Continuous Flow Photocatalysis Enhanced Using an Aluminum Mirror: Rapid and Selective Synthesis of 2'-Deoxy and 2',3'-Dideoxynucleosides

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Experimental Section

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General Experimental

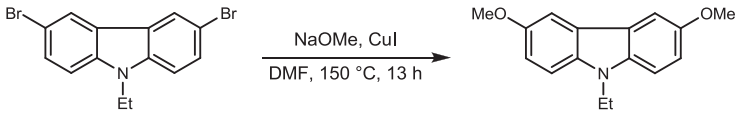
All batch reactions were performed in oven dried glassware. Microwave reactions were performed using Biotage® Initiator microwave synthesizer. Acetonitrile (anhydrous) and isopropanol and water (Aldrich) were used as received. Analytical thin-layer chromatography (TLC) was performed using EMD silica gel 60 F254 plates. Products were visualized by UV light (254 nm), and/or the use of *p*-anisaldehyde. Flash column chromatography was performed using Biotage® Isolera flash purification system on SNAP KP-SIL columns unless otherwise noted.

The quartz immersion well, 450 Watt medium-pressure mercury lamp, the Pyrex sleeve and the accompanying power supply were manufactured by Ace Glass, Inc. (Vineland, NJ). The quartz tubing coils were fabricated by James Glass, Inc. Hanover, MA. The peristaltic pump used to deliver solutions to the flow reactors was an Ismatec IPC ISM 930. The peristaltic pump was operated with Tygon®

MHLL two-stopper tubing. PFA tubing refers to perfluoro alkoxy alkane tubing. PFA and Tygon® MHLL tubing were purchased from IDEX Health & Science (Oak Harbor, WA).

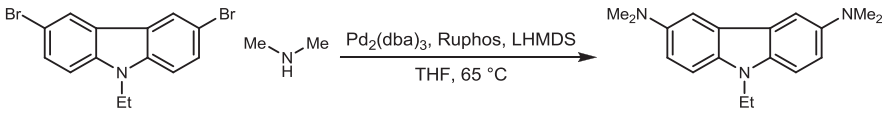
^{1}H NMR spectra were recorded on a Bruker Avance-600 spectrometer (600 MHz) or a Bruker Avance-400 spectrometer (400 MHz) in $CDCl_3$ or MeOD. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual $CHCl_3$ in $CDCl_3$ (7.26 ppm) or MeOH in MeOD (3.30 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad), coupling constant in hertz (Hz), and integration. ^{13}C NMR spectra were recorded on a Bruker Avance-400 spectrometer (100 MHz) in $CDCl_3$ or MeOD. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.1 ppm) or MeOD (49.15 ppm) on the δ scale. ^{13}C signals with identical chemical shifts for more than one carbon are specified. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 2000 FT-IR. High resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXIV 4.7 Tesla Fourier Transform Ion Cyclotron Resonance Mass Spectrometer at Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility.

Preparation of carbazole photosensitizers



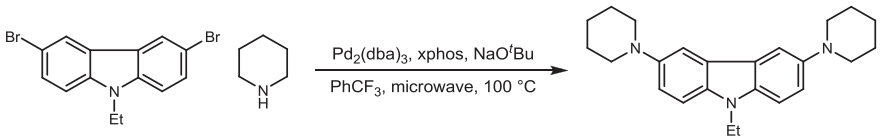
9-Ethyl-3,6-dimethoxy-9*H*-carbazole (2c)

CuI (800 mg, 4.20 mmol) was added to the solution of the carbazole (353 mg, 1.00 mmol) in DMF (5.0 mL), followed by NaOMe in MeOH (25 wt%, 4.57 mL, 20.0 mmol) in a sealed tube. The mixture was heated under microwave at 150 °C for 16 h. The resulting crude mixture was diluted by EtOAc, washed with saturated NH_4Cl and brine. The organic layer was dried, filtered and concentrated. The residue was purified by chromatography on silica gel (5-20% EtOAc/hexanes) to afford the dimethoxycarbazole as a white solid (236 mg, 92% yield). R_f= 0.35 (20% EtOAc/hexanes); mp 100-102 °C IR (neat) 2958, 1603, 1480, 1297 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 2.4 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 7.13 (dd, J = 8.8, 2.5 Hz, 2H), 4.30 (q, J = 7.2 Hz, 2H), 3.96 (s, 6H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 153.2, 135.6, 122.9, 115.0, 109.3, 103.2, 56.2, 37.7, 14.0; HRMS (EI): Exact mass calcd. for $C_{16}H_{18}NO_2$ $[M+H]^+$ 256.1332, found 256.1322. UV-Vis: λ_{max} (above 280 nm) = 313.0 nm



9-Ethyl-N^3,N^3,N^6,N^6-tetramethyl-9*H*-carbazole-3,6-diamine (2d)

Following Buchwald's protocol,[1] the dibromide (100 mg, 283 µmol) provided the amination product (72.0 mg, 90% yield) as a white solid, which turned brown and amorphous upon standing. R_f = 0.07 (40% EtOAc/hexanes); IR (neat) 2973, 2788, 1498, 1232 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (br s, 2H), 7.27 (d, *J* = 8.8 Hz, 2H), 7.14 (dd, *J* = 8.8, 2.4 Hz, 2H), 4.30 (br s, 2H), 3.05 (br s, 12H), 1.40 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm, 144.9, 134.8, 123.3, 115.5, 108.8, 105.4, 43.1, 37.6, 14.0; HRMS (EI): Exact mass calcd. for $C_{18}H_{24}N_3$ $[M+H]^+$ 282.1965, found 282.1953.



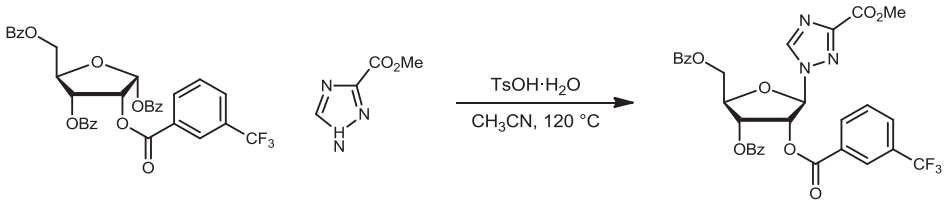
9-Ethyl-3,6-di(piperidin-1-yl)-9*H*-carbazole (2e)

Following Buchwald's protocol,[1] except that the reaction was performed in $PhCF_3$ under microwave heating, the dibromide (200 mg, 567 µmol) provided the amination product (127 mg, 62% yield) as a white solid, which quickly turned brown and amorphous upon standing. R_f = 0.34 (20% EtOAc/hexanes); IR (neat) 2932, 2789, 1483, 1210 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 2.0 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.20 (dd, *J* = 8.8, 2.0 Hz, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.16 (dd, *J* = 5.4, 5.4 Hz, 8H), 1.85-1.78 (m, 8H), 1.63-1.56 (m, 4H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 146.0, 135.8, 123.1, 118.9, 108.7, 108.7, 53.7, 37.5, 26.4, 24.3, 14.0; HRMS (EI): Exact mass calcd. for $C_{24}H_{32}N_3$ $[M+H]^+$ 362.2591, found 362.2586.

Preparation of substrates

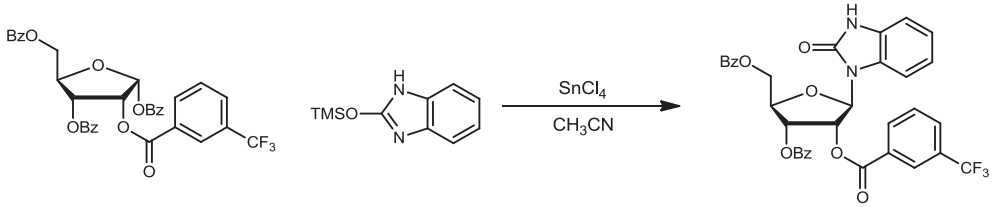
Compounds **1a-1d**, **1f** and **1g** were prepared using Rizzo's protocol.[2] Compounds **1a-1d** are known.

1 M. D. Charles, P. Schultz and S. L. Buchwald, *Org. Lett.*, 2005, **7**, 3965-3968.
2 Z. W. Wang, D. R. Prudhomme, J. R. Buck, M. Park and C. J. Rizzo, *J. Org. Chem.*, 2000, **65**, 5969-5985.



Methyl 1-((2*R*,3*R*,4*R*,5*R*)-4-(benzoyloxy)-5-((benzoyloxy)methyl)-3-((3-(trifluoromethyl)benzoyl)oxy)tetrahydrofuran-2-yl)-1H-1,2,4-triazole-3-carboxylate (1e)

Following Lee's protocol[3] with modification, $TsOH{\cdot}H_2O$ (6.0 mg, 31.5 µmol) was added to the suspension of the protected sugar (200 mg, 315 µmol) and the triazole (48.3 mg, 378 µmol) in CH_3CN (1.6 mL). The mixture was heated at 120 °C for 15 h under microwave. The resulting crude was concentrated. The residue was purified by flash column chromatography on silica gel (30-55% EtOAc in hexanes) to give the nucleoside as a viscous oil (foam, 146 mg, 72% yield). The regioselectivity was assigned by analogy to literature.[3] R_f = 0.18 (50% EtOAc/hexanes); $[\alpha]_D^{25}$ -40.8 (*c* 1.00, $CHCl_3$); IR (neat) 2958, 1730, 1266 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.19 (s, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 8.08-8.06 (m, 2H), 7.97-7.94 (m, 2H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.60-7.55 (m, 3H), 7.46-7.43 (m, 2H), 7.42-7.38 (m, 2H), 6.35 (d, *J* = 3.4 Hz, 1H), 6.21 (dd, *J* = 5.4, 3.4 Hz, 1H), 6.10 (dd, *J* = 5.6, 5.6 Hz, 1H), 4.91-4.88 (m, 1H), 4.81 (dd, *J* = 12.3, 3.4 Hz, 1H), 4.67 (dd, *J* = 12.3, 4.5 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.2, 165.1, 163.9, 159.7, 155.9, 144.8, 134.0, 133.5, 133.1, 131.4 (q, $^2J_{CF}$ = 33.2 Hz), 130.4 (q, $^3J_{CF}$ = 3.6 Hz), 129.8, 129.7, 129.5, 129.3, 129.2, 128.7, 128.6, 128.4, 126.6 (q, $^3J_{CF}$ = 3.8 Hz), 123.4 (q, $^1J_{CF}$ = 272.6 Hz), 90.2, 81.3, 75.7, 71.4, 63.5, 52.8; HRMS (ESI): Exact mass calcd. for $C_{31}H_{24}F_3N_3NaO_9$ $[M+Na]^+$ 662.1362, found 662.1364.

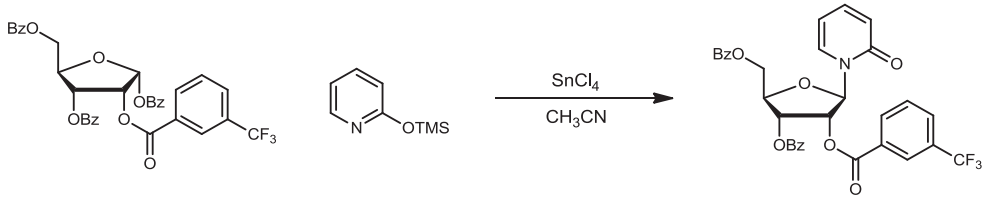


(2*R*,3*R*,4*R*,5*R*)-4-(Benzoyloxy)-5-((benzoyloxy)methyl)-2-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)tetrahydrofuran-3-yl 3-(trifluoromethyl)benzoate (1f)

Following Rizzo's protocol,[2] the protected ribose (200 mg, 315 µmol) and 2 equivalents of the silylated base (formed in situ by silylation of 2-hydroxybenzimidazole using *N*,*O*-bis-trimethylsilylacetamide at

3 a) T.-A. Lee, N.-J. Park, J.-H. Khoo, B.-C. Lee, PCT Int. Appl. WO2003048157. b) Witkowsk.Jt, L. N. Simon, R. W. Sidwell and R. K. Robins, *J. Med. Chem.*, 1972, **15**, 1150-1154.

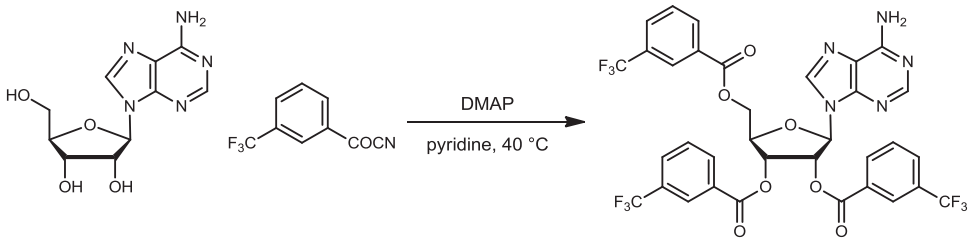
75 °C for 30 min in CH_3CN) provided the nucleoside (chromatography with 30-40% EtOAc in hexanes) as viscous oil (foam, 143 mg, 70% yield). R_f= 0.30 (50% EtOAc/hexanes); $[\alpha]_D^{25}$ -66.2 (*c* 0.35, $CHCl_3$); IR (neat) 3068, 1718, 1266 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.18-8.10 (m, 4H), 8.00-7.97 (m, 2H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.60-7.55 (m, 2H), 7.50-7.37 (m, 5H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.07-7.01 (m, 2H), 6.79-6.75 (m, 1H), 6.39-6.33 (m, 2H), 6.13 (dd, *J* = 5.5, 5.2 Hz, 1H), 4.91-4.86 (m, 1H), 4.76-4.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.3, 165.4, 164.0, 154.9, 133.8, 133.4, 133.1, 131.2 (q, $^2J_{CF}$ = 33.1 Hz), 130.1 (q, $^3J_{CF}$ = 3.5 Hz), 129.8, 129.8, 129.7, 129.5, 129.3, 128.7, 128.6, 128.6, 128.2, 128.0, 126.6 (q, $^3J_{CF}$ = 3.8 Hz), 123.4 (q, $^1J_{CF}$ = 272.6 Hz), 122.7, 121.7, 110.3, 109.5, 85.2, 79.6, 72.0, 70.8, 63.8; HRMS (ESI): Exact mass calcd. for $C_{34}H_{26}F_3N_2O_8$ $[M+H]^+$ 647.1636, found 647.1621.



(2*R*,3*R*,4*R*,5*R*)-4-(Benzoyloxy)-5-((benzoyloxy)methyl)-2-(2-oxopyridin-1(2H)-yl)tetrahydrofuran-3-yl 3-(trifluoromethyl)benzoate (1g)

Following Rizzo's protocol,[2] the protected ribose (250 mg, 394 μmol) and 1.4 equivalents of the silylated base provided the nucleoside (chromatography with 30-40% EtOAc in hexanes) as a white solid (225 mg, 94% yield). R_f= 0.28 (50% EtOAc/hexanes); mp 90-92 °C; $[\alpha]_D^{25}$ 57.2 (*c* 1.00, CH_2Cl_2); IR (neat) 3065, 1729, 1670, 1265 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.15 (d, *J* = 7.9 Hz, 1H), 8.11-8.08 (m, 1H), 7.93 (d, *J* = 8.2 Hz, 2H), 7.79 (d, *J* = 7.8 Hz, 2H), 7.62-7.50 (m, 4H), 7.46 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.37 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.34-7.29 (m, 1H), 6.58 (d, *J* = 4.0 Hz, 1H), 6.53 (dd, *J* = 9.2, 0.4 Hz, 1H), 6.10 (dd, *J* = 6.8, 6.8 Hz, 1H), 5.92 (dd, *J* = 5.8, 5.8 Hz, 1H), 5.90-5.87 (m, 1H), 4.88 (dd, *J* = 12.3, 2.8 Hz, 1H), 4.82-4.79 (m, 1H), 4.70 (dd, *J* = 12.3, 3.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.1, 165.3, 164.0, 162.2, 140.0, 133.8, 133.6, 133.2, 132.5, 131.2 (q, $^2J_{CF}$ = 33.1 Hz), 130.1 (q, $^3J_{CF}$ = 3.6 Hz), 129.8, 129.7, 129.4, 129.3, 128.7, 128.6, 128.5, 126.7 (q, $^3J_{CF}$ = 3.8 Hz), 123.5 (q, $^1J_{CF}$ = 272.6 Hz), 121.4, 106.5, 88.8, 80.2, 75.4, 70.8, 63.6; HRMS (ESI): Exact mass calcd. for $C_{32}H_{25}F_3NO_8$ $[M+H]^+$ 608.1527, found 608.1521.

