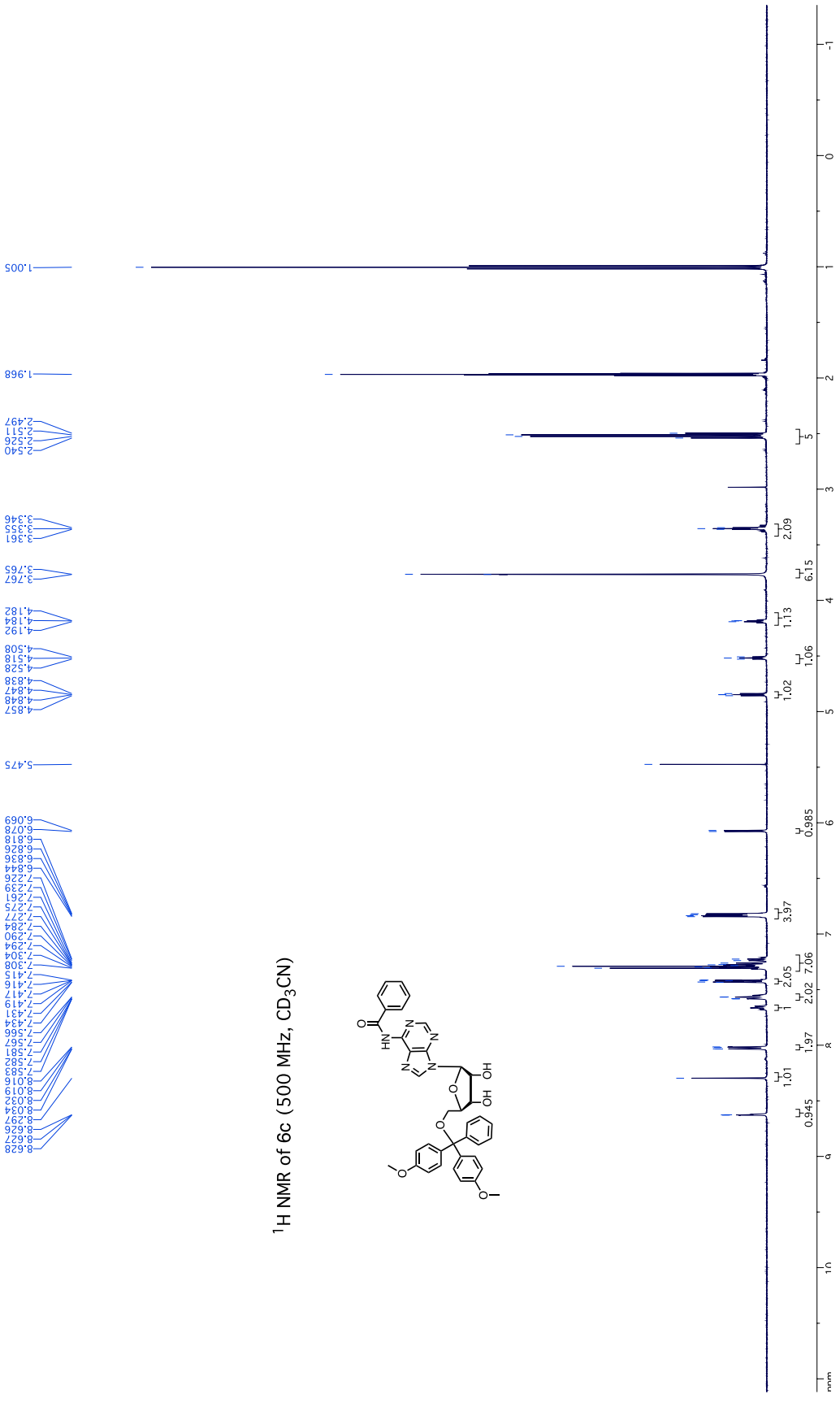


Figure S4-8: ^{1}H NMR Spectrum of **6c** synthesized via RAM

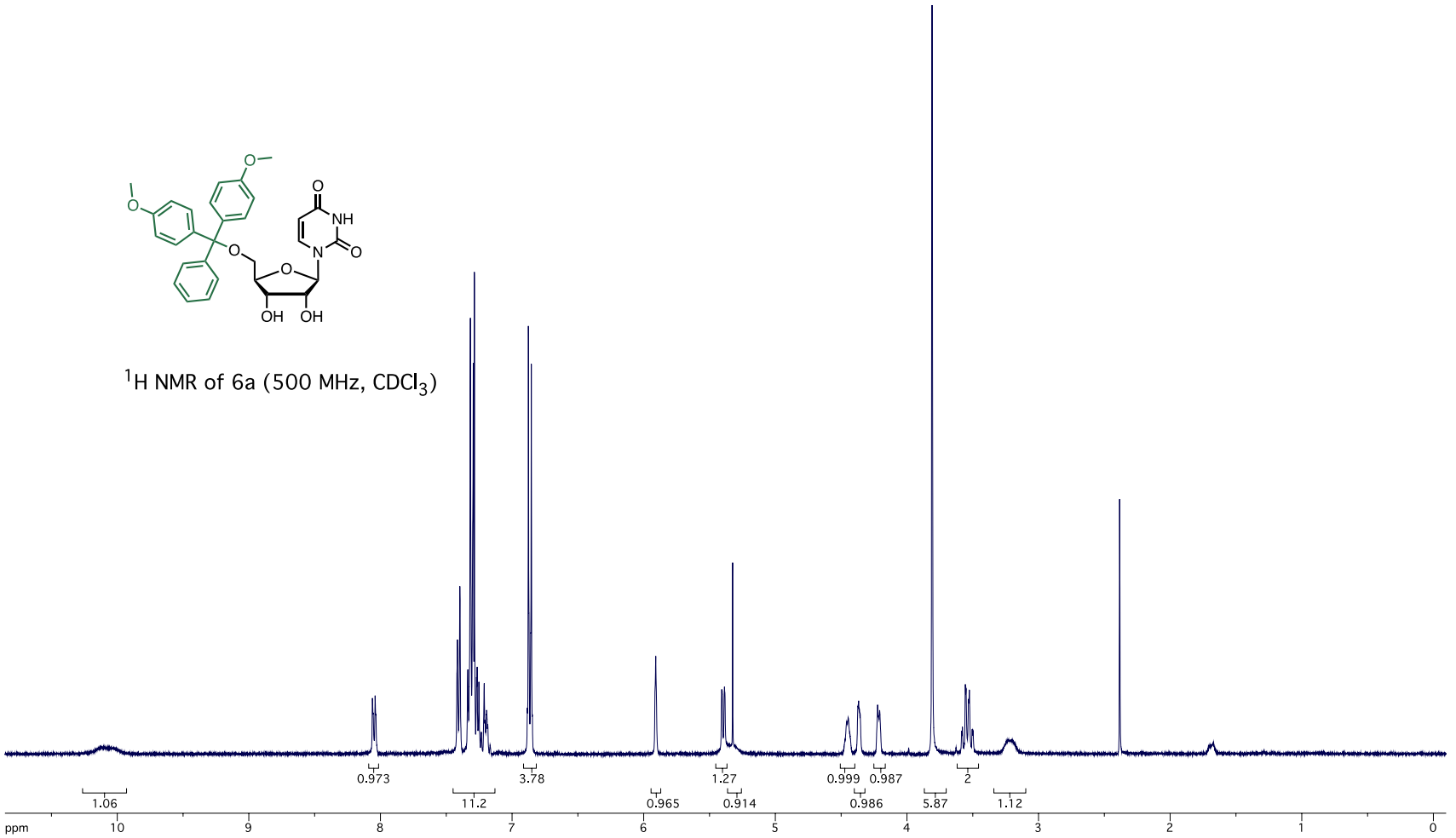


Figure S4-9: ^{1}H NMR Spectrum of **6c** synthesized via RAM, scale up

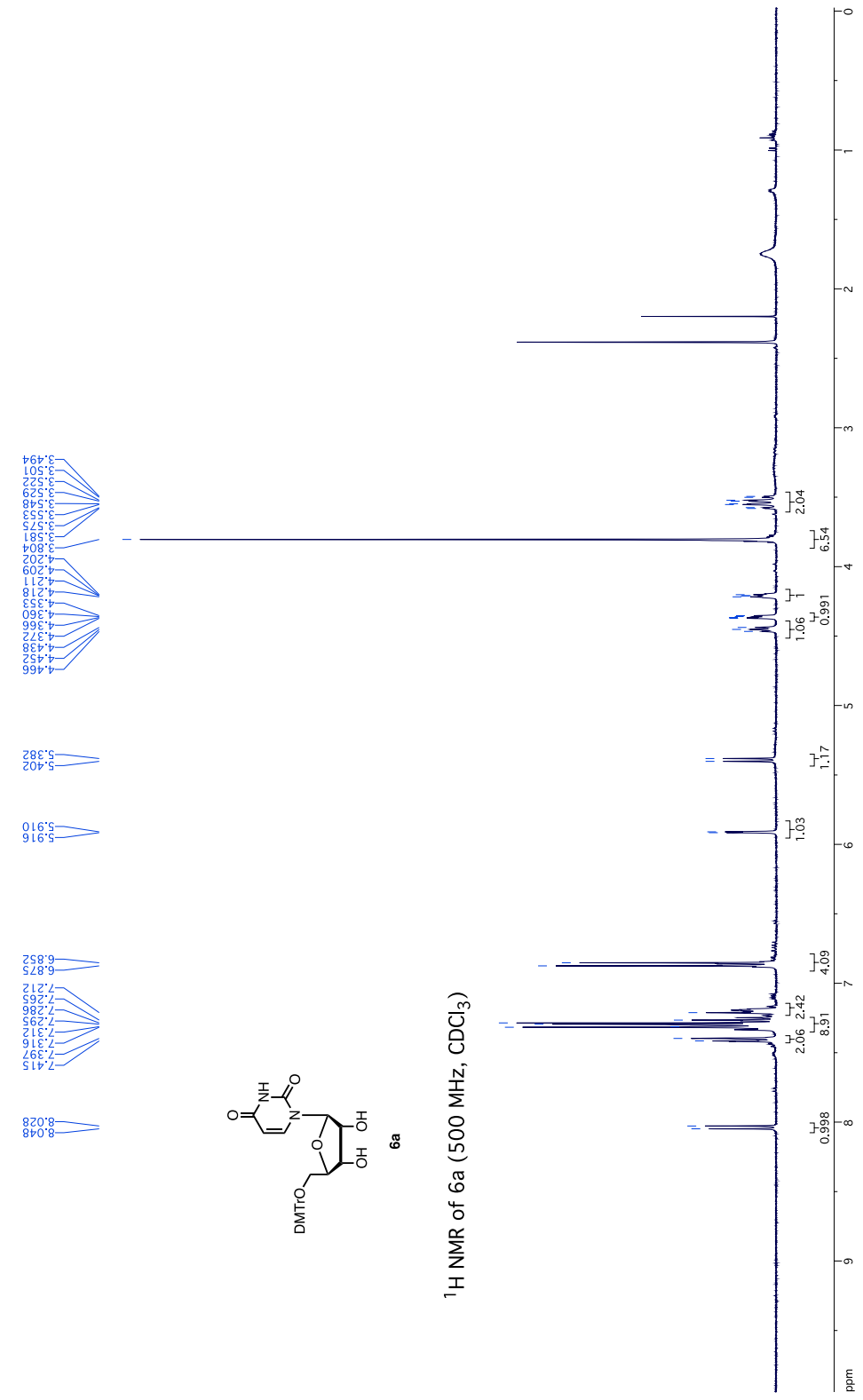


Figure S4-10: ^{1}H NMR Spectrum of **6c** synthesized in solution, scale up