Compounds **4a**, **4b** and **4d** are known,[2] and were prepared by esterification of the correspoding nucleosides using *m*-trifluoromethylbenzoyl chloride.



(2*R*,3*R*,4*R*,5*R*)-2-(6-Amino-9H-purin-9-yl)-5-(((3-(trifluoromethyl)benzoyl)oxy)methyl)tetrahydrofuran-3,4-diyl bis(3-(trifluoromethyl)benzoate) (4c)

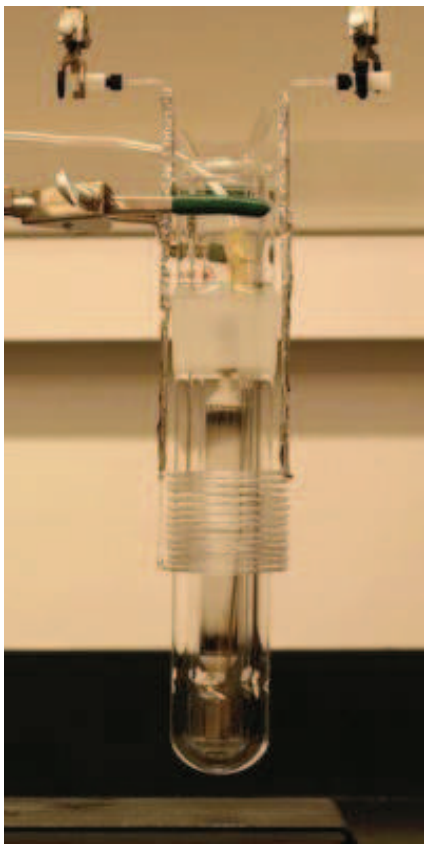
The acylation of adenosine using acyl chloride generated a complex mixture, including the undesired *N*-acylation product. Selective *O*-acylation of adenosine was performed using acyl cyanide following Sanghvi's protocol (not optimized for the best yield).[4] *m*-Trifluoromethylbenzoyl cyanide was prepared using Normant's protocol.[5] This acyl cyanide was not stable to silica gel, and was directly used without purification. DMAP (22.0 mg, 180 μmol) was added to the suspension of adenosine (160 mg, 599 μmol) in pyridine (3 mL), followed by the acyl cyanide (715 mg, 3.59 mmol). The mixture was heated at 40 °C for 24 h. The resulting crude was diluted with EtOAc and washed with saturated NH_4Cl. The organic layer was dried, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (60-90% EtOAc in hexanes) to give the triester as a viscous oil (foam, 319 mg, 68% yield). R_f = 0.32 (100% EtOAc); $[\alpha]_D^{25}$ -58.6 (*c* 1.00, CH_2Cl_2); IR (neat) 3169, 1734, 1653, 1336, 1250 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.25-8.22 (m, 2H), 8.18-8.13 (m, 4H), 7.95 (s, 1H), 7.82-7.79 (m, 3H), 7.57-7.52 (m, 3H), 6.54-6.51 (m, 1H), 6.42 (dd, *J* = 5.7, 5.7 Hz, 1H), 6.39 (d, *J* = 4.2 Hz, 1H), 6.08 (s, 2H), 4.93 (dd, *J* = 12.0, 3.4 Hz, 1H), 4.87 (dd, *J* = 9.0, 4.7 Hz, 1H), 4.78 (dd, *J* = 12.0, 4.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 164.9, 164.0, 164.0, 156.1, 153.3, 149.5, 139.4, 132.9 (3C), 131.3 (q, $^2J_{CF}$ = 33.2 Hz, 2C), 131.0 (q, $^2J_{CF}$ = 33.0 Hz), 130.4 (q, $^3J_{CF}$ = 4.5 Hz, 2C), 130.2, 129.8 (q, $^3J_{CF}$ = 3.3 Hz), 129.4, 129.2, 129.2, 126.6 (q, $^3J_{CF}$ = 3.8 Hz), 126.4 (q, $^3J_{CF}$ = 3.9 Hz, 2C), 124.7, 123.5

4 A. K. Prasad, V. Kumar, J. Maity, Z. W. Wang, V. T. Ravikumar, Y. S. Sanghvi and V. S. Parmar, *Synth. Commun.*, 2005, **35**, 935-945.
5 a) J. F. Normant and Piechuck.C, *Bull. Soc. Chim. Fr.*, 1972, 2402-&. b) C. Duplais, F. Bures, I. Sapountzis, T. J. Korn, G. Cahiez and P. Knochel, *Angew. Chem. Int. Ed.*, 2004, **43**, 2968-2970.

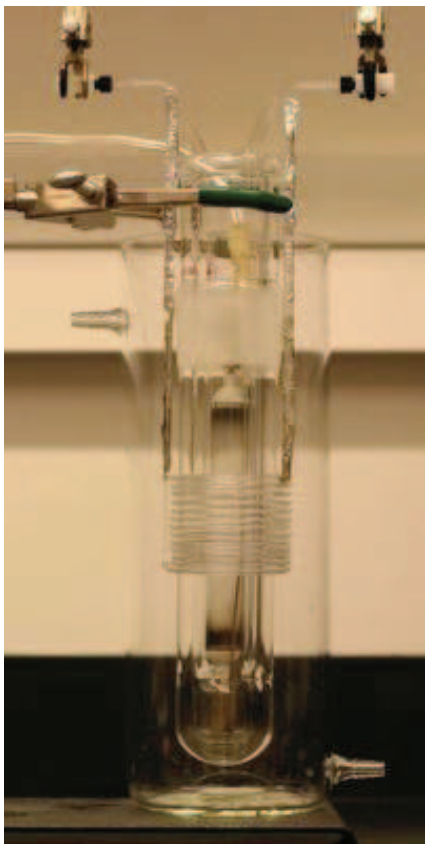
(q, $^1J_{CF}$ = 272.6 Hz), 123.3 (q, $^1J_{CF}$ = 272.6 Hz, 2C), 122.0, 120.2, 87.5, 80.1, 74.4, 71.8, 64.0; HRMS (ESI): Exact mass calcd. for $C_{34}H_{23}F_9N_5O_7$ $[M+H]^+$ 784.1448, found 784.1439.

General procedure for the synthesis of deoxynucleosides in flow

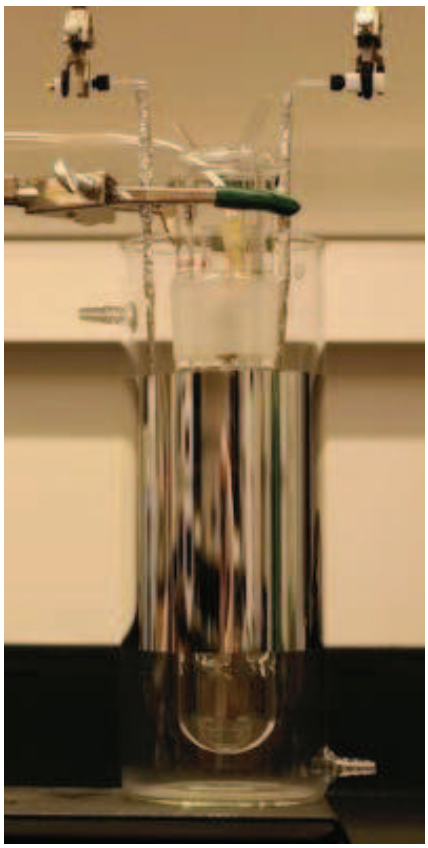
Photoreactor A 450 W medium pressure Hg lamp with a Pyrex sleeve (280 nm cutoff) was positioned in the center of a quartz jacketed immersion well with tap water running through to prevent overheating. Customized quartz tubing coils (1 mm inner diameter, 1.84 mL volume) were placed around the immersion well (approximately 2 cm from the surface of the lamp). Both arms of the quartz tubing coils were wrapped with aluminum foil, so that the photochemical reaction only occurred in the coils. The quartz tubing was extended with PFA tubing, with the entry connected to a peristaltic pump, and the exit connected to a 20 psi back pressure regulator and then a collection vial. The apparatus described above was placed in a Pyrex cylinder (115 mm outer diameter) coated with aluminum through which water was circulated with the aid of a water pump immersed in a temperature controlled bath. Coating of aluminum on the outside of the cylinder was performed by Evaporated Coatings, Inc.



a) photoreactor (quartz tubing coils) around the UV lamp



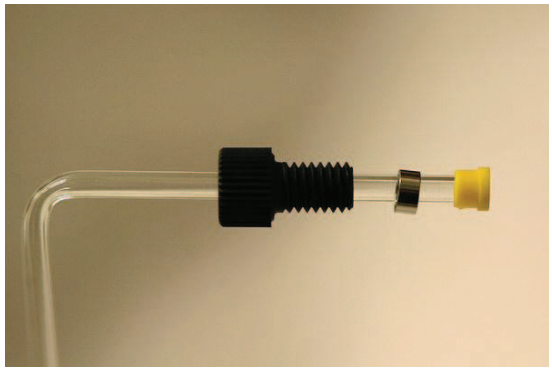
b) photoreactor in the cylinder to hold water for temperature control



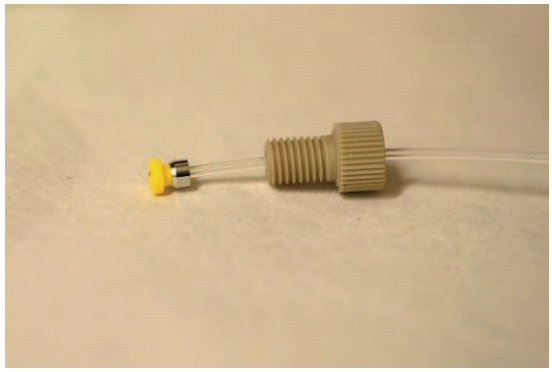
c) photoreactor in the cylinder coated with aluminum

Connection of quartz tubing and PFA tubing

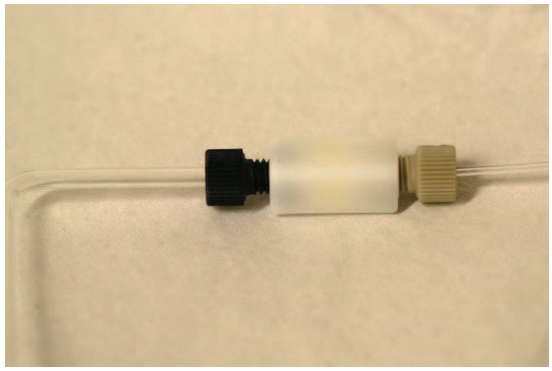
quartz tubing (0.04” i.d.; 1/8” o.d.)
male nut (1/4-28, 1/8” o.d., Upchurch Scientific P-308)
ferrule (1/8” o.d., TEFZEL, Upchurch Scientific P-359x)



PFA Tubing (0.02” i.d.; 1/16” o.d.)
male nut (1/4-28, 1/16” o.d., Upchurch Scientific P-235)
ferrule (1/16” o.d., TEFZEL, Upchurch Scientific P-259x)



standard union (1/4-28, Upchurch Scientific P-603)

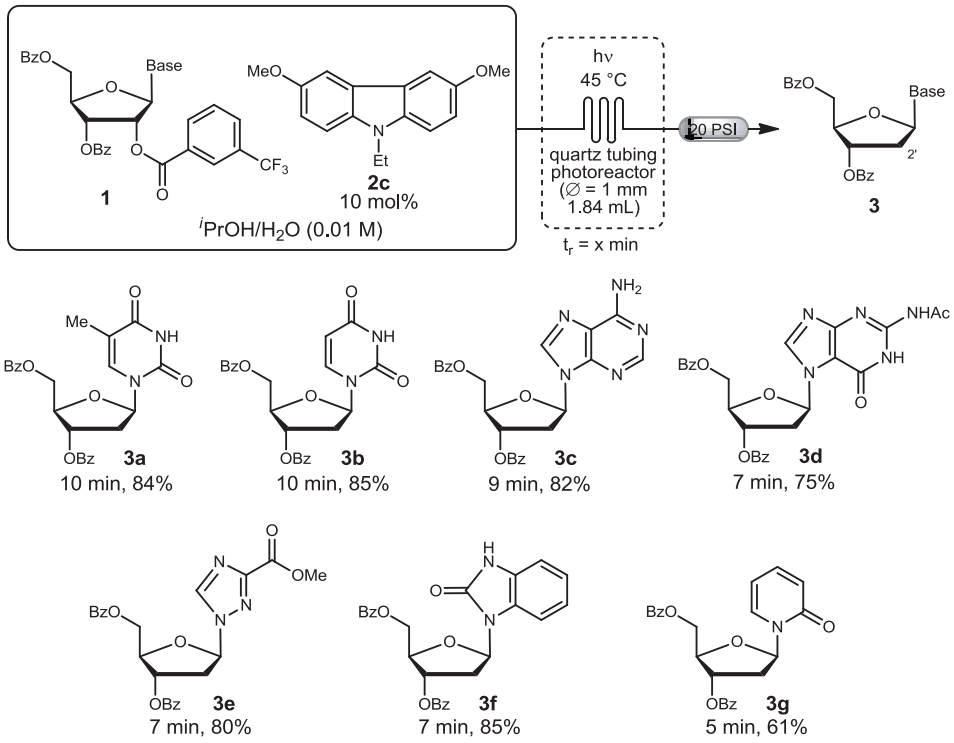


Photoreactor equilibration

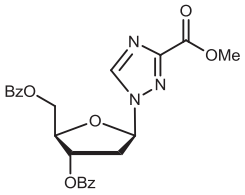
Prior to starting each photochemical reaction, the lamp and cooling water were kept on for 20 min in order to reach the lamp’s maximum operating output. During this time the blank ^{i}PrOH/H_2O (9:1) solvent was pumped through the reactor. Circulating water was flowing through the cylinder outside of the quartz tubing coils. A digital thermometer with a flexible probe was placed next to the tubing coils. The bath temperature of the circulating water was set between 50 and 55 °C. The digital thermometer next to the tubing coils read 45±2 °C. After this equilibration period, the flow of the reaction solution was initiated.

Photo-induced deoxygenation reaction for the synthesis of 2'-deoxynucleosides

The nucleoside substrate and carbazole **2c** (10 mol%) were dissolved in ^{i}PrOH/H_2O (9:1, 0.01 M) in a pear-shaped falsk. The solution was sparged by bubbling argon gas through it under ultrasonication for 30 min. Then the solution was pumped from the flask using a peristaltic pump through the photoreactor described above. The residence time of the reaction solution flowing through the photoreactor was determined by the flow rate set by the peristaltic pump. The exiting solution was collected in a round-bottom flask. Once the reaction mixture was exhausted, the pump inlet was quickly inserted into the blank ^{i}PrOH/H_2O (9:1) solvent reservoir and the reaction mixture was kept pushing through the photoreactor and flushed for 30 minutes. The entire exiting solution collected was concentrated, and the residue was purified by chromatography to afford the deoxygenation product.

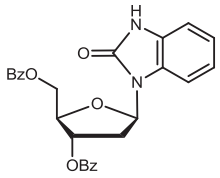


Compounds **3a-3d** are known.[2]



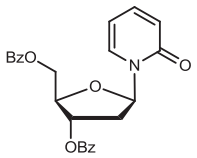
Methyl 1-((2*R*,4*S*,5*R*)-4-(benzoyloxy)-5-((benzoyloxy)methyl)tetrahydrofuran-2-yl)-1H-1,2,4-triazole-3-carboxylate (3e)

Following the general procedure with the flow rate of 0.263 mL/min (t_r = 7 min), the nucleoside (50.1 mg, 78.3 μmol) provided the 2'-deoxynucleoside (chromatography with 50-70% EtOAc in hexanes) as a colorless oil (28.3 mg, 80% yield). R_f = 0.07 (50% EtOAc/hexanes); $[\alpha]_D^{25}$ -21.1 (*c* 1.45, $CHCl_3$); IR (neat) 2956, 1723, 1271 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.05-8.03 (m, 2H), 8.00-7.98 (m, 2H), 7.63-7.59 (m, 1H), 7.57-7.54 (m, 1H), 7.47 (dd, *J* = 7.8, 7.8 Hz, 2H), 7.42 (dd, *J* = 7.8, 7.8 Hz, 2H), 6.38 (dd, *J* = 6.3, 6.3 Hz, 1H), 5.76 (ddd, *J* = 6.1, 3.1, 3.0 Hz, 1H), 4.70-4.60 (m, 3H), 3.97 (s, 3H), 3.16 (ddd, *J* = 14.3, 6.6, 6.4 Hz, 1H), 2.86 (ddd, *J* = 14.4, 6.2, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.1, 165.8, 160.0, 155.3, 144.1, 133.8, 133.4, 129.8, 129.8, 129.3, 129.1, 128.7, 128.6, 89.1, 84.0, 74.9, 64.0, 52.8, 38.3; HRMS (ESI): Exact mass calcd. for $C_{23}H_{21}N_3NaO_7$ $[M+Na]^+$ 474.1272, found 412.1290.



Methyl 1-((2*R*,4*S*,5*R*)-4-(benzoyloxy)-5-((benzoyloxy)methyl)tetrahydrofuran-2-yl)-1H-1,2,4-triazole-3-carboxylate (3f)

Following the general procedure with the flow rate of 0.184 mL/min (t_r = 10 min), the nucleoside (50.7 mg, 78.3 μmol) provided the 2'-deoxynucleoside (chromatography with 30-50% EtOAc in hexanes) as a yellow oil (30.6 mg, 85% yield). R_f = 0.21 (50% EtOAc/hexanes); $[\alpha]_D^{25}$ -53.0 (*c* 1.50, $CHCl_3$); IR (neat) 3189, 3066, 1718, 1270 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 10.09 (s, 1H), 8.11 (d, *J* = 6.6 Hz, 4H), 7.64-7.58 (m, 2H), 7.50 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.46 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 7.01 (dd, *J* = 7.7, 7.7 Hz, 1H), 6.69 (dd, *J* = 7.7, 7.7 Hz, 1H), 6.48 (dd, *J* = 8.9, 6.1 Hz, 1H), 5.82 (dd, *J* = 4.4, 3.1 Hz, 1H), 4.83 (dd, *J* = 12.0, 2.6 Hz, 1H), 4.75 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.53 (dd, *J* = 7.0, 3.5 Hz, 1H), 3.25-3.19 (m, 1H), 2.51 (ddd, *J* = 14.3, 5.9, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.3, 166.1, 154.8, 133.6, 133.4, 129.9, 129.8, 129.8, 129.4, 128.6, 128.6, 128.1, 127.9, 122.3, 121.5, 110.3, 110.1, 82.7, 81.4, 74.7, 64.3, 34.6; HRMS (ESI): Exact mass calcd. for $C_{26}H_{22}N_2NaO_6$ $[M+Na]^+$ 481.1370, found 481.1381.

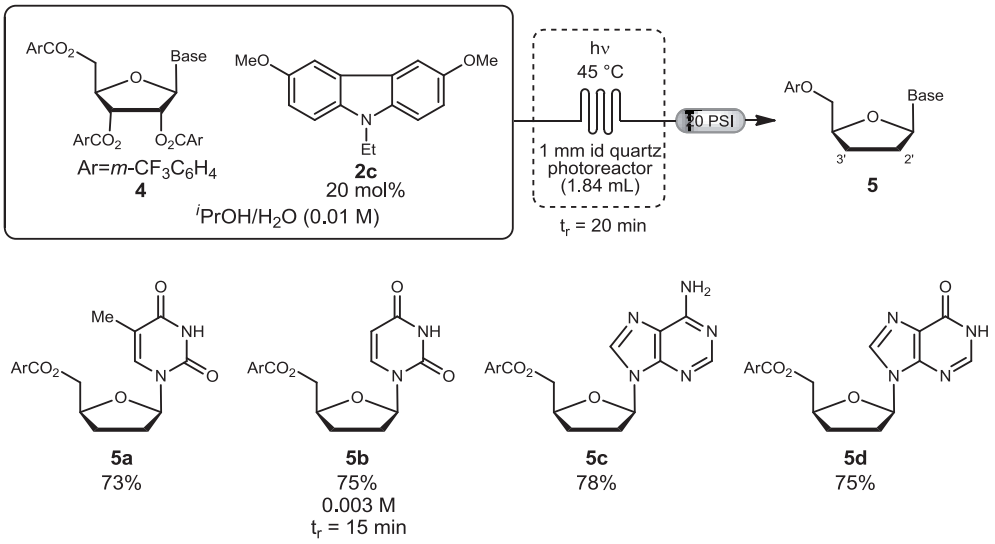


((2*R*,3*S*,5*R*)-3-(Benzoyloxy)-5-(2-oxopyridin-1(2H)-yl)tetrahydrofuran-2-yl)methyl benzoate (3g)

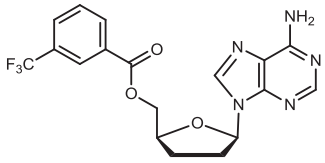
Following the general procedure with the flow rate of 0.368 mL/min (t_r = 5 min), the nucleoside (47.6 mg, 78.3 μmol) provided the 2'-deoxynucleoside (chromatography with 30-60% EtOAc in hexanes) as a yellow oil (20.1 mg, 61% yield). R_f= 0.11 (50% EtOAc/hexanes); $[\alpha]_D^{25}$ 20.1 (*c* 0.45, CHCl3); IR (neat) 2956, 1719, 1662, 1269 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.9 Hz, 2H), 7.99 (d, *J* = 7.9 Hz, 2H), 7.69 (d, *J* = 6.8 Hz, 1H), 7.63-7.57 (m, 2H), 7.48 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.43 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.32-7.29 (m, 1H), 6.61 (dd, *J* = 7.8, 5.9 Hz, 1H), 6.54 (d, *J* = 9.1 Hz, 1H), 6.11 (dd, *J* = 6.8, 6.8 Hz, 1H), 5.63 (d, *J* = 6.5 Hz, 1H), 4.76 (dd, *J* = 12.1, 3.2 Hz, 1H), 4.72 (dd, *J* = 12.1, 3.6 Hz, 1H), 4.63 (dd, *J* = 6.0, 3.1 Hz, 1H), 3.03 (ddd, *J* = 14.5, 5.7, 1.6 Hz, 1H), 2.28 (ddd, *J* = 14.5, 7.4, 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.2, 166.1, 162.1, 139.7, 133.7, 133.5, 131.6, 129.9, 129.7, 129.4, 129.2, 128.7, 128.6, 120.7, 106.3, 86.3, 83.1, 77.3, 75.3, 64.5, 39.3; HRMS (ESI): Exact mass calcd. for $C_{24}H_{21}NNaO_6$ $[M+Na]^+$ 442.1267, found 442.1251.

Photo-induced deoxygenation reaction for the synthesis of 2',3-deoxynucleosides

The nucleoside substrate and carbazole **2c** (20 mol%) were dissolved in ^{i}PrOH/H_2O (9:1, 0.01 M) in a pear-shaped falsk. The solution was sparged by bubbling argon gas through it under ultrasonication for 30 min. Then the solution was pumped from the flask using a peristaltic pump through the photoreactor described above. The residence time of the reaction solution flowing through the photoreactor was determined by the flow rate set by the peristaltic pump. The exiting solution was collected in a round-bottom flask. Once the reaction mixture was exhausted, the pump inlet was quickly inserted into the blank ^{i}PrOH/H_2O (9:1) solvent reservoir and the reaction mixture was kept pushing through the photoreactor and flushed for 30 minutes. The entire exiting solution collected was concentrated, and the residue was purified by chromatography to afford the deoxygenation product.



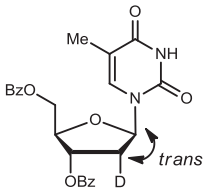
Compounds **5a**, **5b** and **5d** are known.[2]



((2*S*,5*R*)-5-(6-Amino-9H-purin-9-yl)tetrahydrofuran-2-yl)methyl 3-(trifluoromethyl)benzoate (5c)

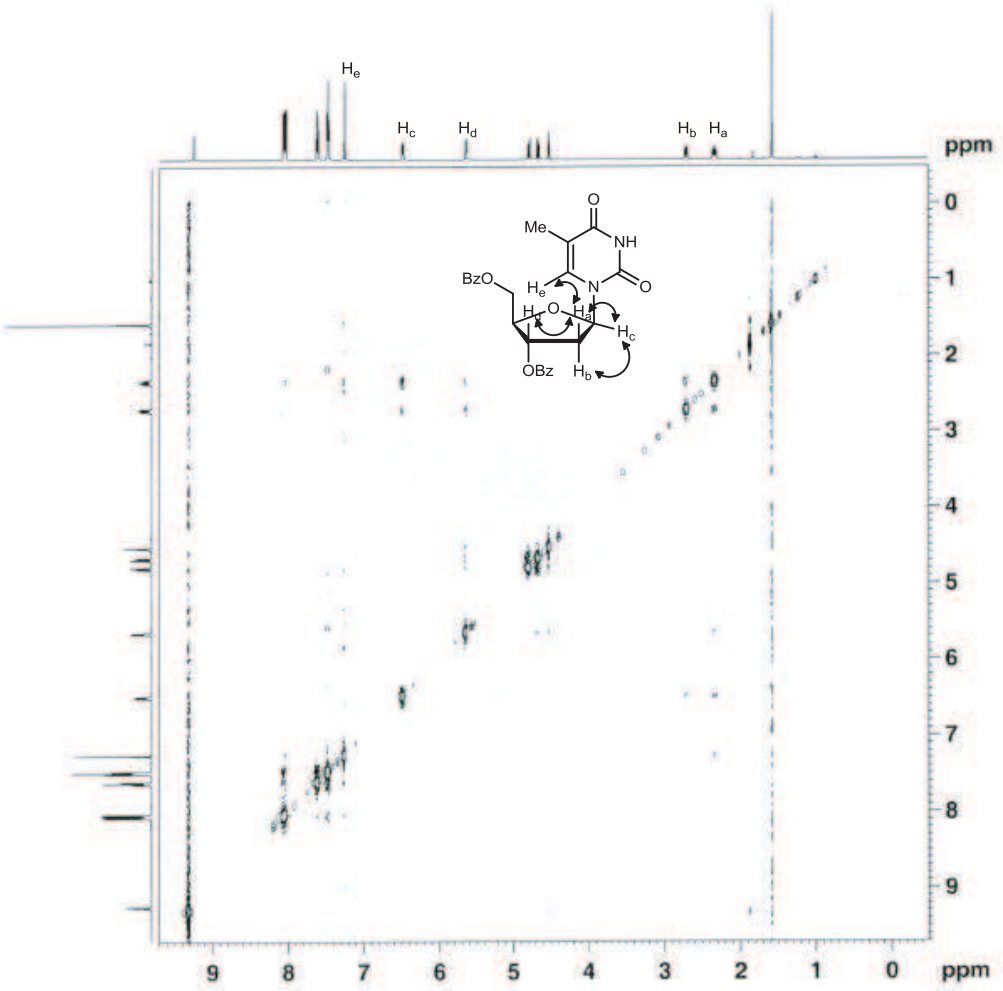
Following the general procedure with the flow rate of 92.0 μL/min (t_r = 20 min), the nucleoside (53.7 mg, 68.6 μmol) provided the 2',3'-dideoxynucleoside (chromatography with 5-10% MeOH in CH_2Cl_2) as an off-white solid (21.8 mg, 78% yield). R_f= 0.13 (5% MeOH/CH_2Cl_2); mp 143-145°C; $[\alpha]_D^{25}$ 13.2 (*c* 1.05, $CHCl_3$); IR (neat) 3162, 1725, 1653, 1599, 1251 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.26 (s, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 8.02 (s, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.56 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.29 (dd, *J* = 6.9, 3.1 Hz, 1H), 5.88 (s, 2H), 4.65-4.61 (m, 1H), 4.58-4.53 (m, 2H), 2.77-2.72 (m, 1H), 2.63-2.56 (m, 1H), 2.31-2.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 165.1, 155.6, 153.0, 149.3, 138.8, 132.9, 131.2 (q, $^2J_{CF}$ = 33.1 Hz), 130.5, 129.8 (q, $^3J_{CF}$ = 3.6 Hz), 129.2, 126.7 (q, $^3J_{CF}$ = 3.8 Hz), 123.4 (q, $^1J_{CF}$ = 272.6 Hz), 120.4, 86.0, 79.2, 66.4, 32.2, 26.6; HRMS (ESI): Exact mass calcd. for $C_{18}H_{17}F_3N_5O_3$ $[M+H]^+$ 408.1278, found 408.1250.

Synthesis of Deuterium-labeled 2'-Deoxynucleoside 6

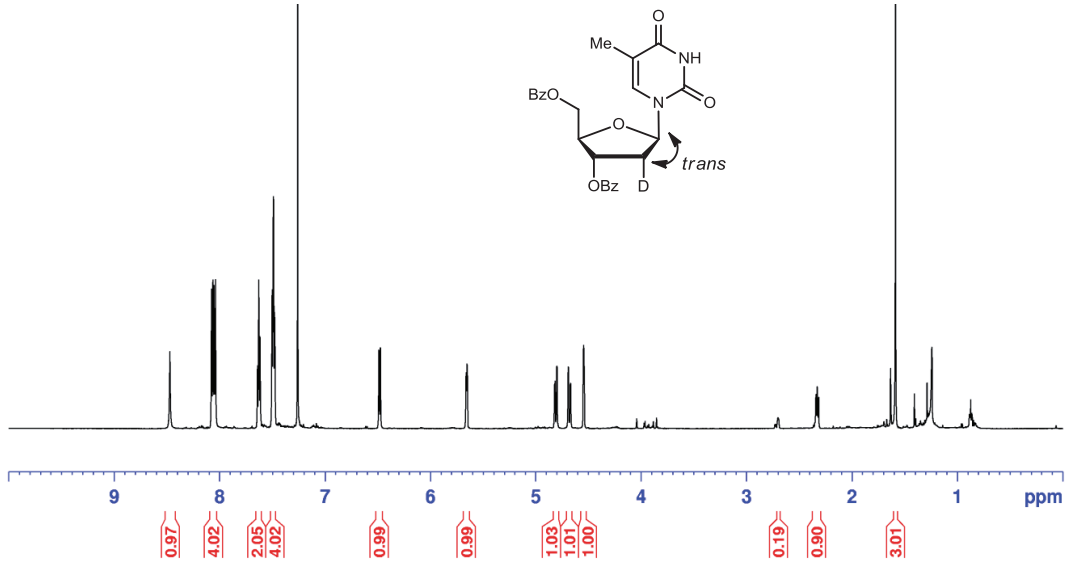


Following the general procedure and using 20 mol% carbazole **2c** with the flow rate of 73.6 μL/min (t_r = 25 min), the nucleoside (25.0 mg, 39.2 μmol) in 3.9 mL (0.01 M) ^{i}PrOD (*d*-8) provided the 2'-*D*-deoxynucleoside (chromatography with 30-60% EtOAc in hexanes) as a white solid (14.8 mg, 84% yield, ~5:1 dr at C-2', favoring the C1'-C2' *trans* diastereomer). HRMS (ESI): Exact mass calcd. for $C_{24}H_{21}DN_2O_7$ $[M+H]^+$ 452.1563, found 452.1559.