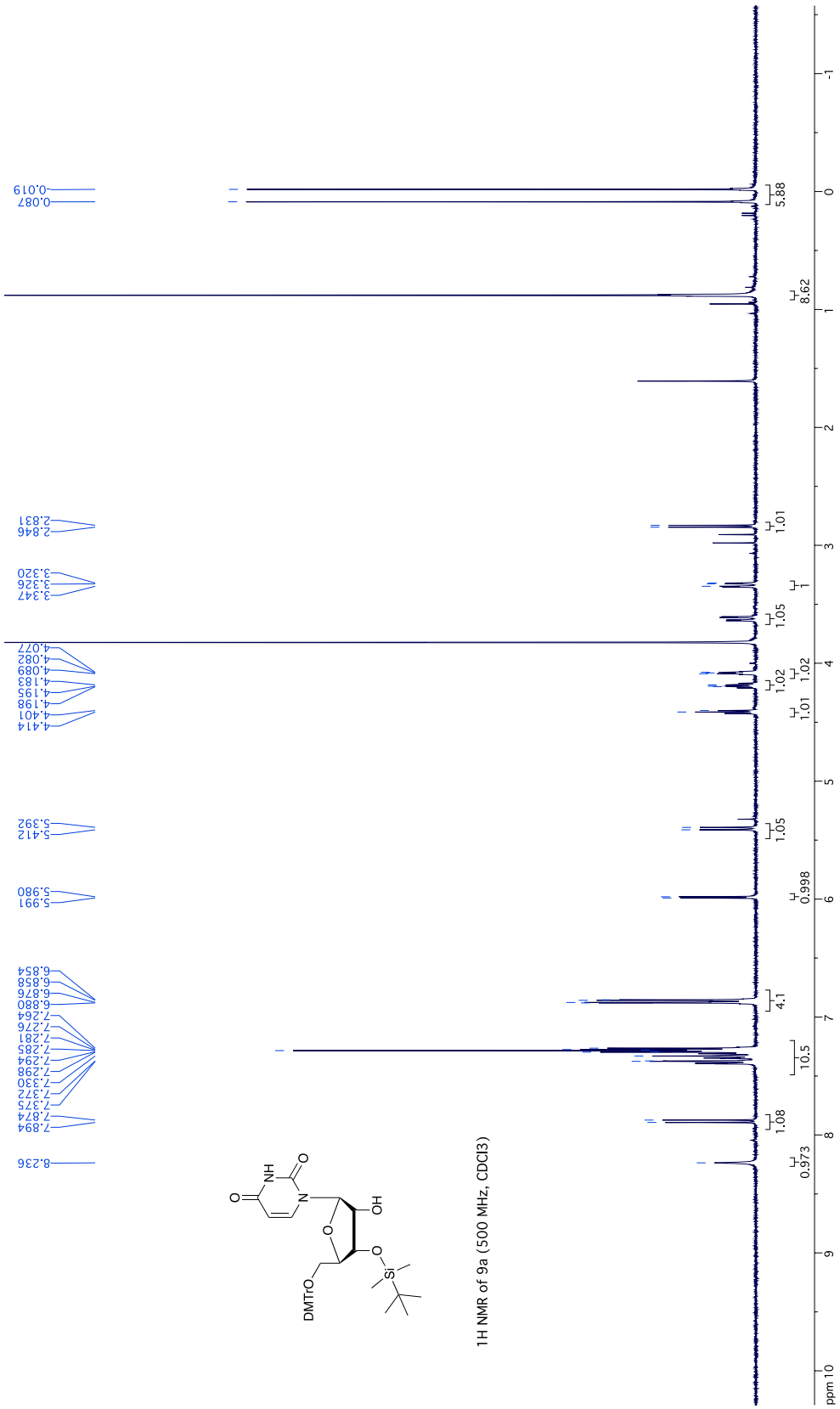


Figure S4-11: ^{1}H NMR Spectrum of **9a**, synthesized via RAM

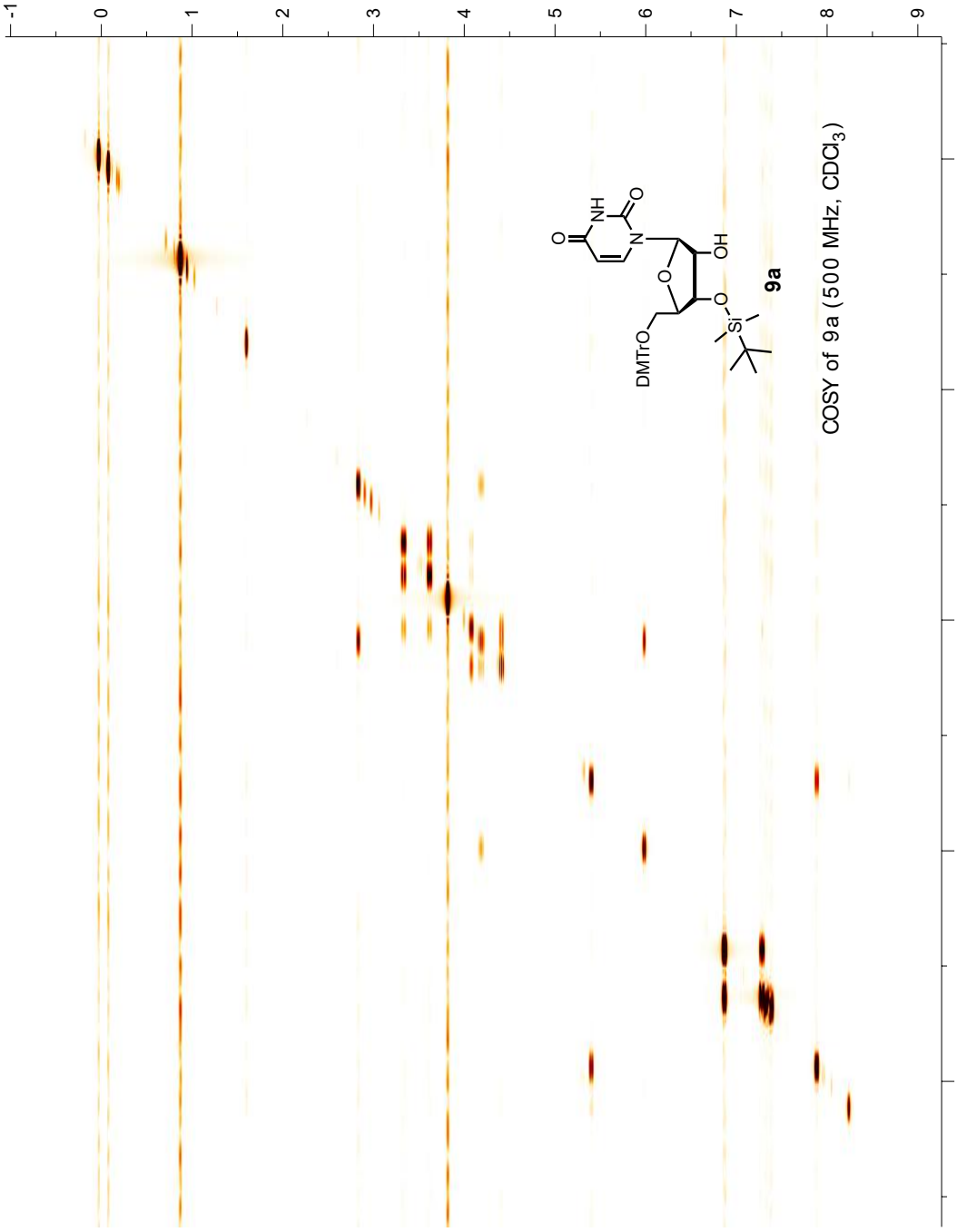


Figure S4-12: COSY Spectrum of **9a**, synthesized via RAM

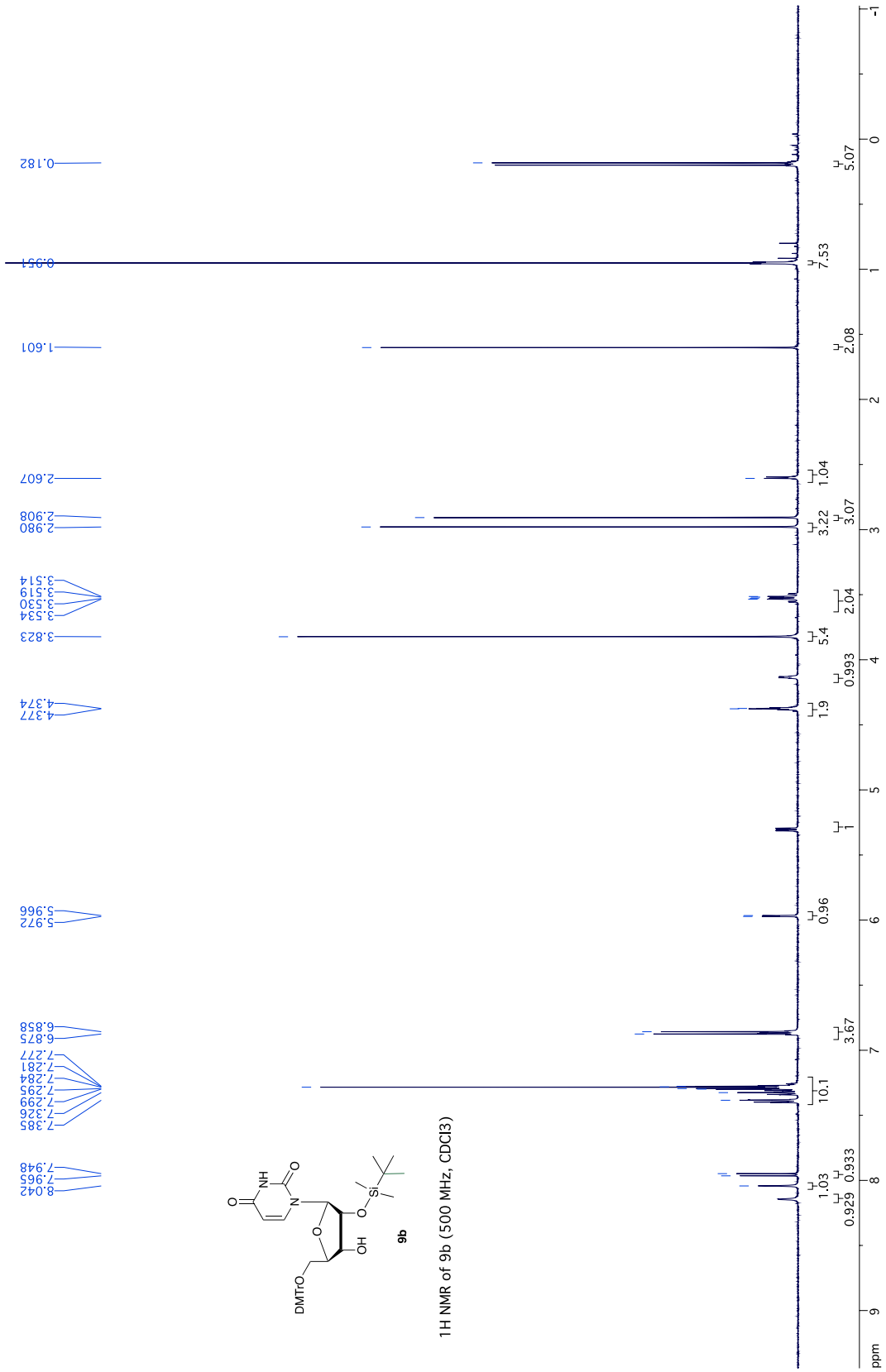


Figure S4-13: ^{1}H NMR Spectrum of **9b**, synthesized via RAM

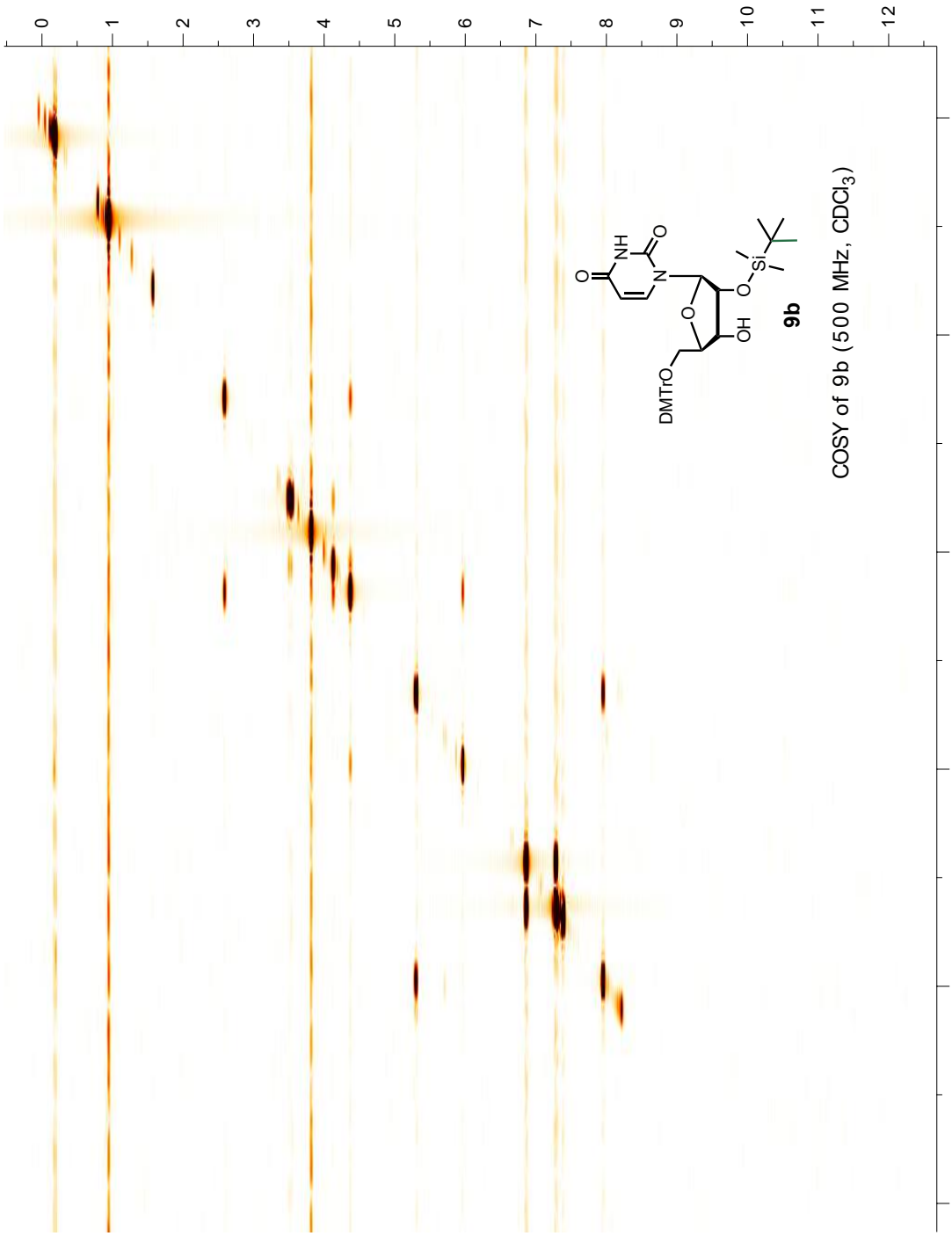