NOESY NMR of **3a**



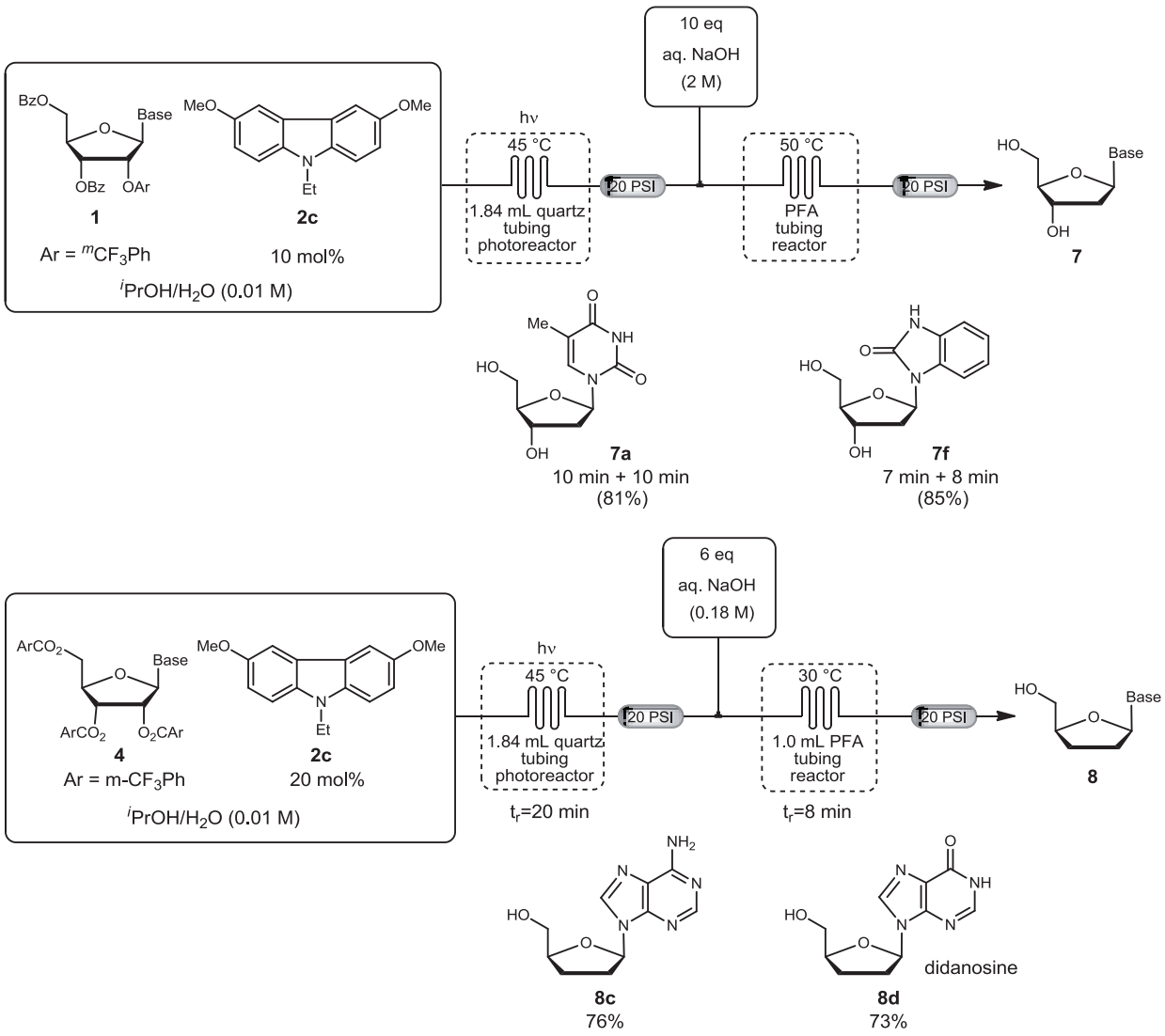
^{1}H NMR of **6a**



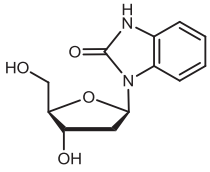
One-flow, two-step synthesis of 2'-deoxy and 2',3'-dideoxynucleosides

An aqueous solution of NaOH was introduced using a syringe pump via a T-mixer to the exiting stream from the PET deoxygenation reaction.[6] The solution then entered a PFA tubing reactor which was submerged in an oil bath with temperature control. The exit of the PFA tubing reactor was connected to a 20 psi back pressure regulator and then a collection vial. The product solution was quenched with 1 M aqueous HOAc to pH 7-8. The crude was concentrated and the residue was purified by chromatography to afford the deoxygenation product.

6 For the flow set-up of the deprotection step, see: A. Sniady, M. W. Bedore and T. F. Jamison, *Angew. Chem. Int. Ed.*, 2011, **50**, 2155-2158.



Compounds **7a**, **8c** and **8d** are known.

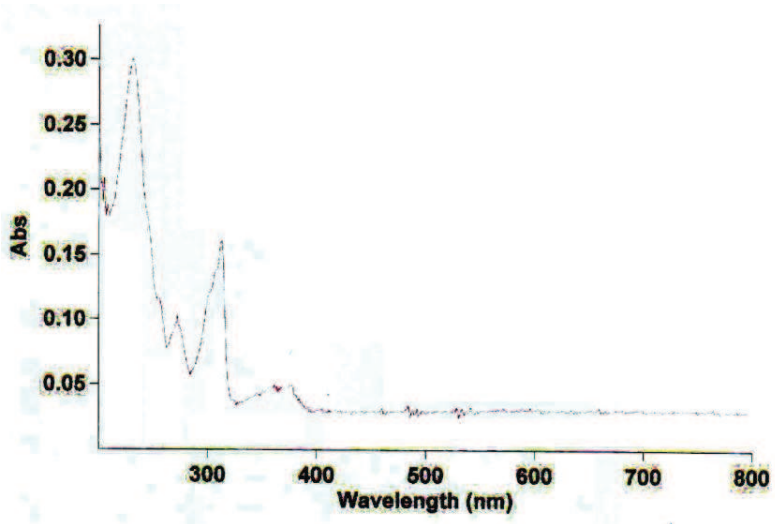


1-((2*R*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1H-benzoimidazol-2(3H)-one (7f)

The flow rate of the deoxygenation reaction was set to 0.263 mL/min by the peristaltic pump. The flow rate of aqueous NaOH (2 M) was set to 13.2 μL/min by the syringe pump. The PFA tubing reactor (2.21 mL) was heated at 50 °C. After the steady state was reached (monitored by TLC, 20 min (2.5 residence

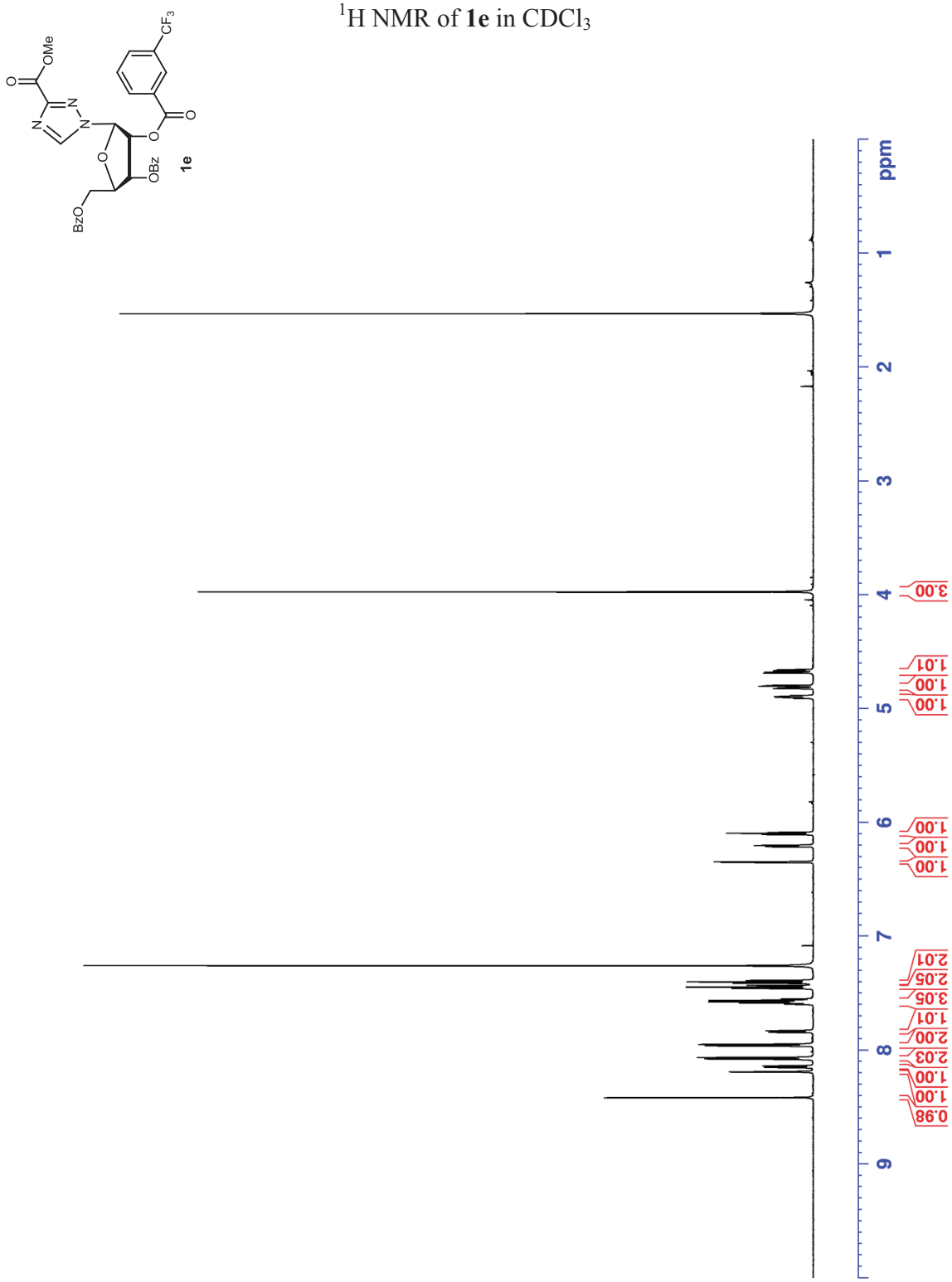
times of the second step) after the first drop), the reaction crude was collected for 70 min. The product solution was quenched with 1 M aqueous HOAc to pH 7-8. The crude was concentrated and the residue was purified by chromatography (5-10% MeOH in CH_2Cl_2 on SNAP KP-NH columns) to afford **7f** as a colorless oil (39.2 mg). R_f= 0.22 (10% MeOH/CH_2Cl_2 on KP-NH plate); $[\alpha]_D^{25}$ -14.1 (*c* 0.86, MeOH); IR (neat) 3310, 1700, 1486 cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 7.38-7.35 (m, 1H), 7.07-7.03 (m, 3H), 6.27 (dd, *J* = 8.5, 6.4 Hz, 1H), 4.53-4.48 (m, 1H), 3.91 (dd, *J* = 8.0, 3.6 Hz, 1H), 3.81 (dd, *J* = 12.0, 3.6 Hz, 1H), 3.74 (dd, *J* = 12.0, 4.6 Hz, 1H), 2.87 (ddd, *J* = 13.5, 8.4, 7.0 Hz, 1H), 2.11 (ddd, *J* = 13.5, 6.4, 2.8 Hz, 1H), N*H* and O*H* not observed; ^{13}C NMR (100 MHz, MeOD) ppm 156.1, 130.0, 129.7, 123.3, 122.6, 111.3, 110.6, 88.4, 84.2, 72.8, 63.7, 38.1; HRMS (ESI): Exact mass calcd. for $C_{12}H_{14}N_2NaO_4$ $[M+Na]^+$ 273.0846, found 273.0847.

UV-Vis spectrum of carbazole **2c**

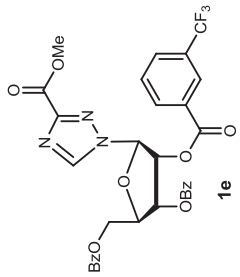


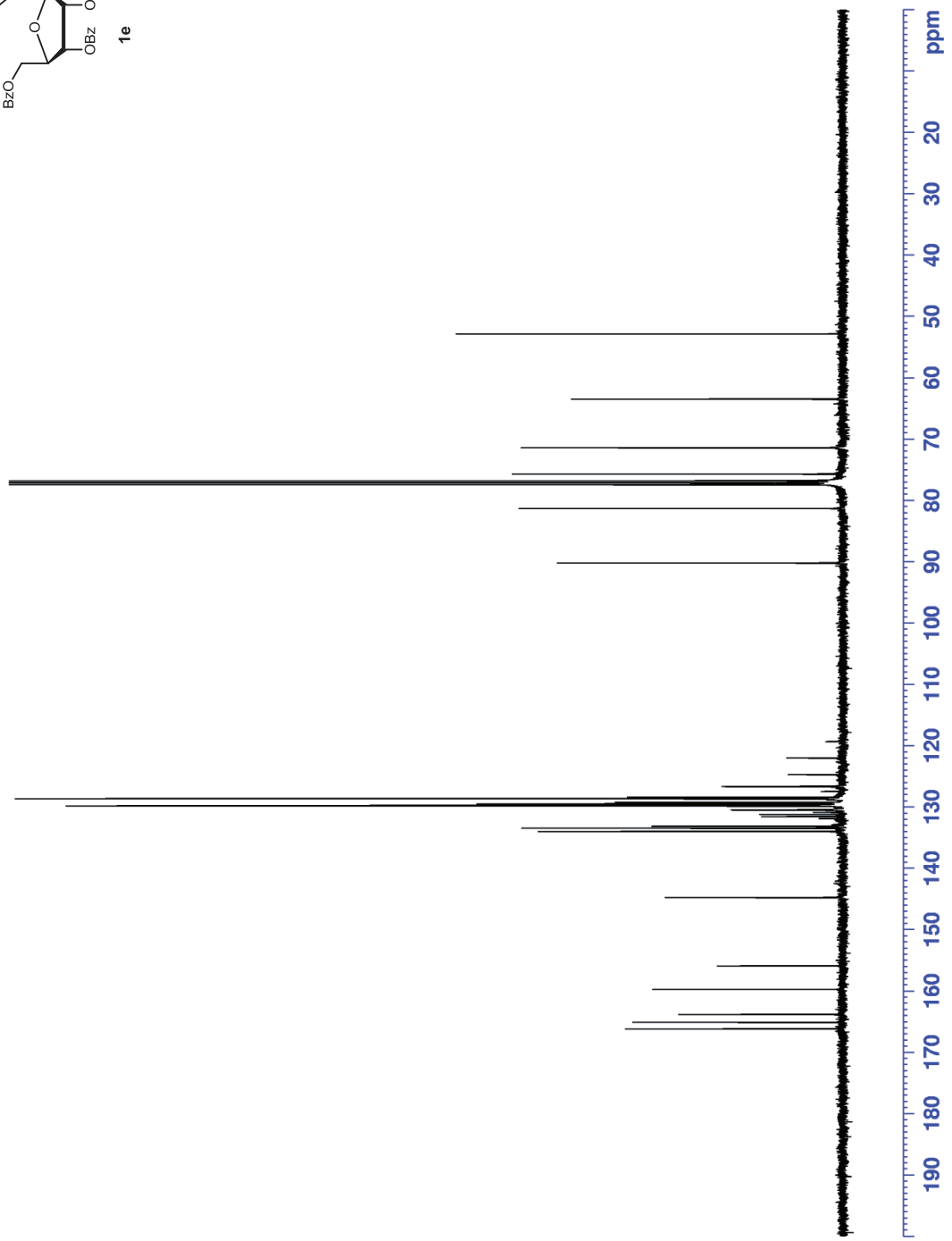
Wavelength (nm)	Abs
361.0	0.050
313.0	0.161
272.0	0.103