Figure S4-14: COSY spectrum of **9b**, synthesized via RAM

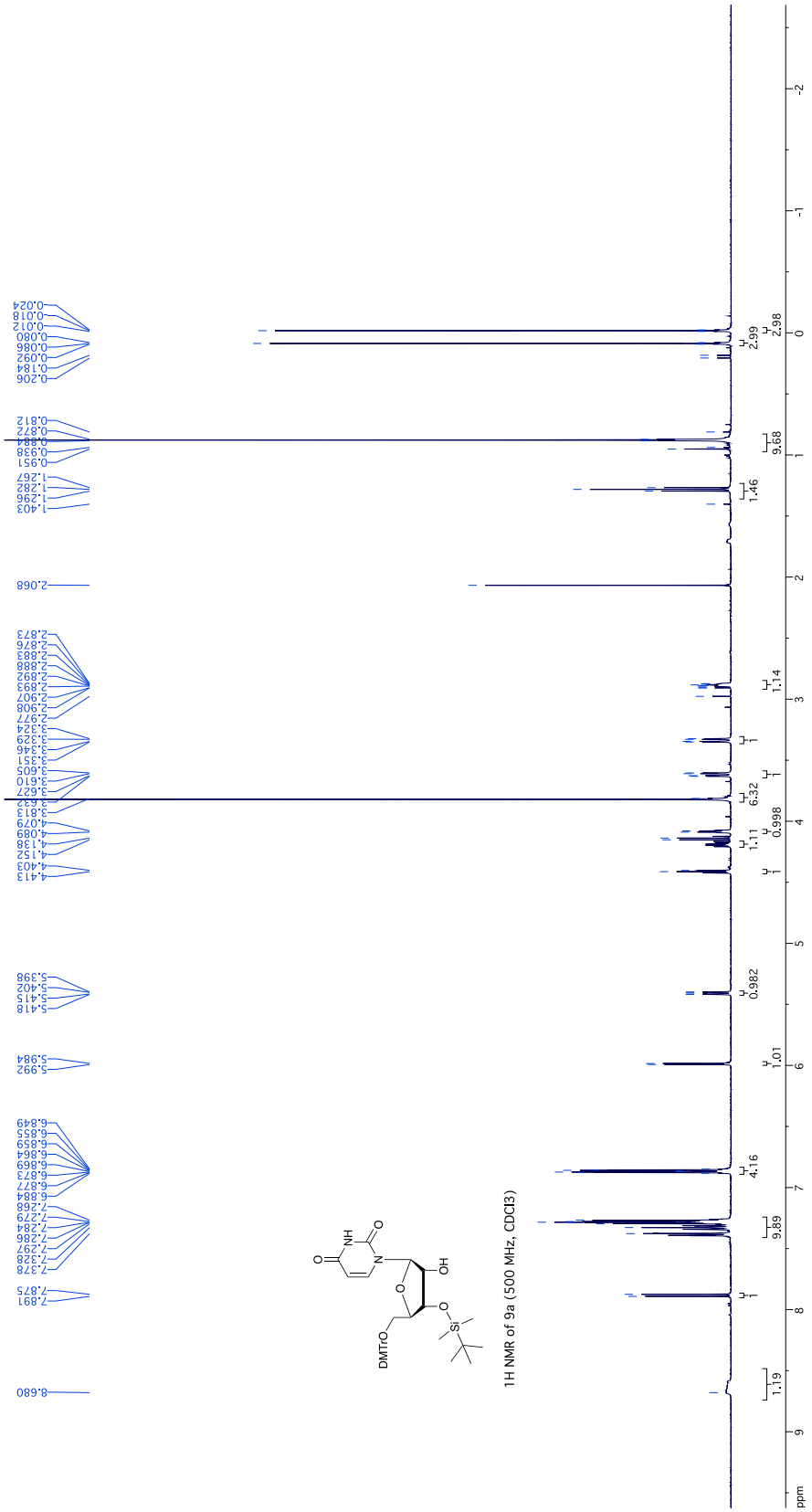


Figure S4-15: ^{1}H NMR spectrum of **9a**, synthesized in solution

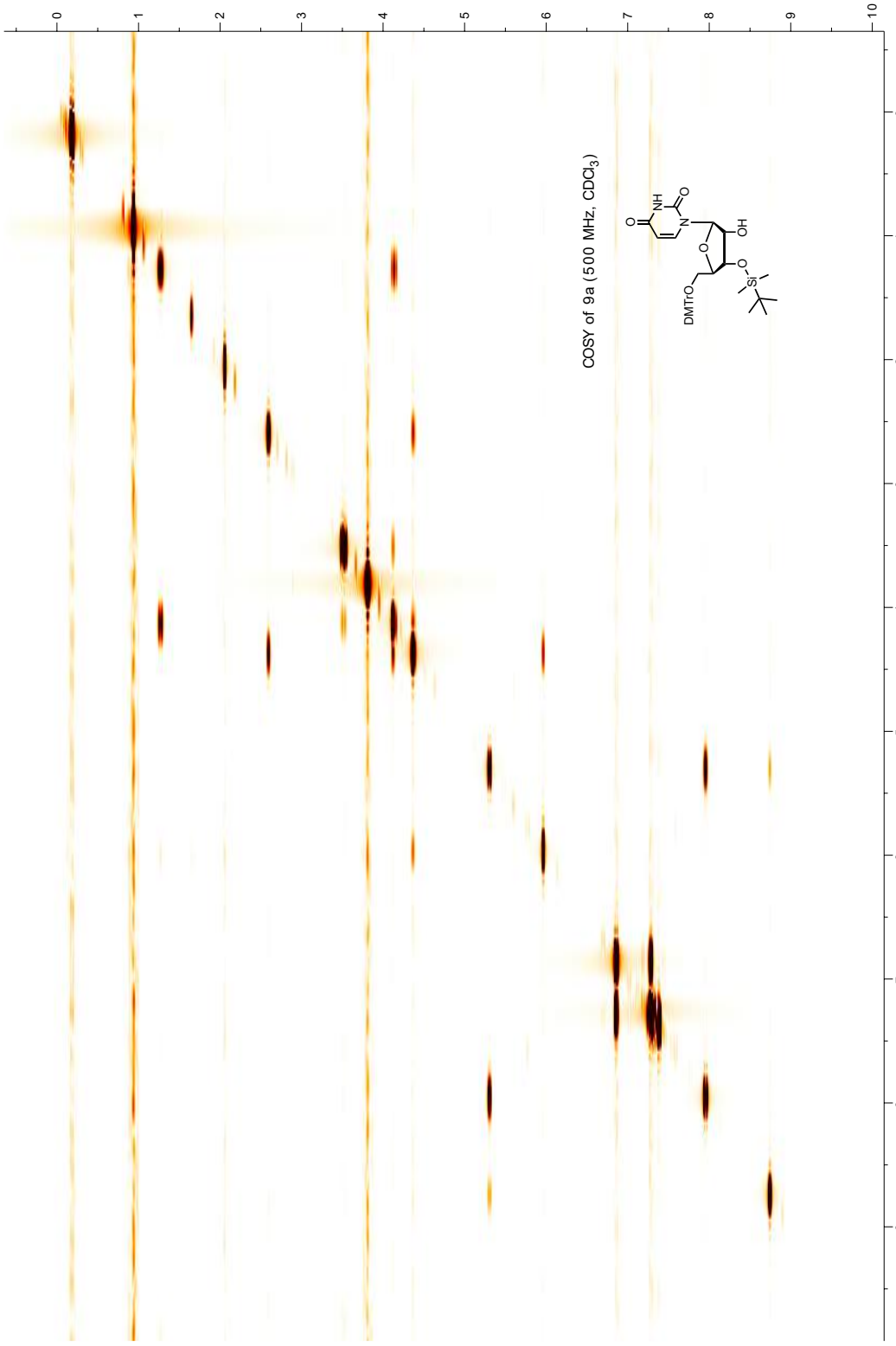


Figure S4-16: COSY spectrum of **9a**, synthesized in solution

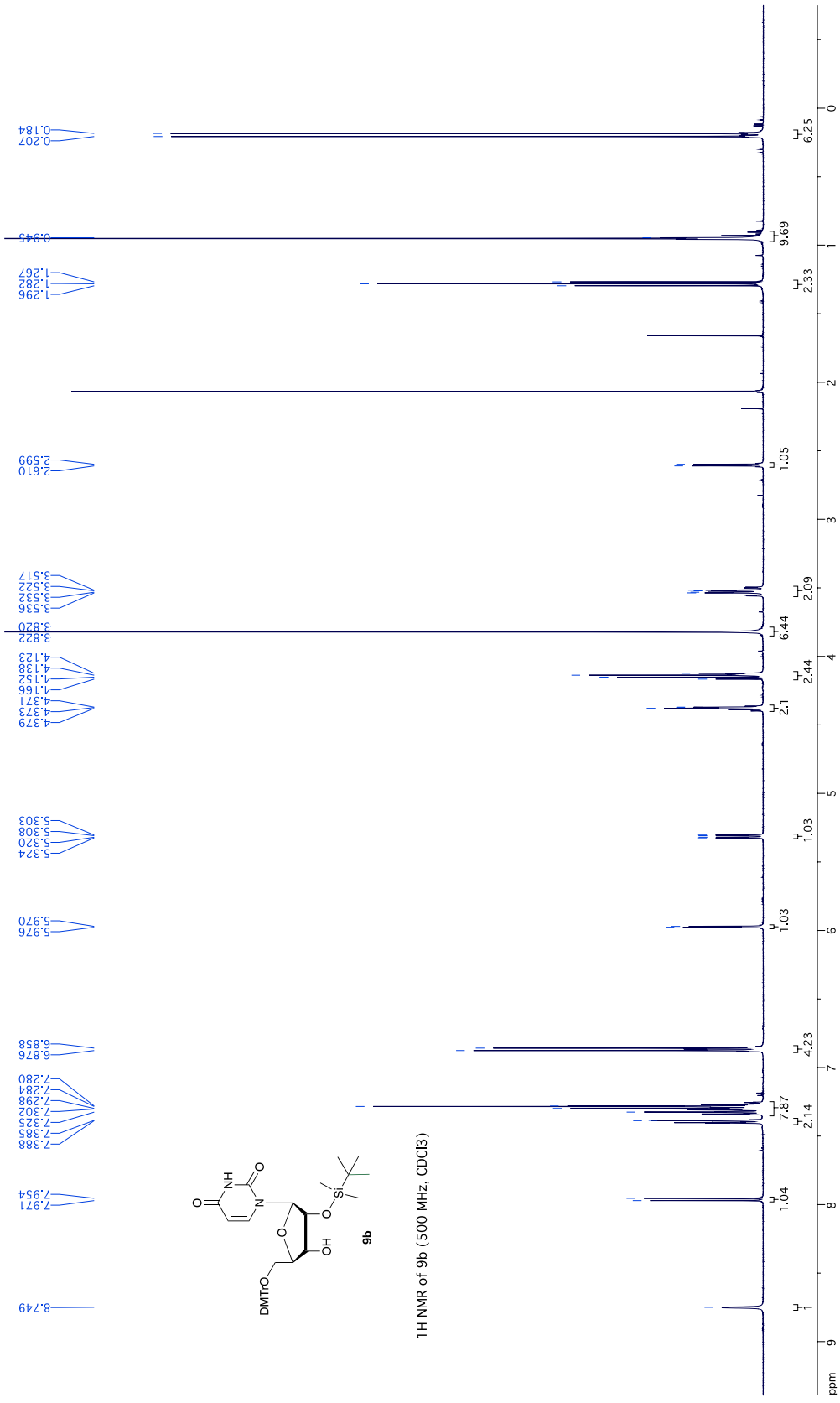


Figure S4-17: ^{1}H NMR spectrum of **9b**, synthesized in solution