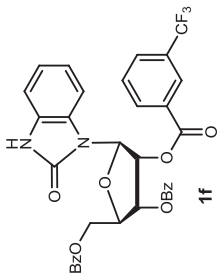
^{1}H NMR of **1e** in $CDCl_3$



^{13}C NMR of **1e** in $CDCl_3$

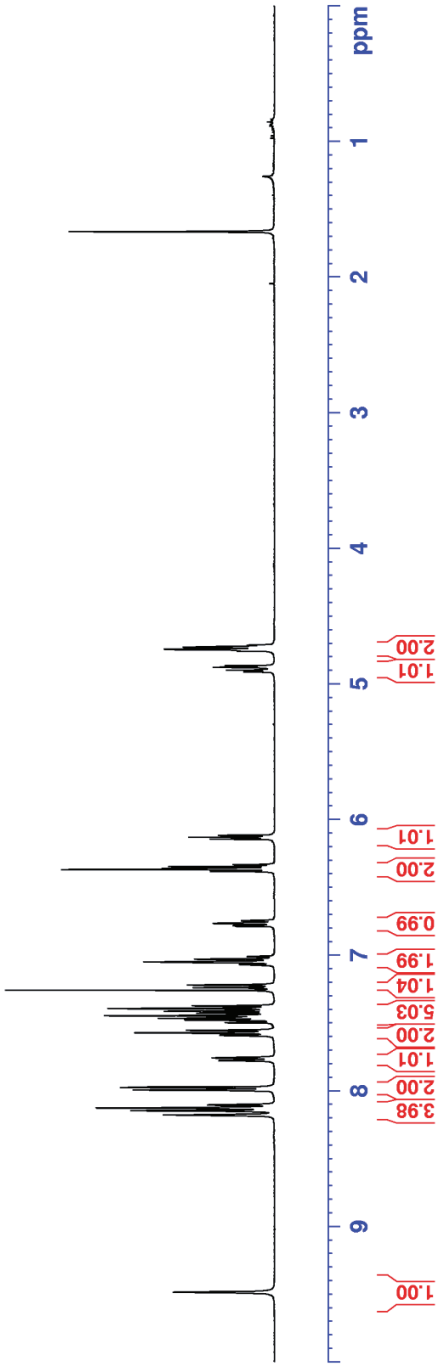




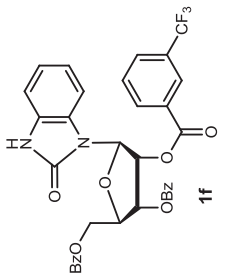


1f

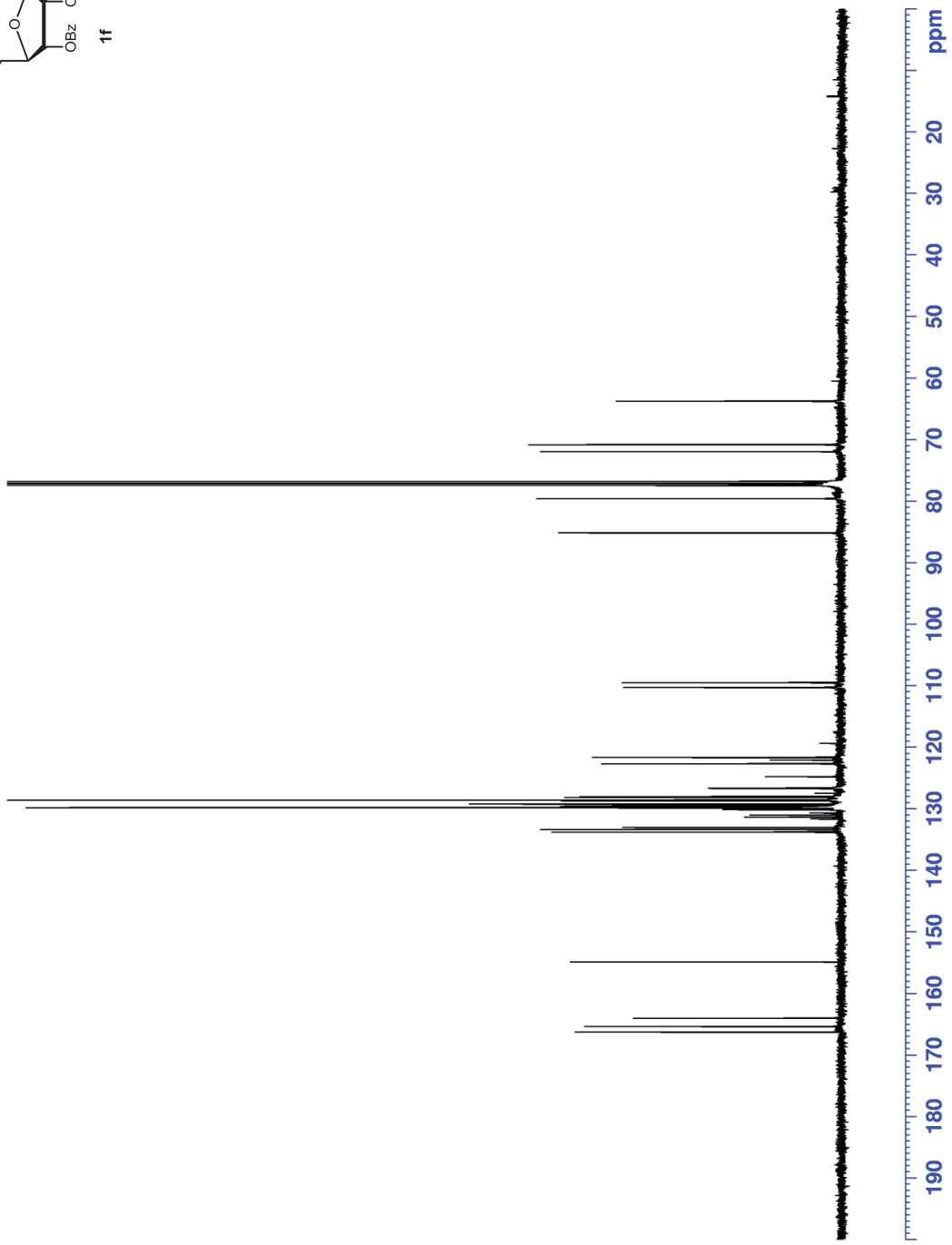
^{1}H NMR of **1f** in $CDCl_3$

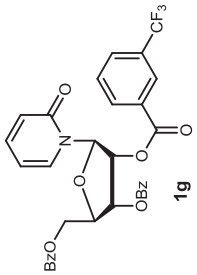


^{13}C NMR of **1f** in $CDCl_3$



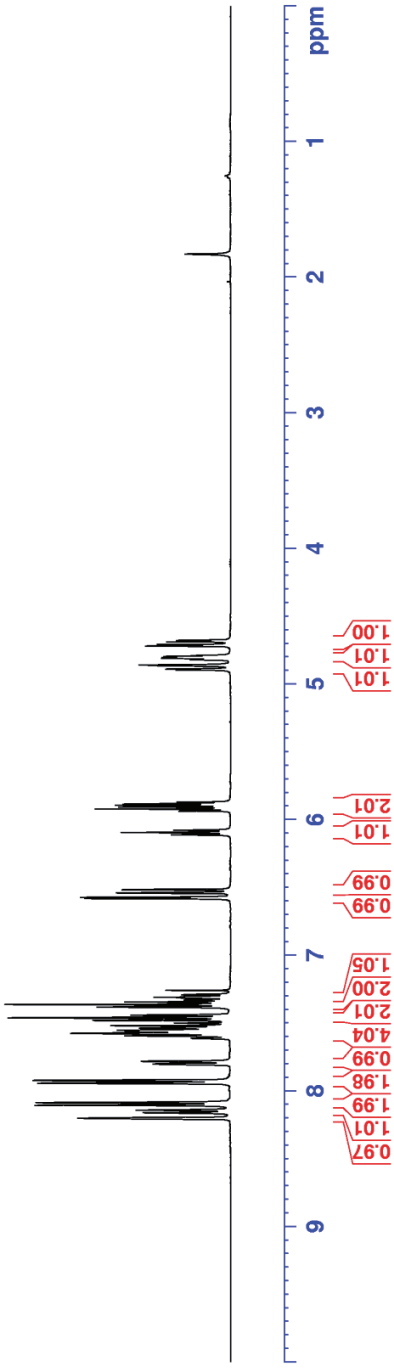
1f



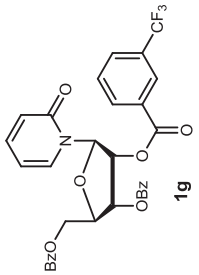


1g

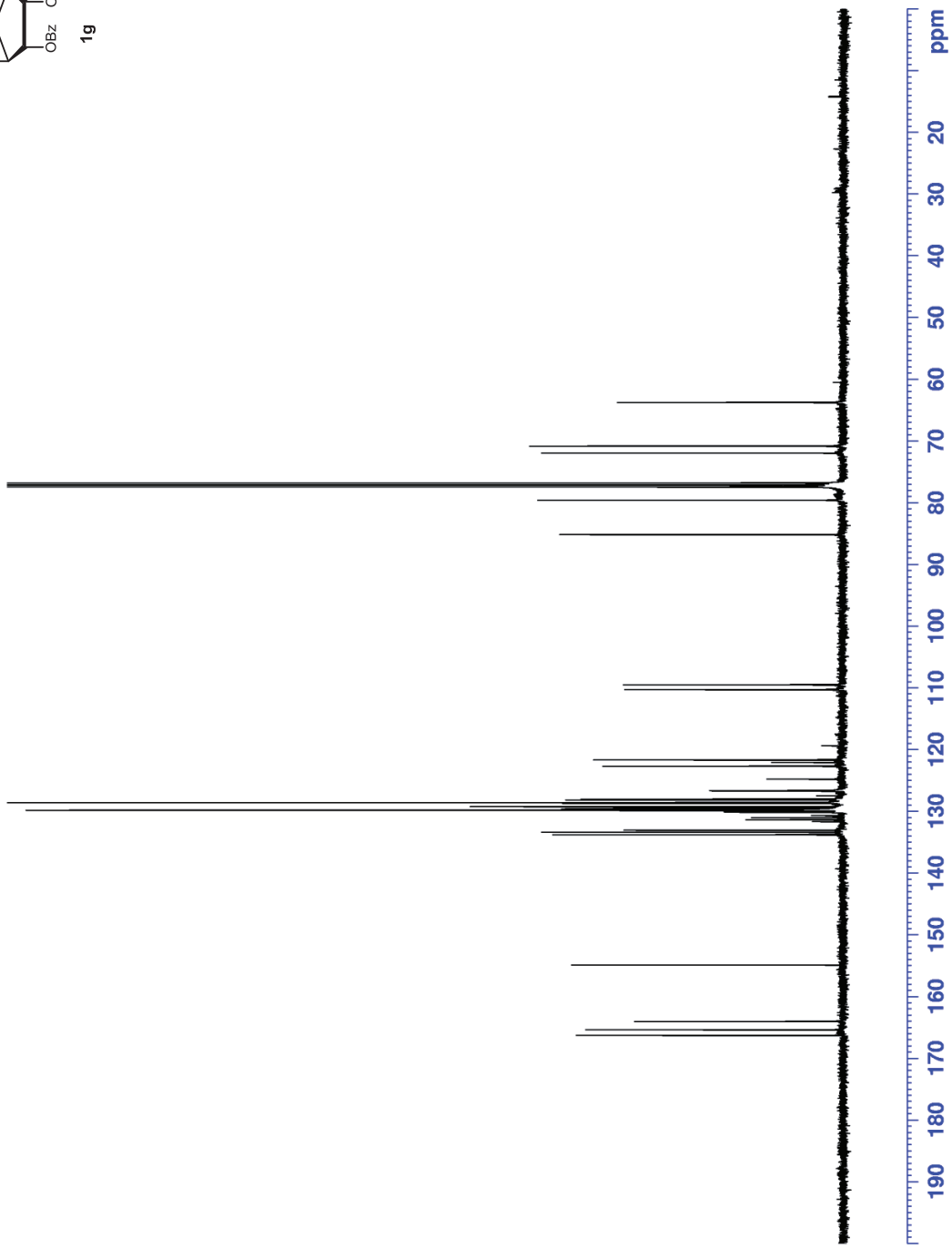
^{1}H NMR of **1g** in $CDCl_3$



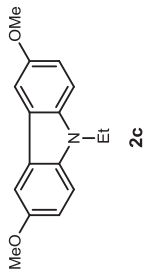
^{13}C NMR of **1g** in $CDCl_3$



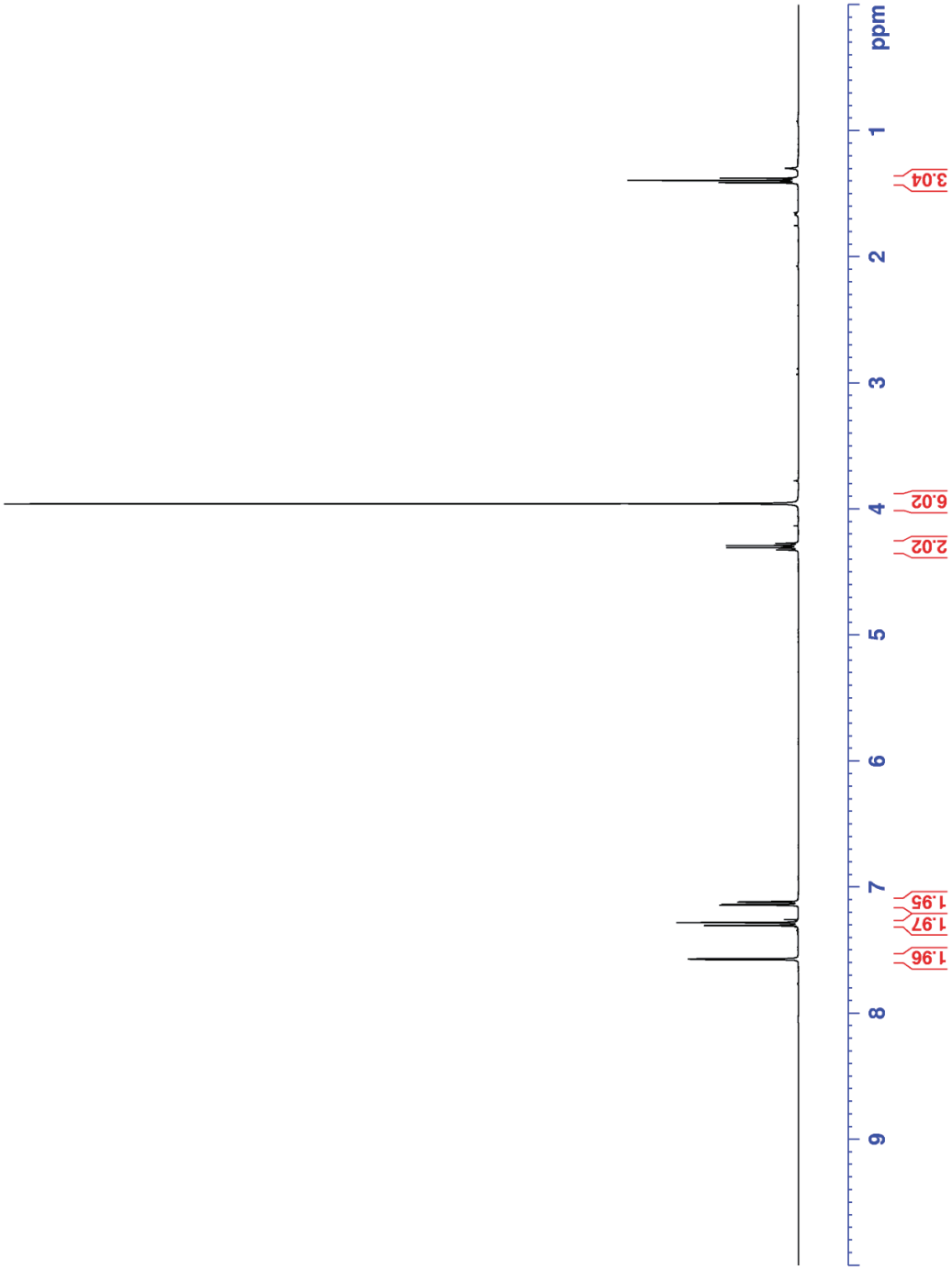