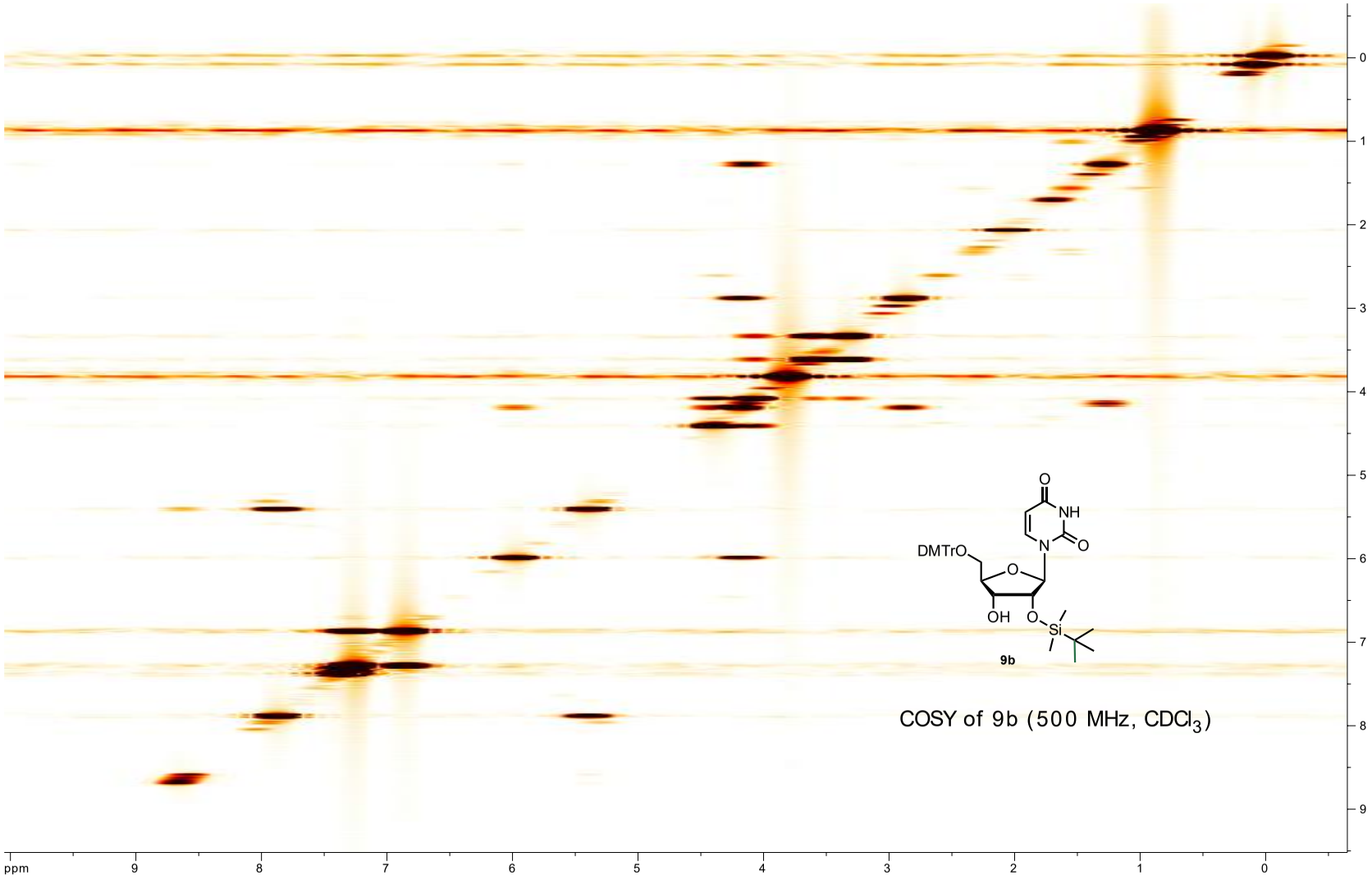
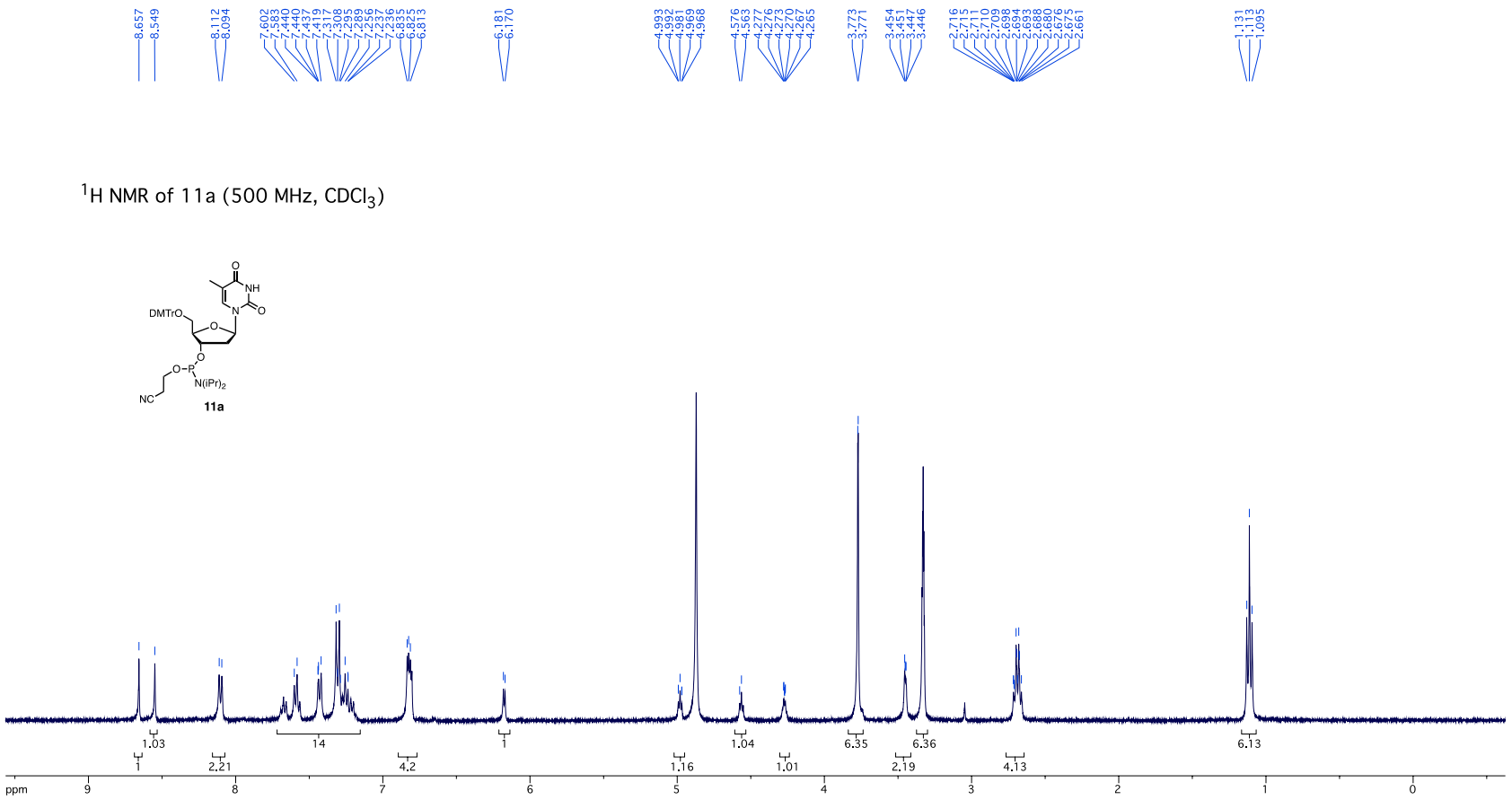
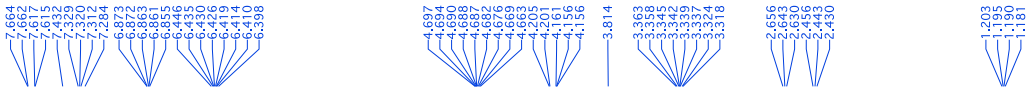


Figure S4-18: COSY spectrum of **9b**, synthesized in solution

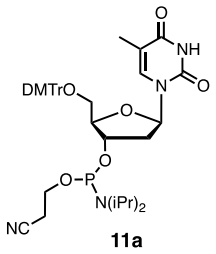


^{1}H NMR of 11a (500 MHz, $CDCl_3$)

Figure S4-19: ^{1}H NMR spectrum of **11a**, synthesized via RAM



^{1}H NMR of 11a (500 MHz, $CDCl_3$) solution phase control



11a

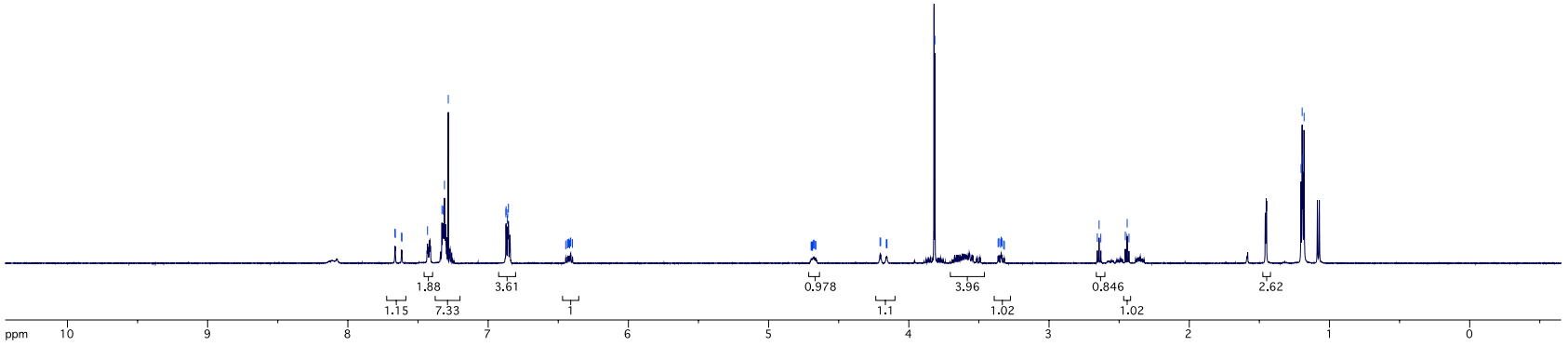
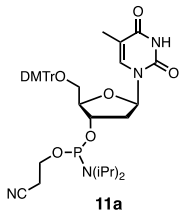


Figure S4-20: ^{1}H NMR spectrum of **11a**, synthesized in solution

148.941
148.513

^{31}P NMR of 11a (203 MHz, $CDCl_3$)



11a

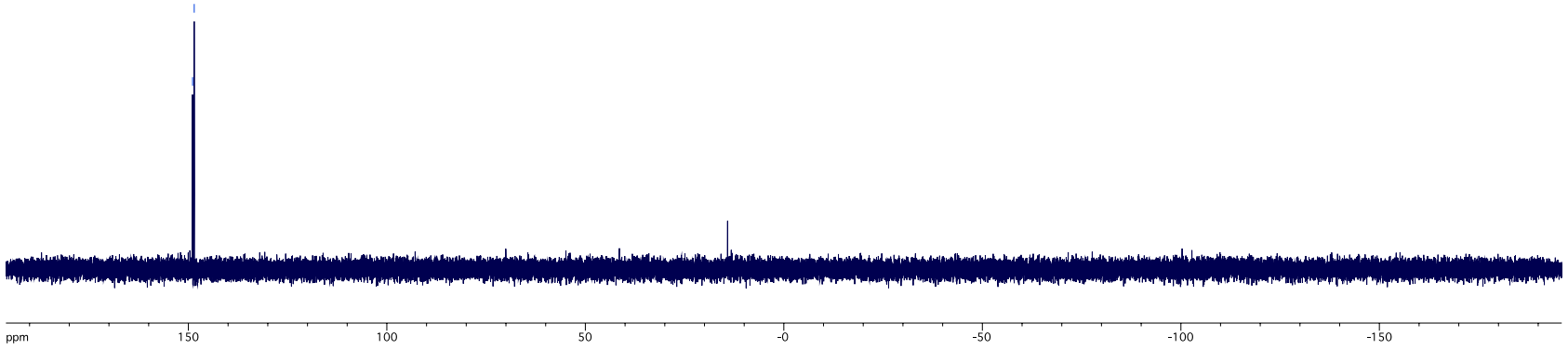
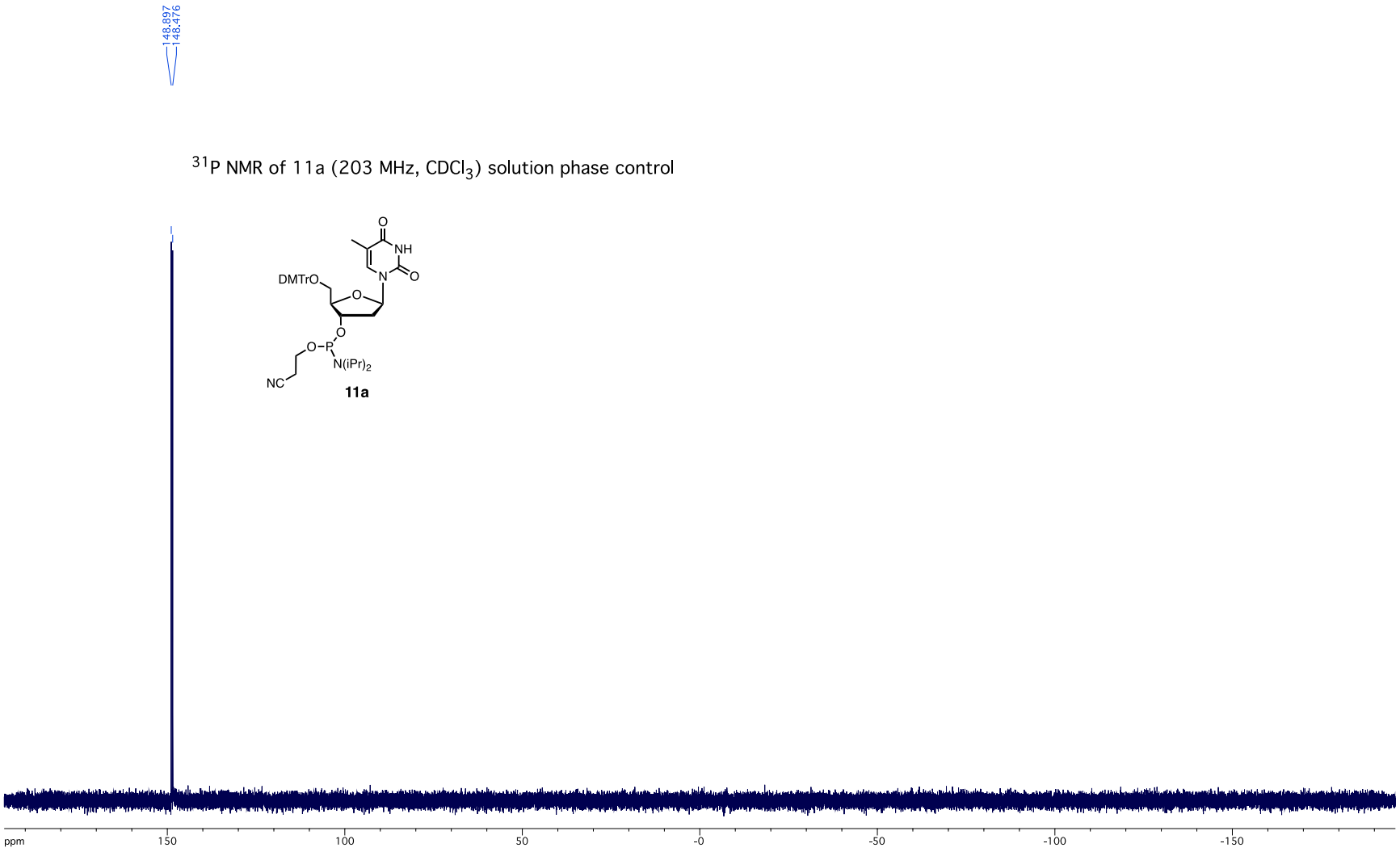