1g

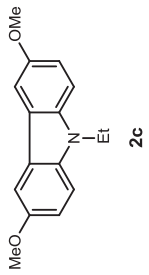


^{1}H NMR of **2c** in $CDCl_3$



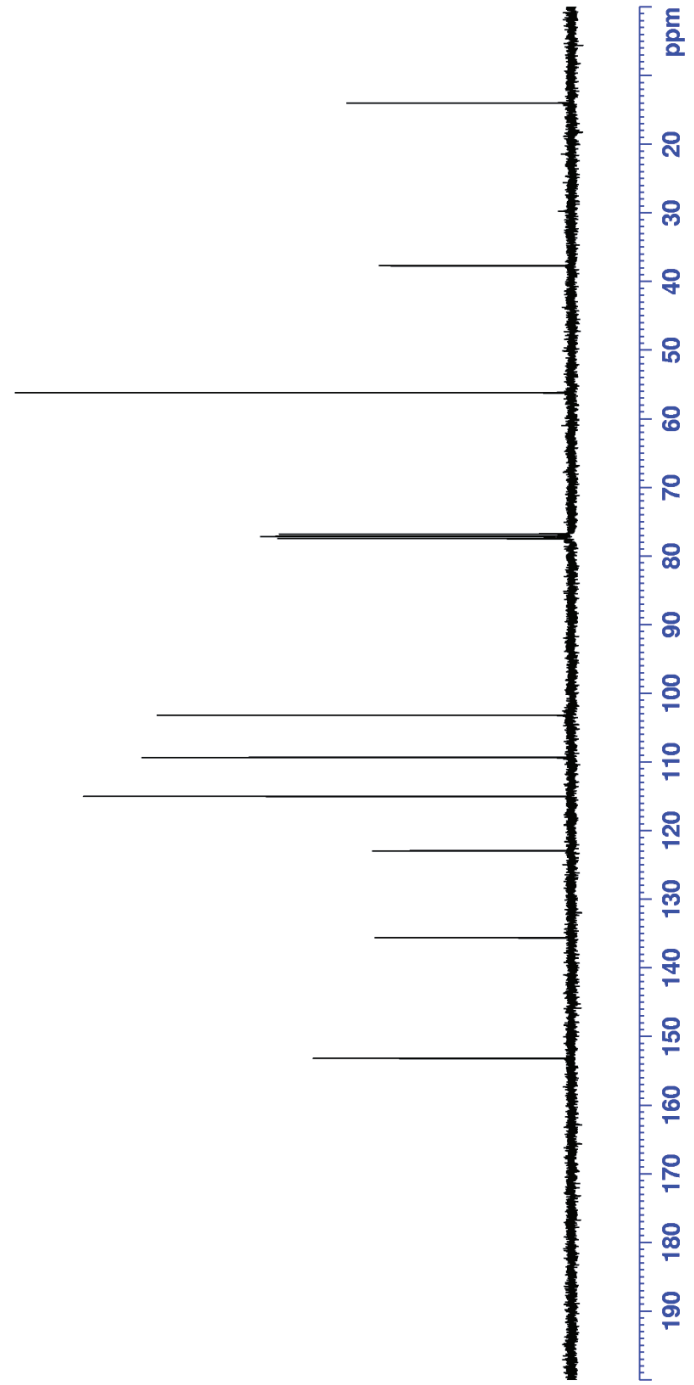
2c

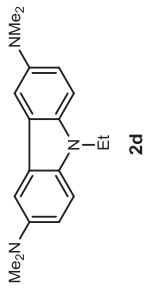




2c

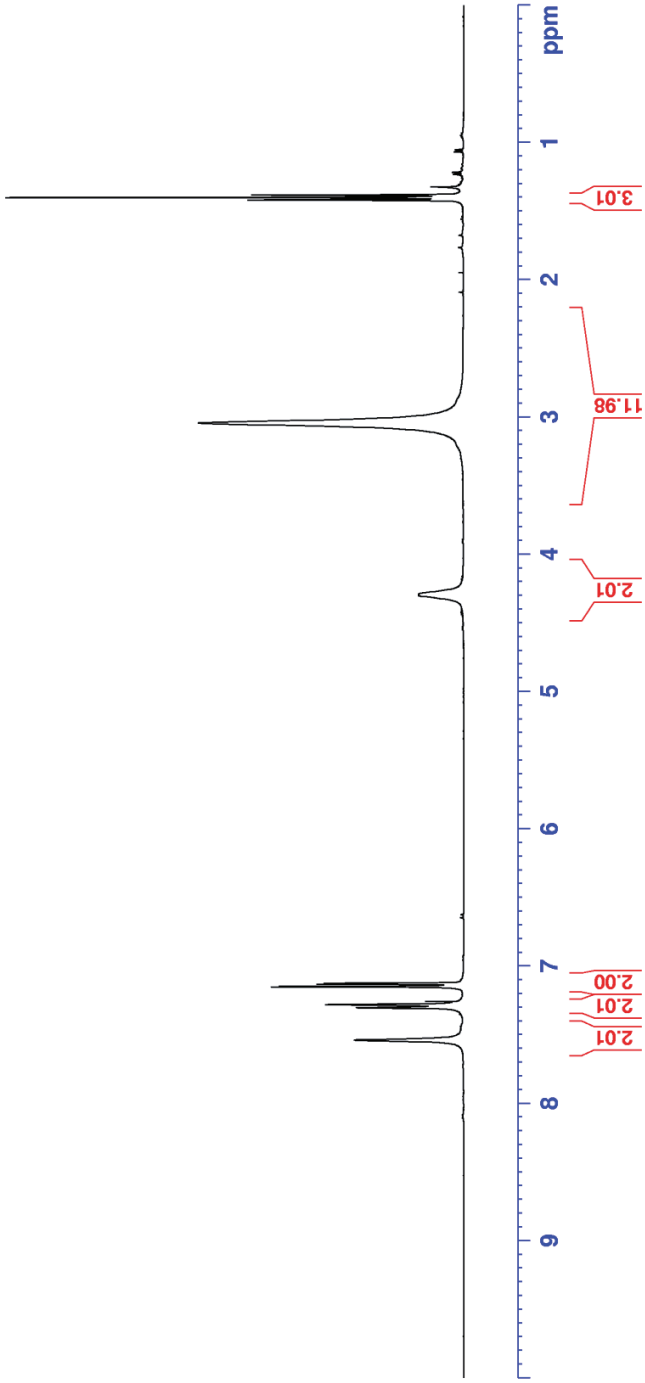
^{13}C NMR of **2c** in $CDCl_3$

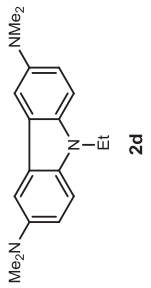




2d

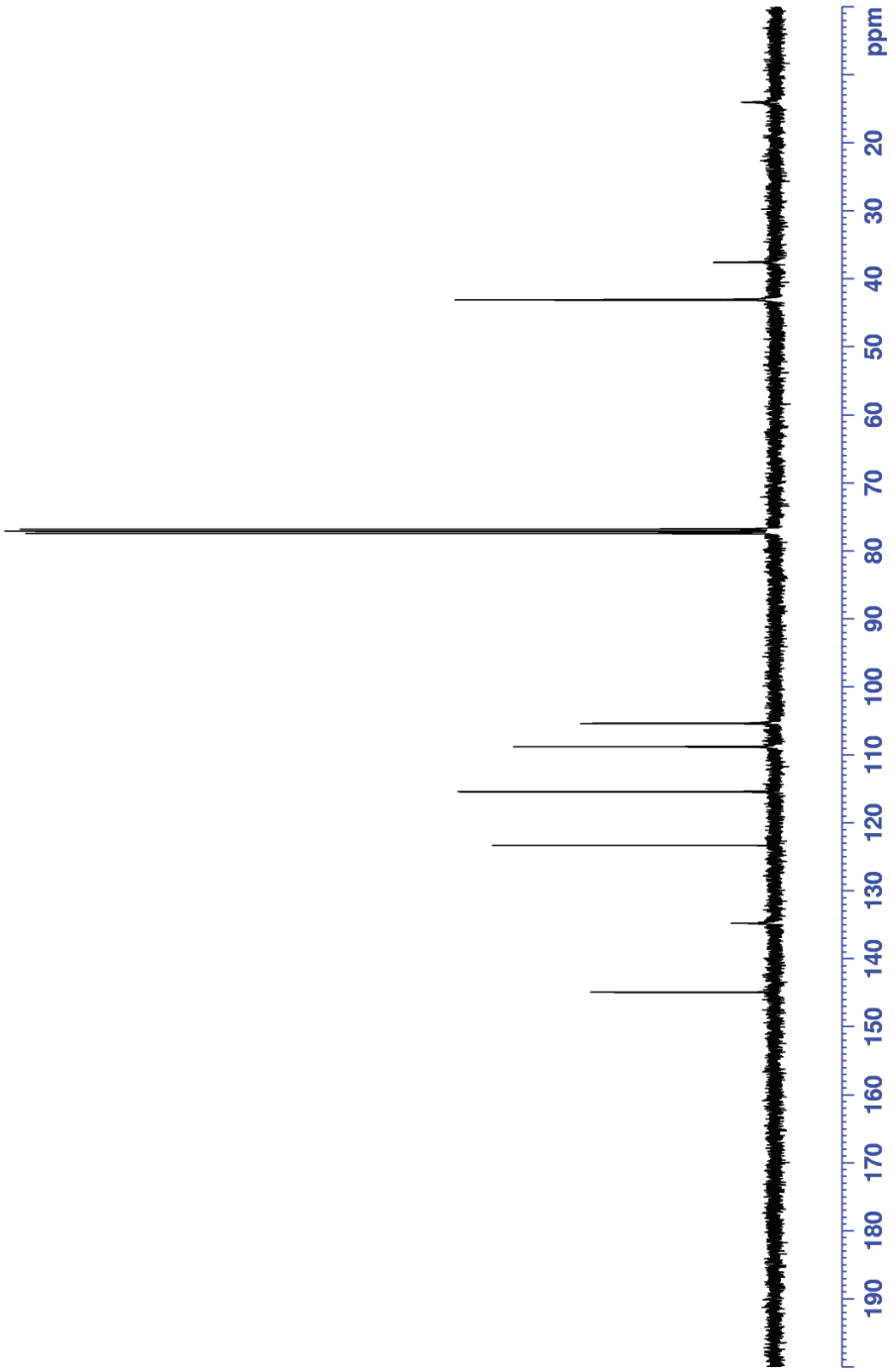
^{1}H NMR of **2d** in $CDCl_3$

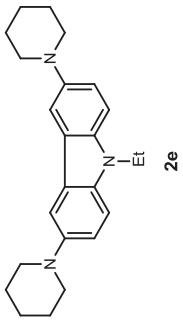




2d

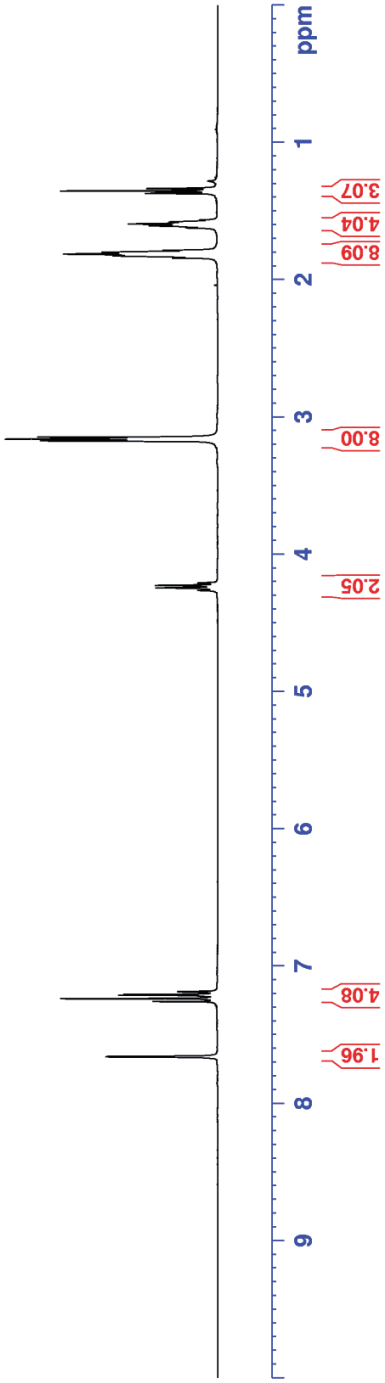
^{13}C NMR of **2d** in $CDCl_3$

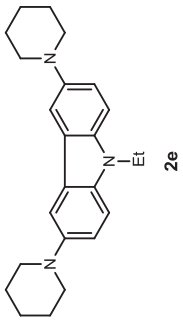




2e

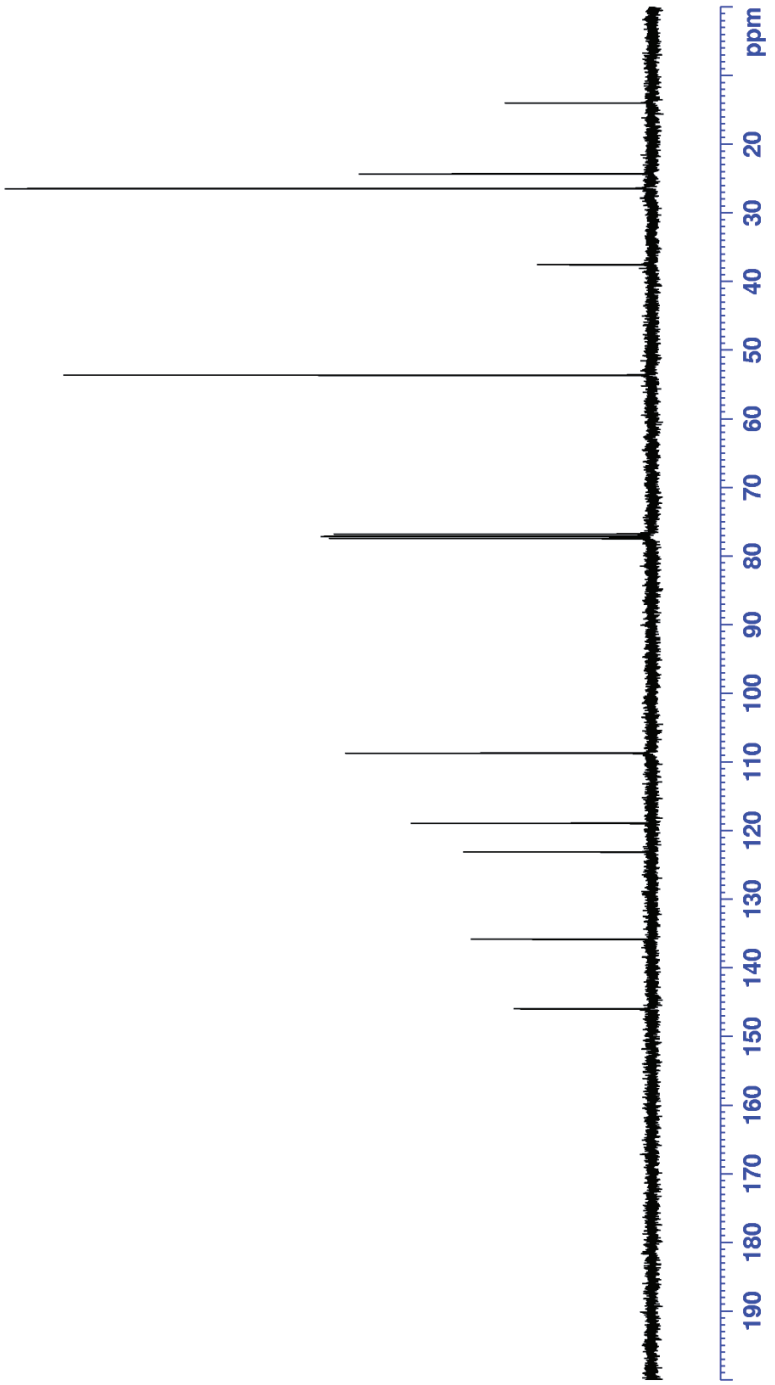
^{1}H NMR of **2e** in $CDCl_3$