Figure S4-21: ^{31}P NMR spectrum of **11a**, synthesized via RAM



^{31}P NMR of 11a (203 MHz, $CDCl_3$) solution phase control

Figure S4-22: ^{31}P NMR spectrum of **11a**, synthesized in solution

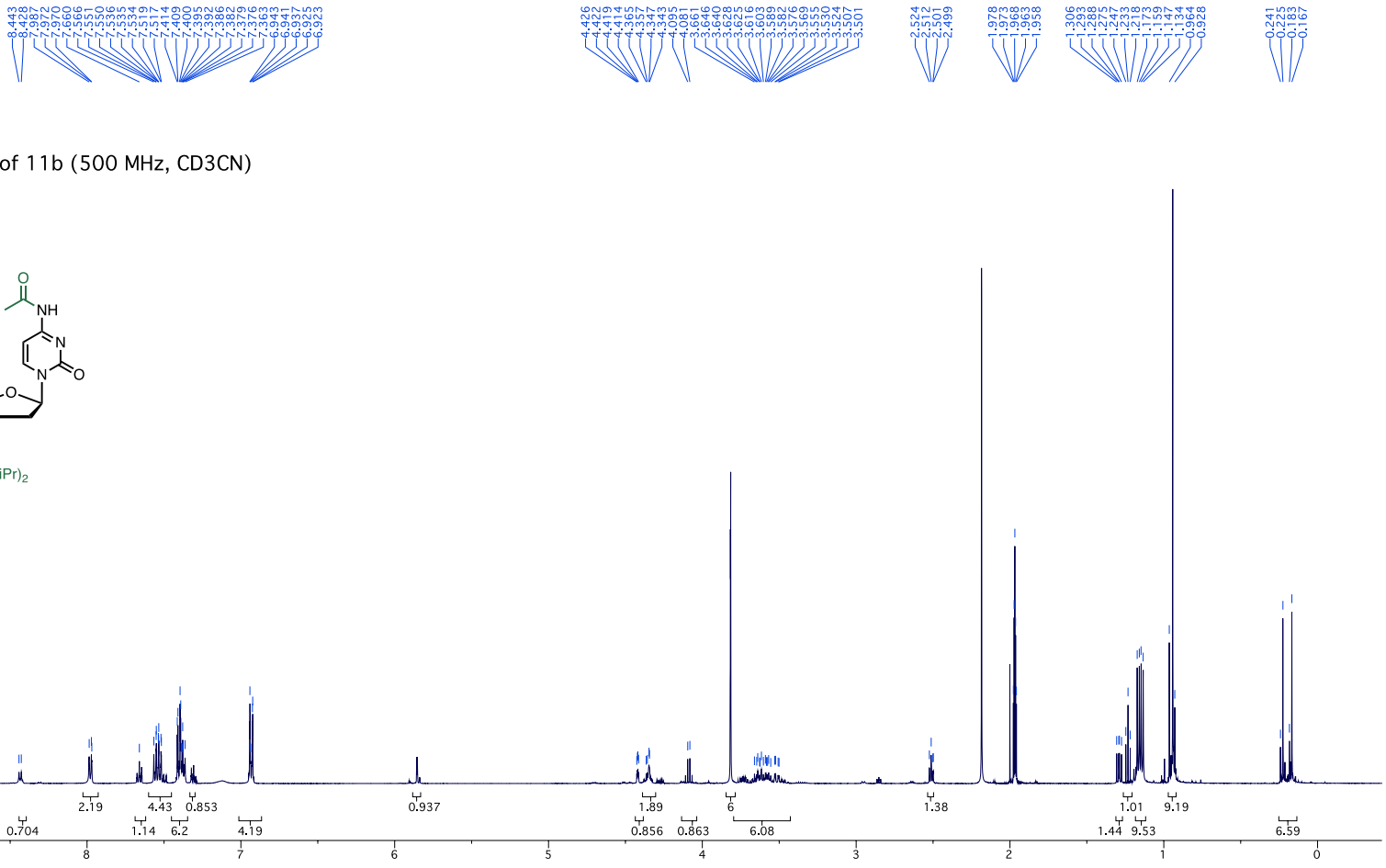


Figure S4-23: ^{1}H NMR spectrum of **11b**

^{31}P NMR of 11b (500 MHz, CD_3CN)

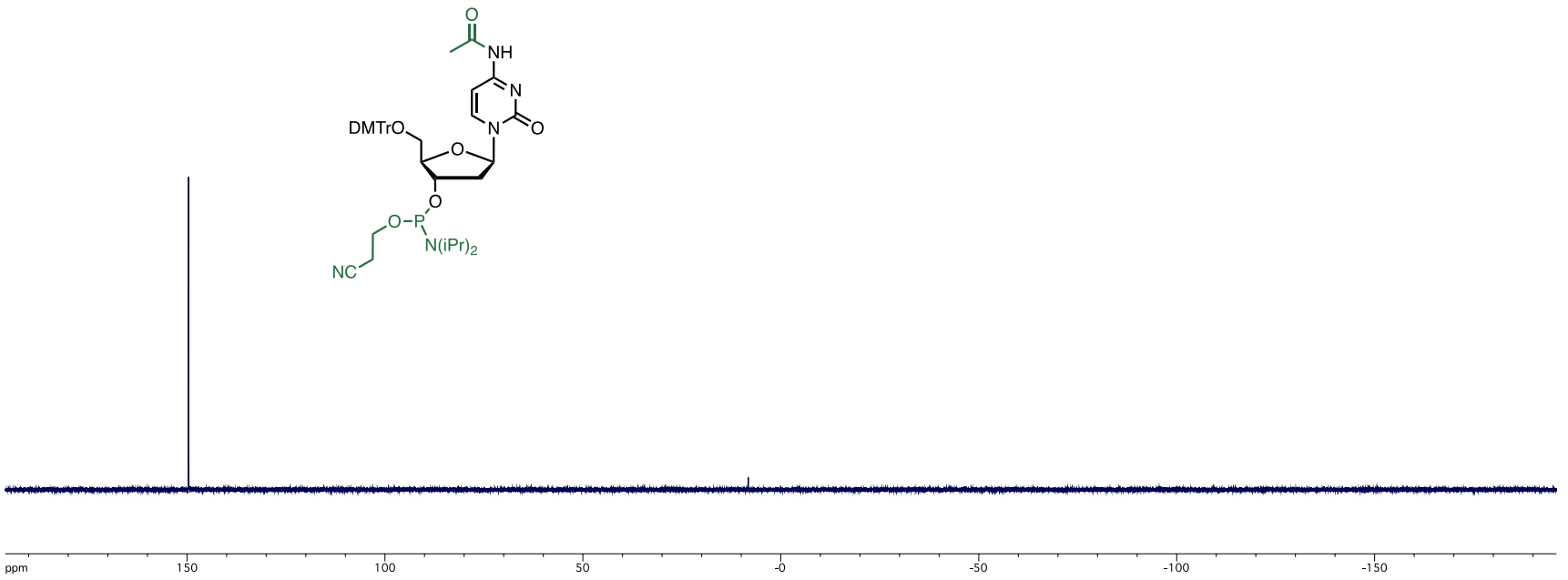
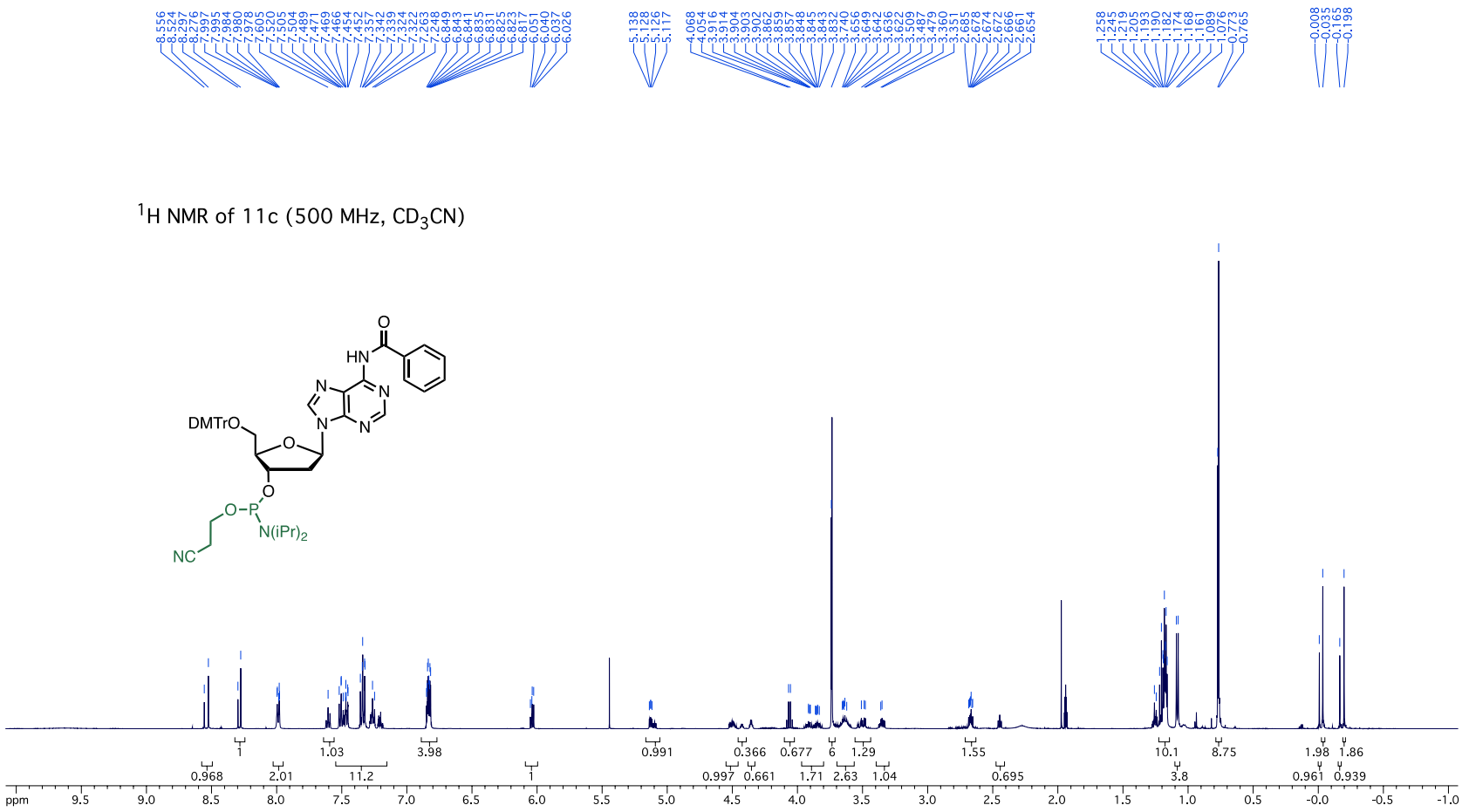


Figure S4-24: ^{31}P NMR spectrum of **11b**



^{1}H NMR of 11c (500 MHz, CD_3CN)

Figure S4-25: ^{1}H NMR spectrum of **11c**

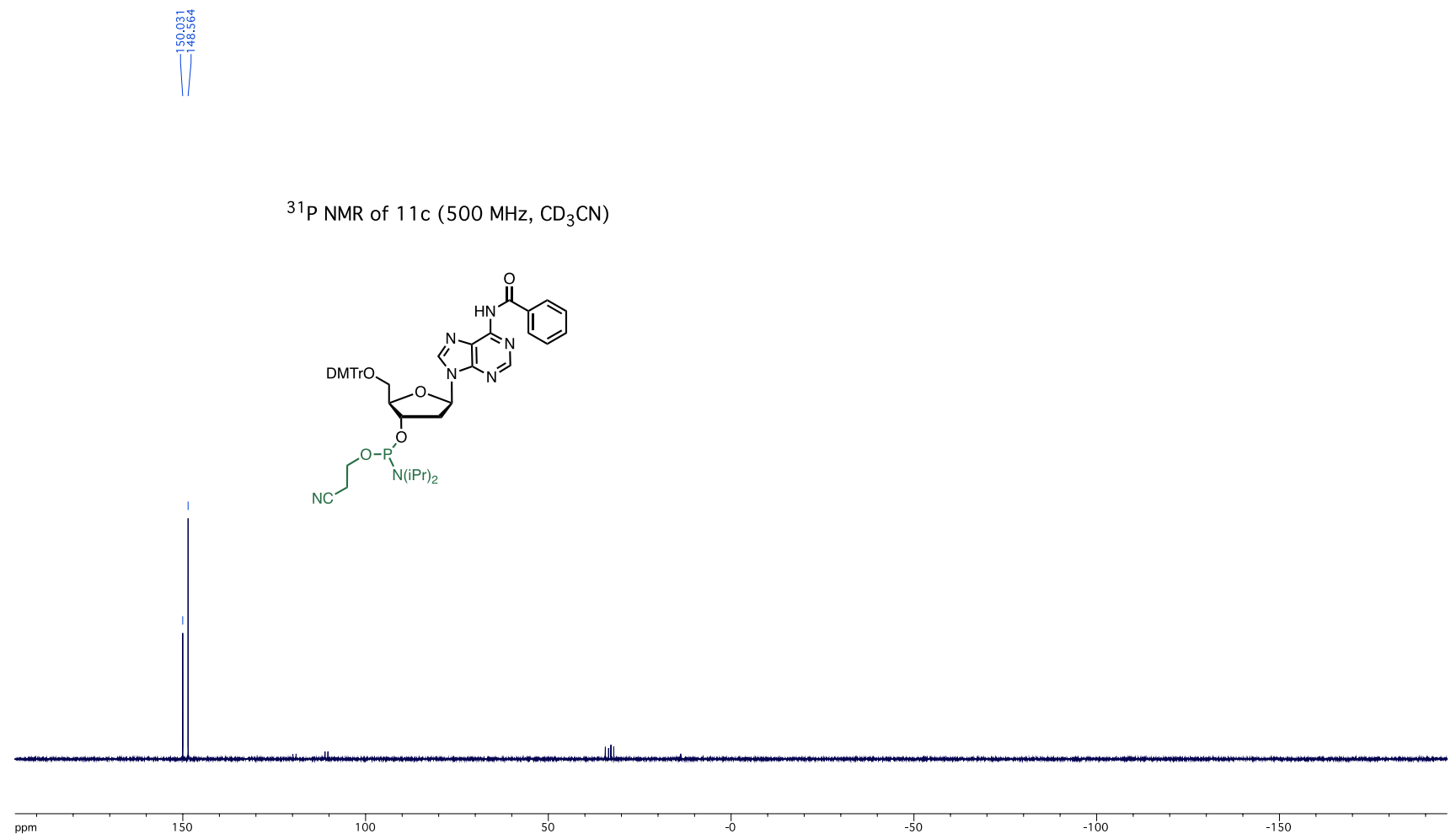
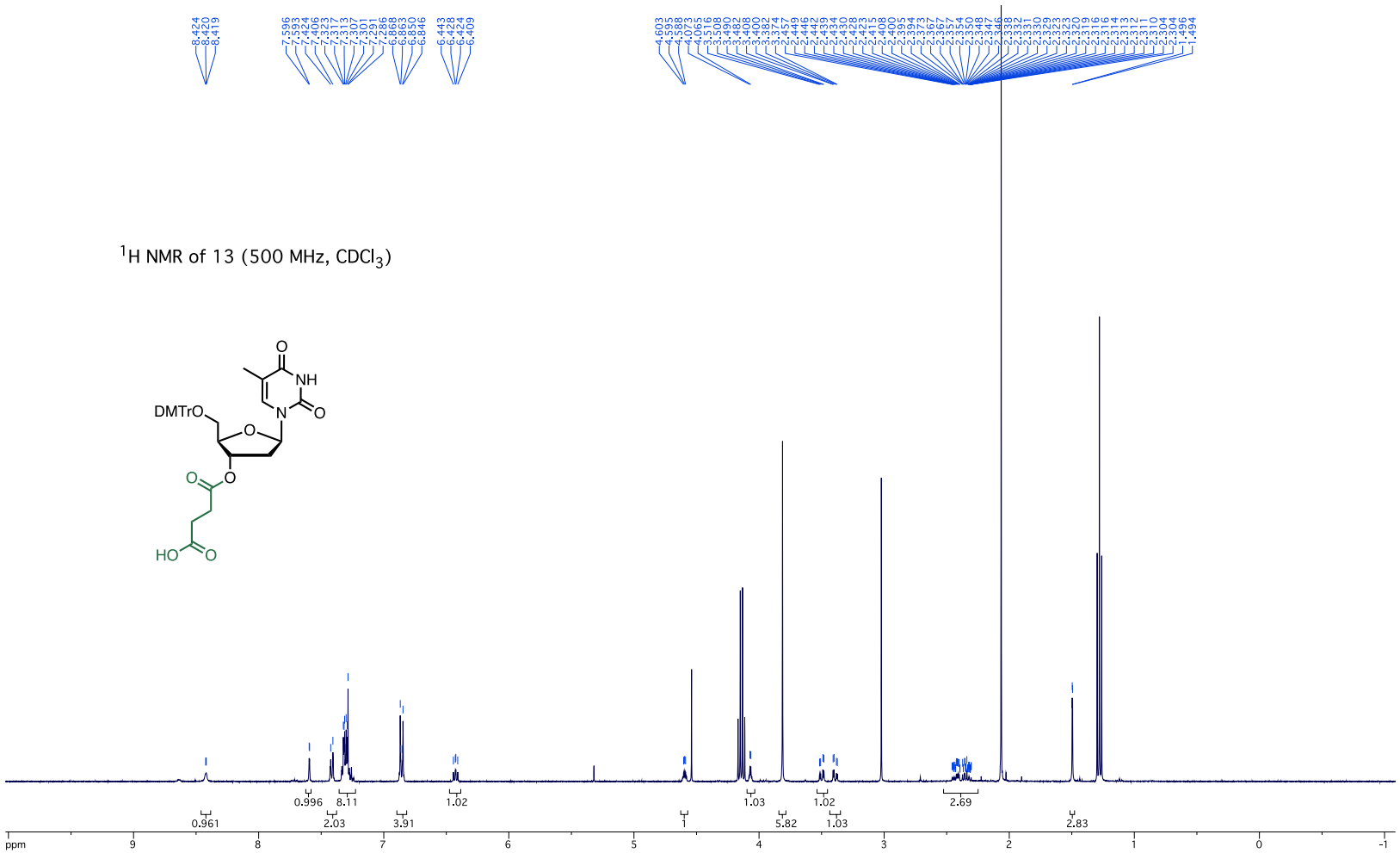