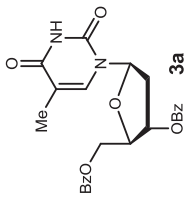




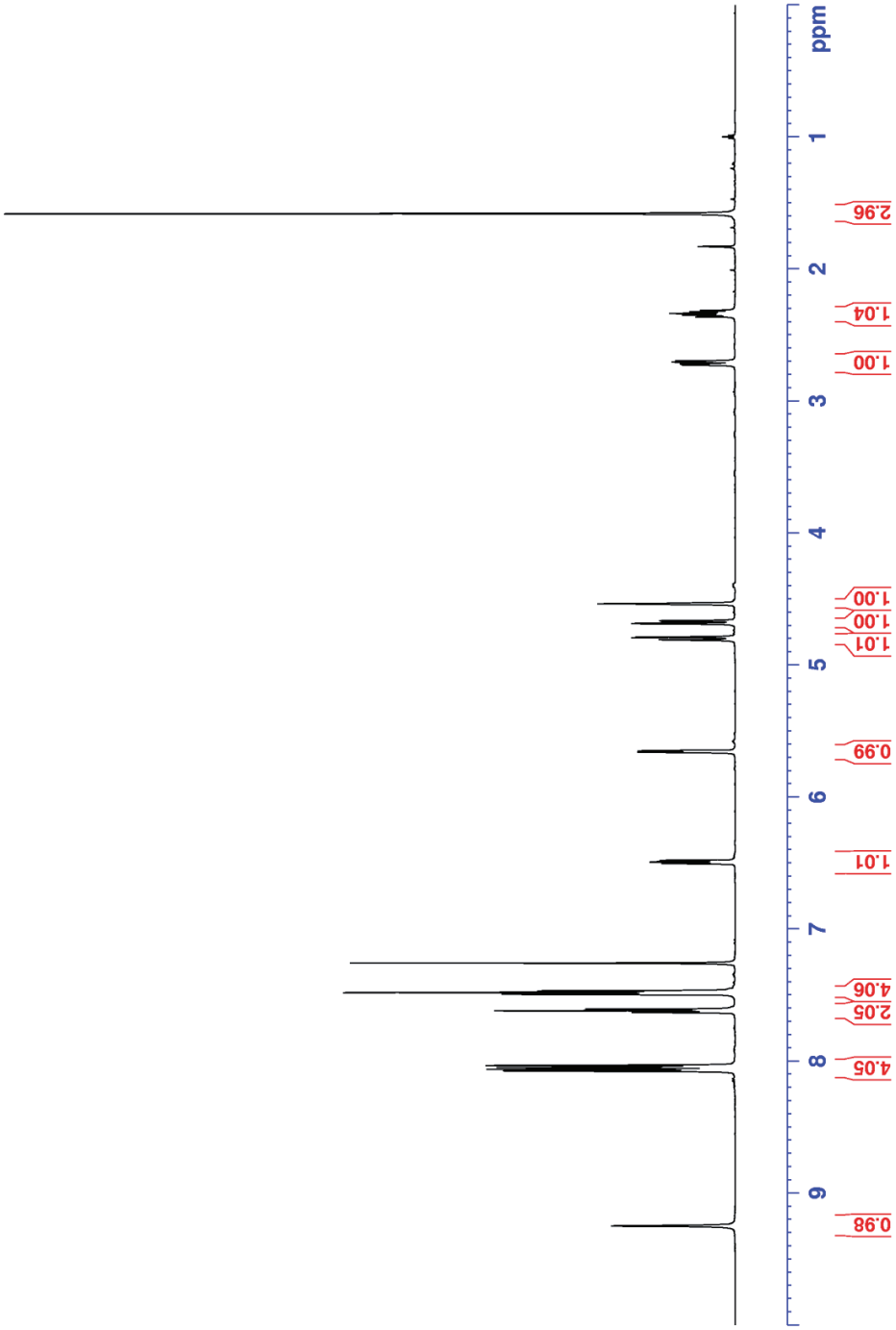
2e

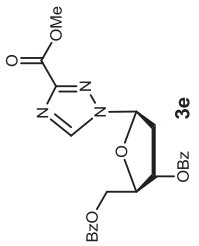
^{13}C NMR of **2e** in $CDCl_3$



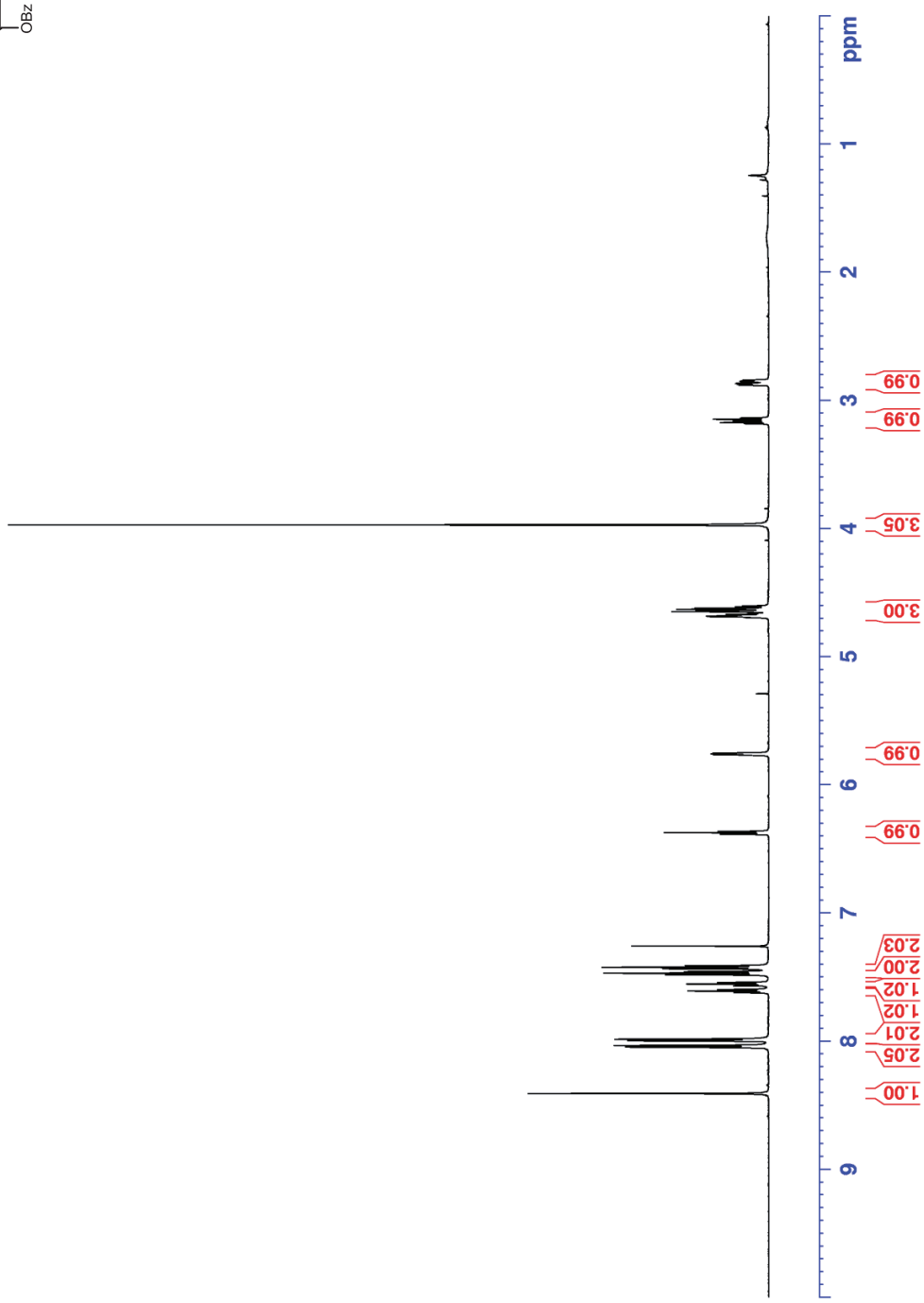


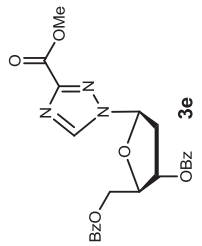
^{1}H NMR of **3a** in $CDCl_3$





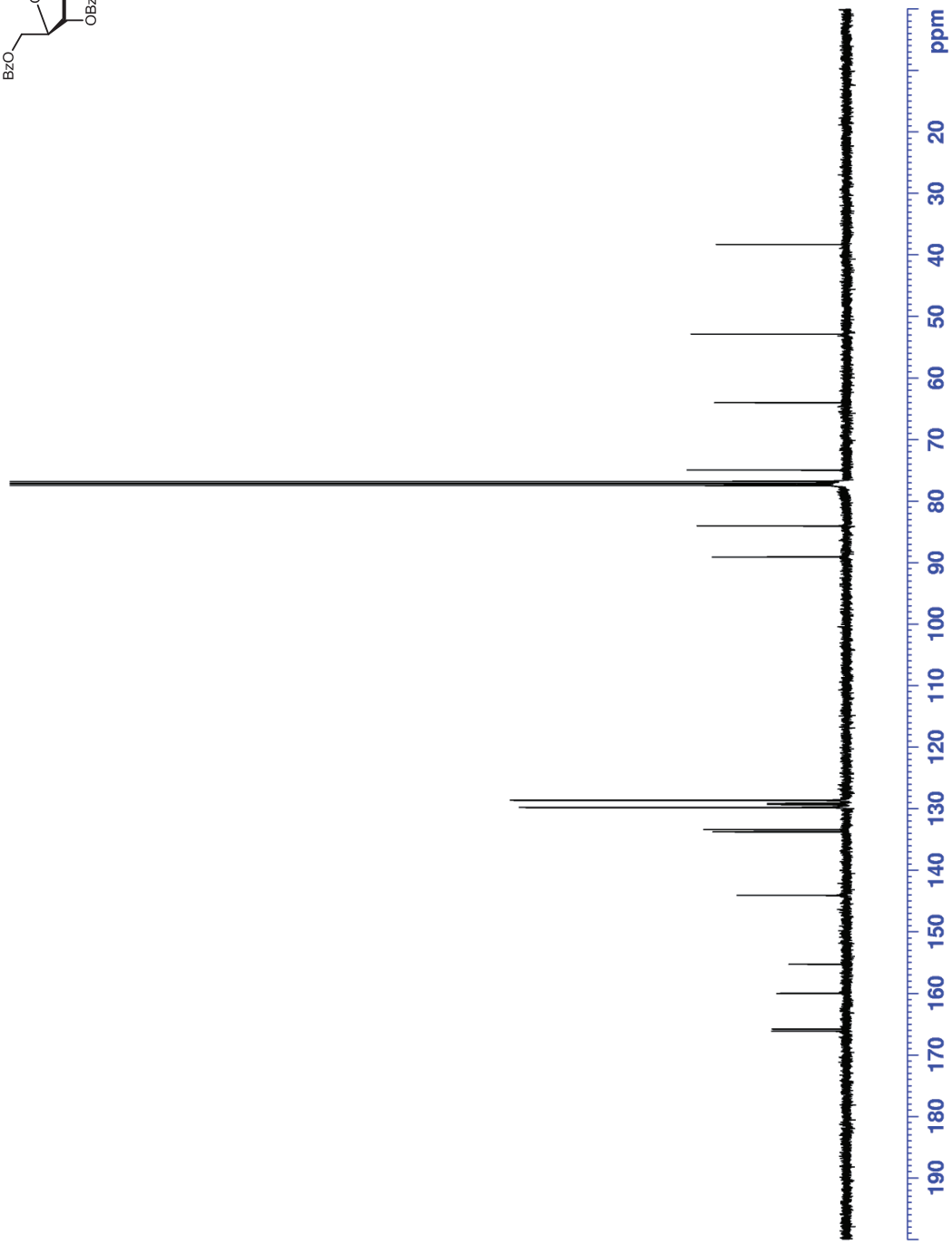
^{1}H NMR of **3e** in $CDCl_3$

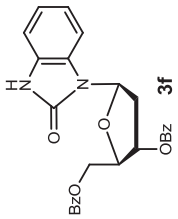




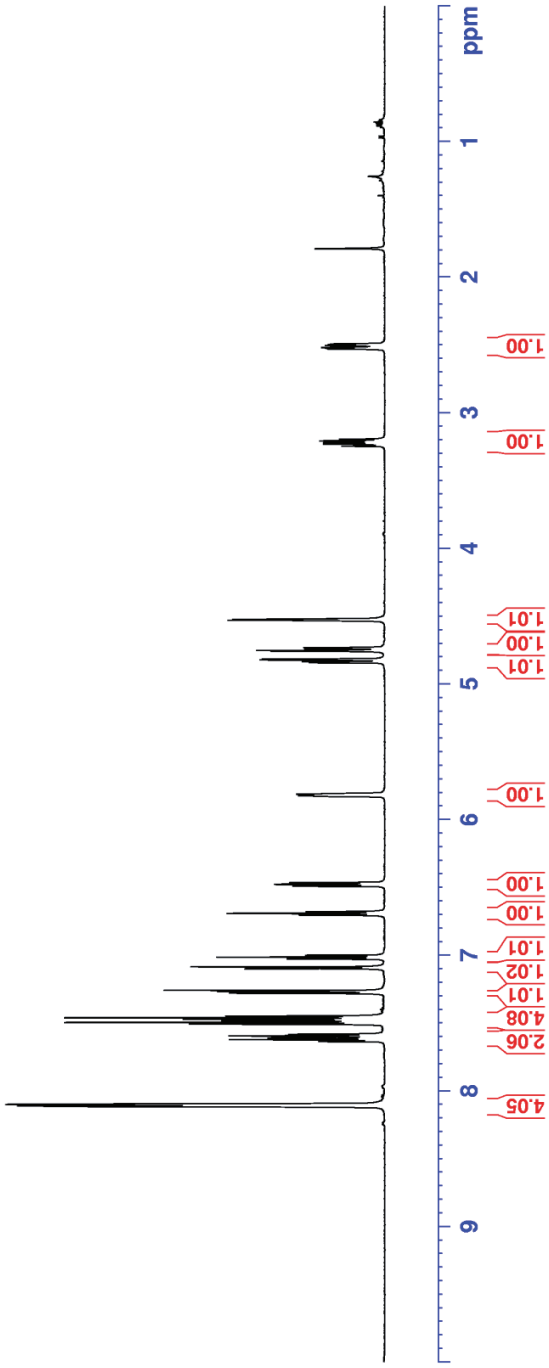
3e

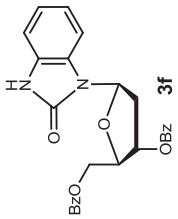
^{13}C NMR of **3e** in $CDCl_3$



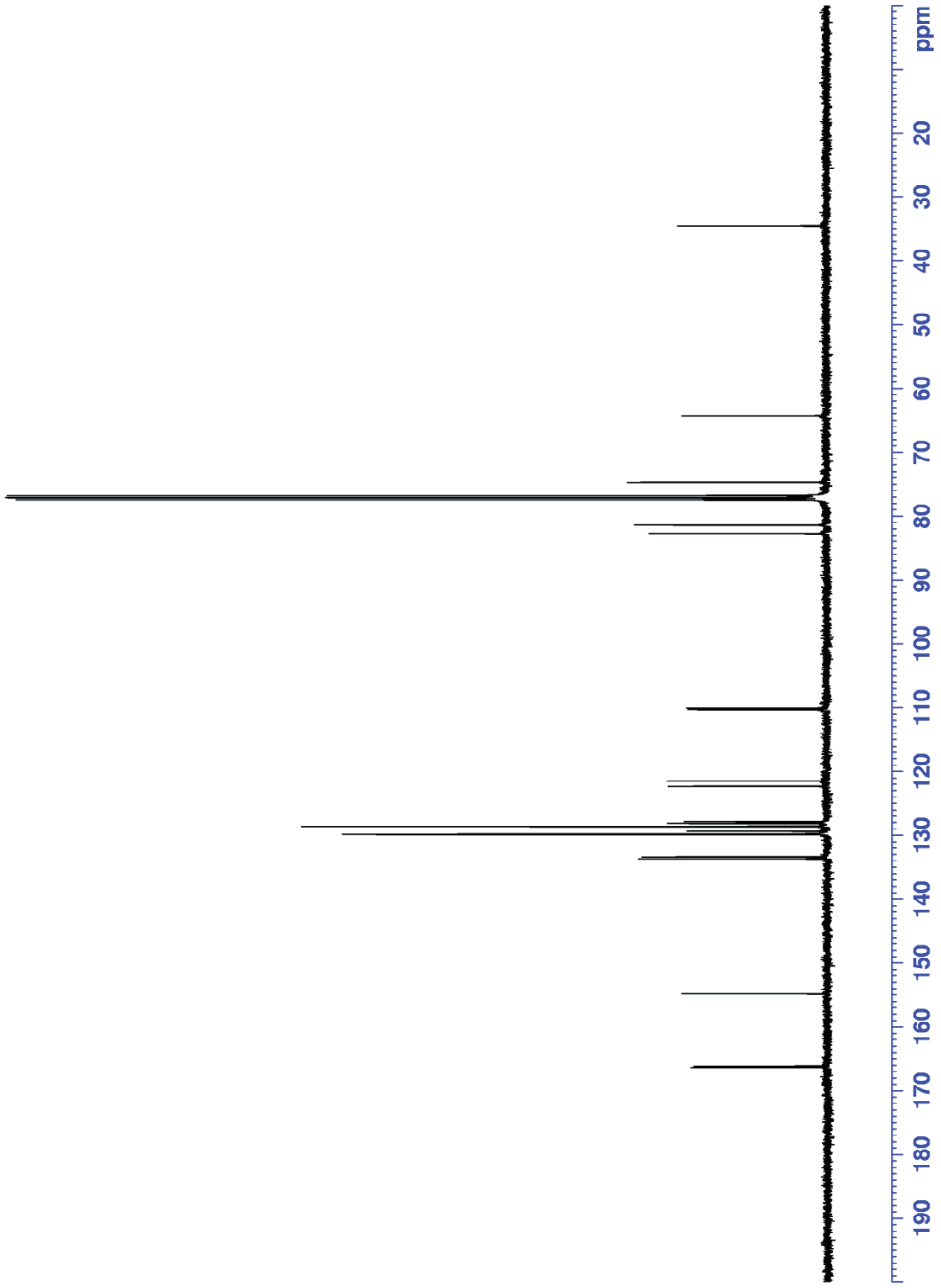


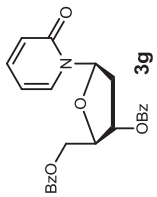