Figure S4-26: ^{31}P NMR spectrum of **11c**



^{1}H NMR of 13 (500 MHz, $CDCl_3$)

Figure S4-27: ^{1}H NMR spectrum of **13**

^{1}H NMR of 15 (500 MHz, $CDCl_3$)

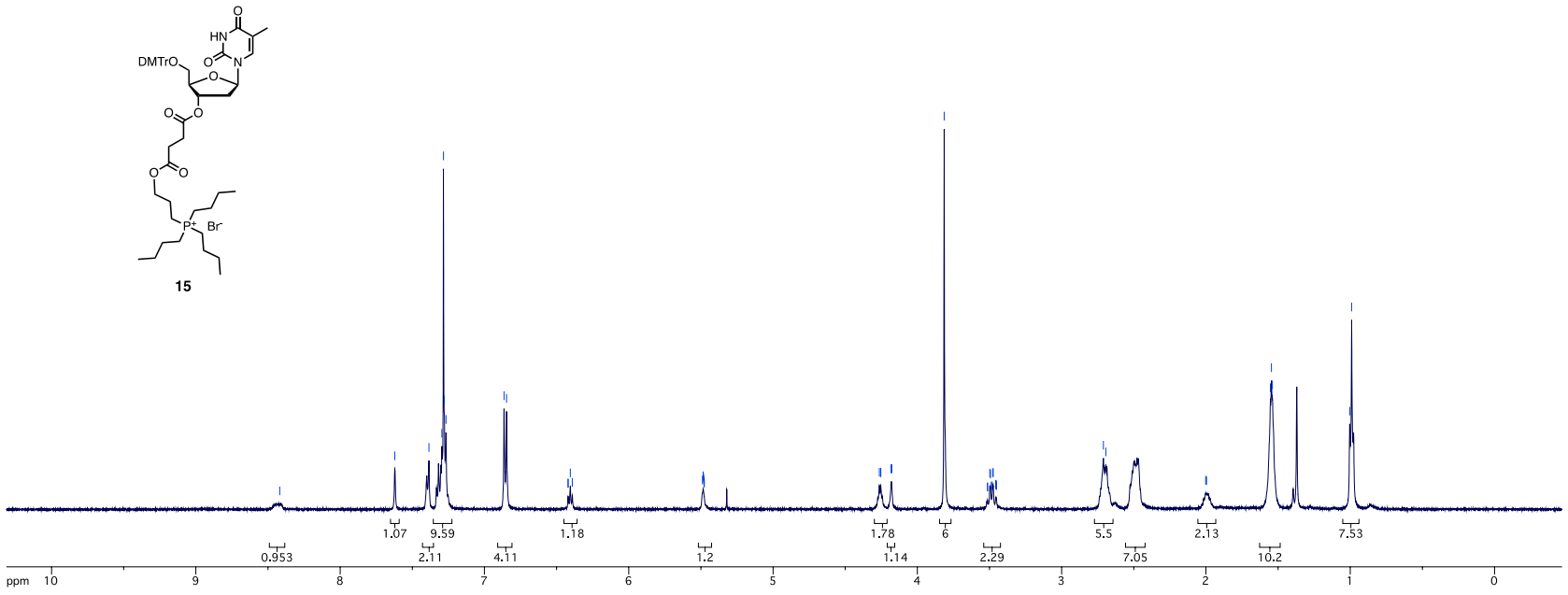
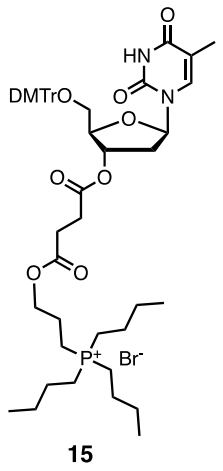


Figure S4-28: ^{1}H NMR spectrum of **15**

^{31}P NMR of 15 (203 MHz, $CDCl_3$)



15

Figure S4-29: ^{31}P NMR spectrum of **15**

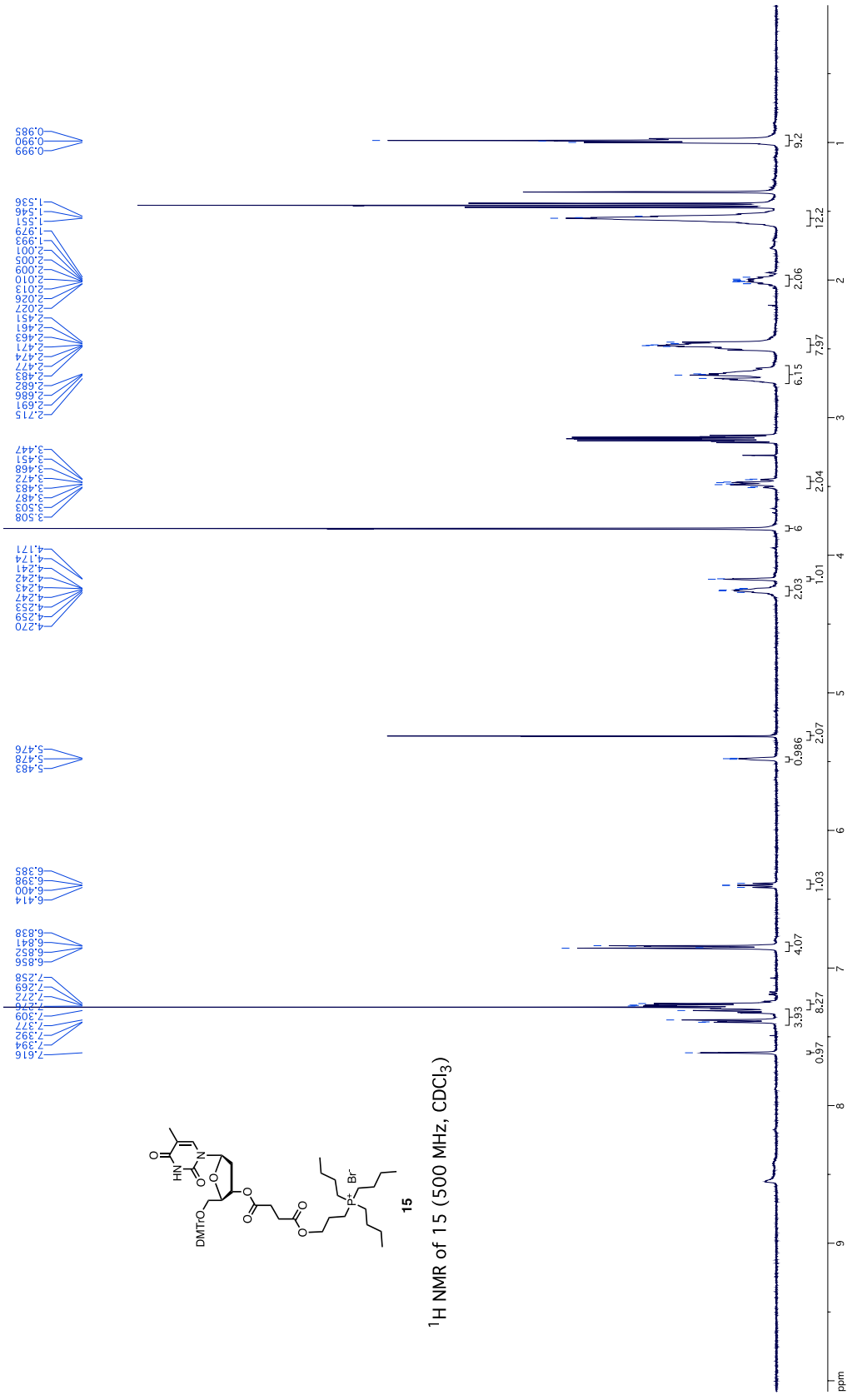
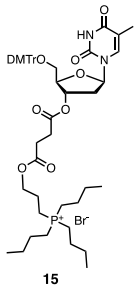


Figure S4-30: ^{1}H NMR spectrum of **15,** solution phase control

^{31}P NMR (203 MHz; $CDCl_3$)



15

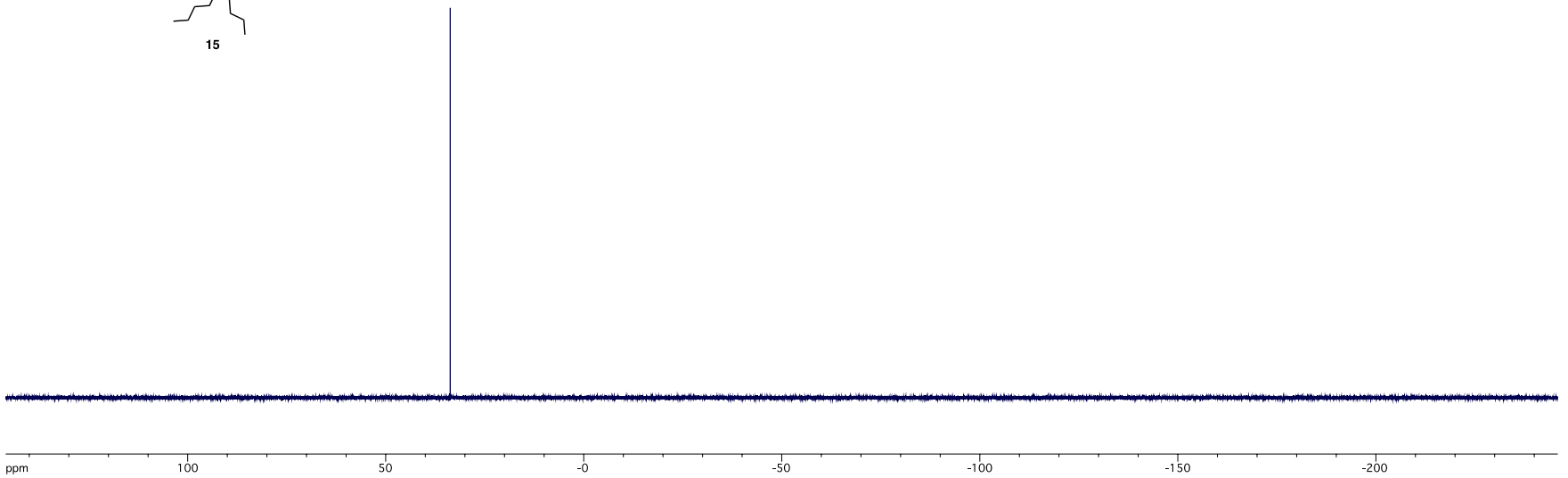


Figure S4-31: ^{31}P NMR spectrum of **15**, solution phase control