^{1}H NMR of **3f** in $CDCl_3$



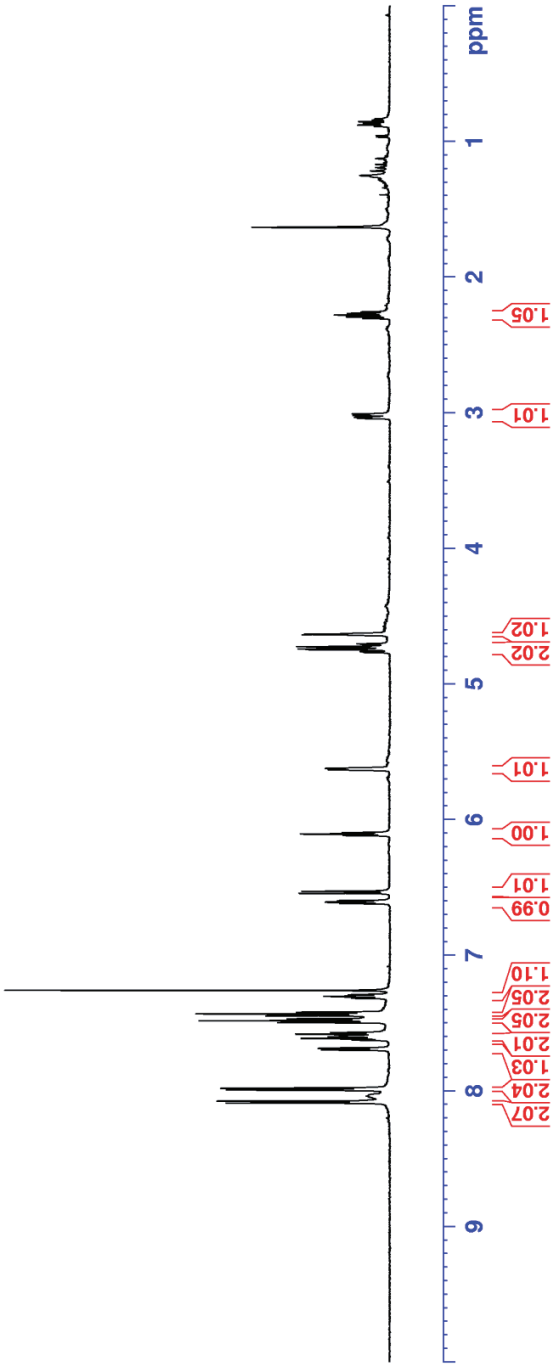


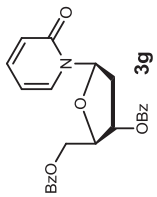
^{13}C NMR of **3f** in $CDCl_3$



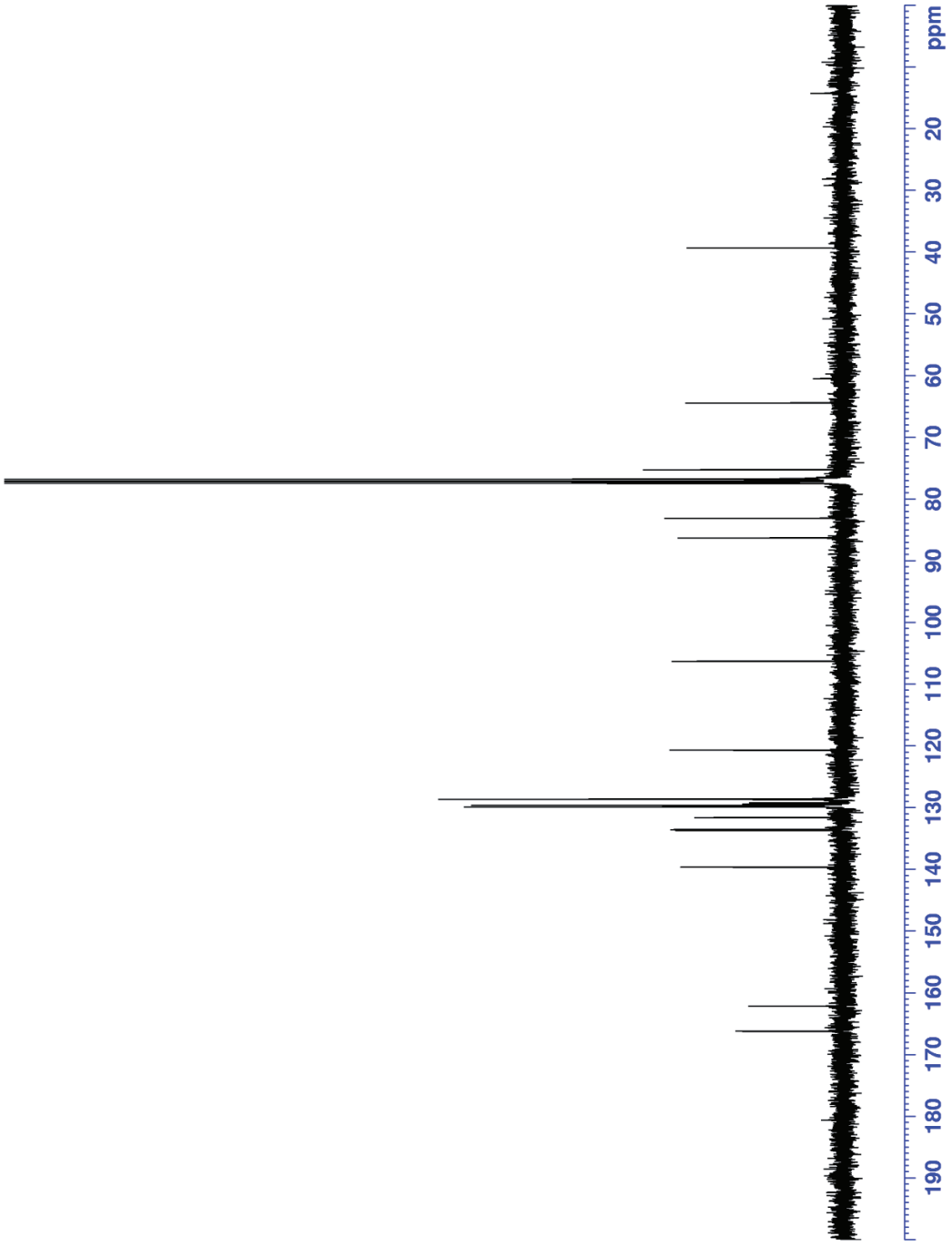


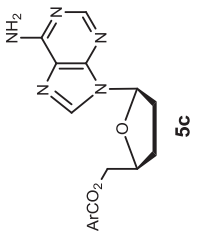
^{1}H NMR of **3g** in $CDCl_3$





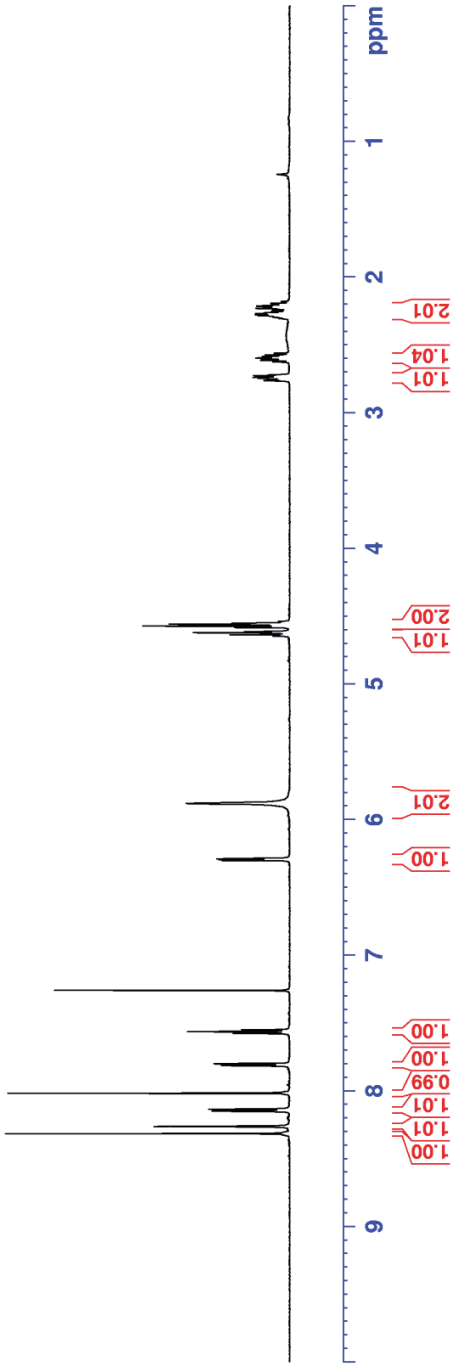
^{13}C NMR of **3g** in $CDCl_3$

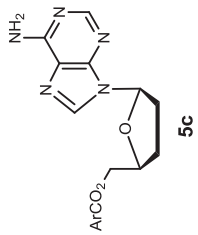




5c

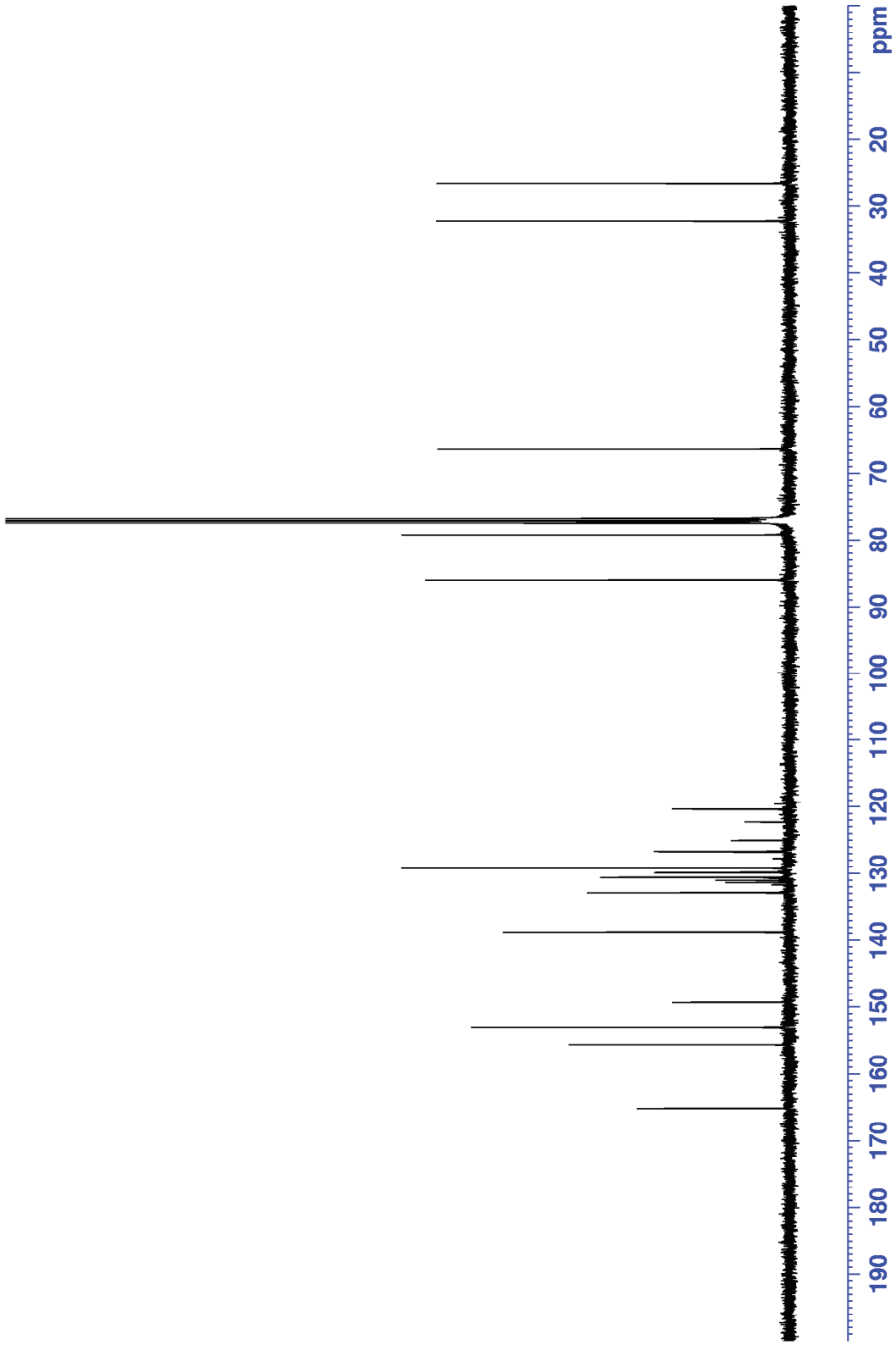
^{1}H NMR of **5c** in $CDCl_3$

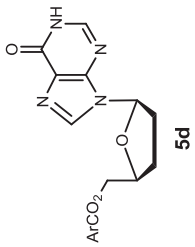




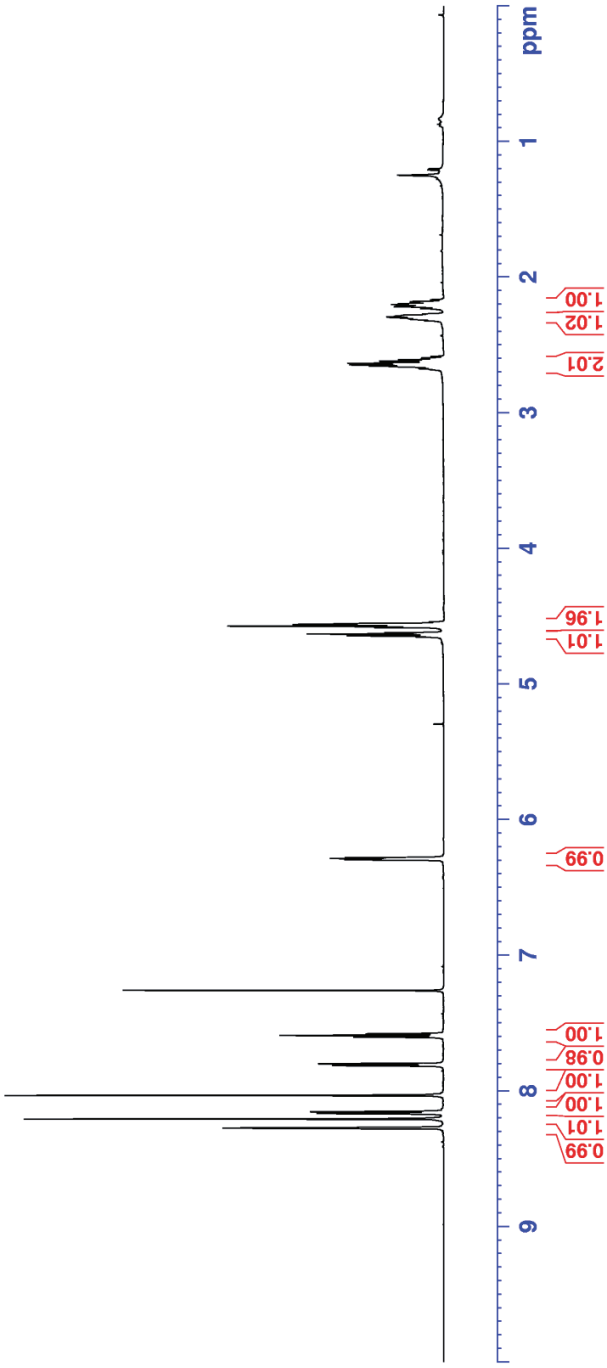
5c

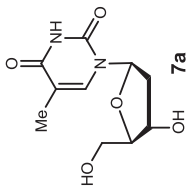
^{13}C NMR of **5c** in $CDCl_3$



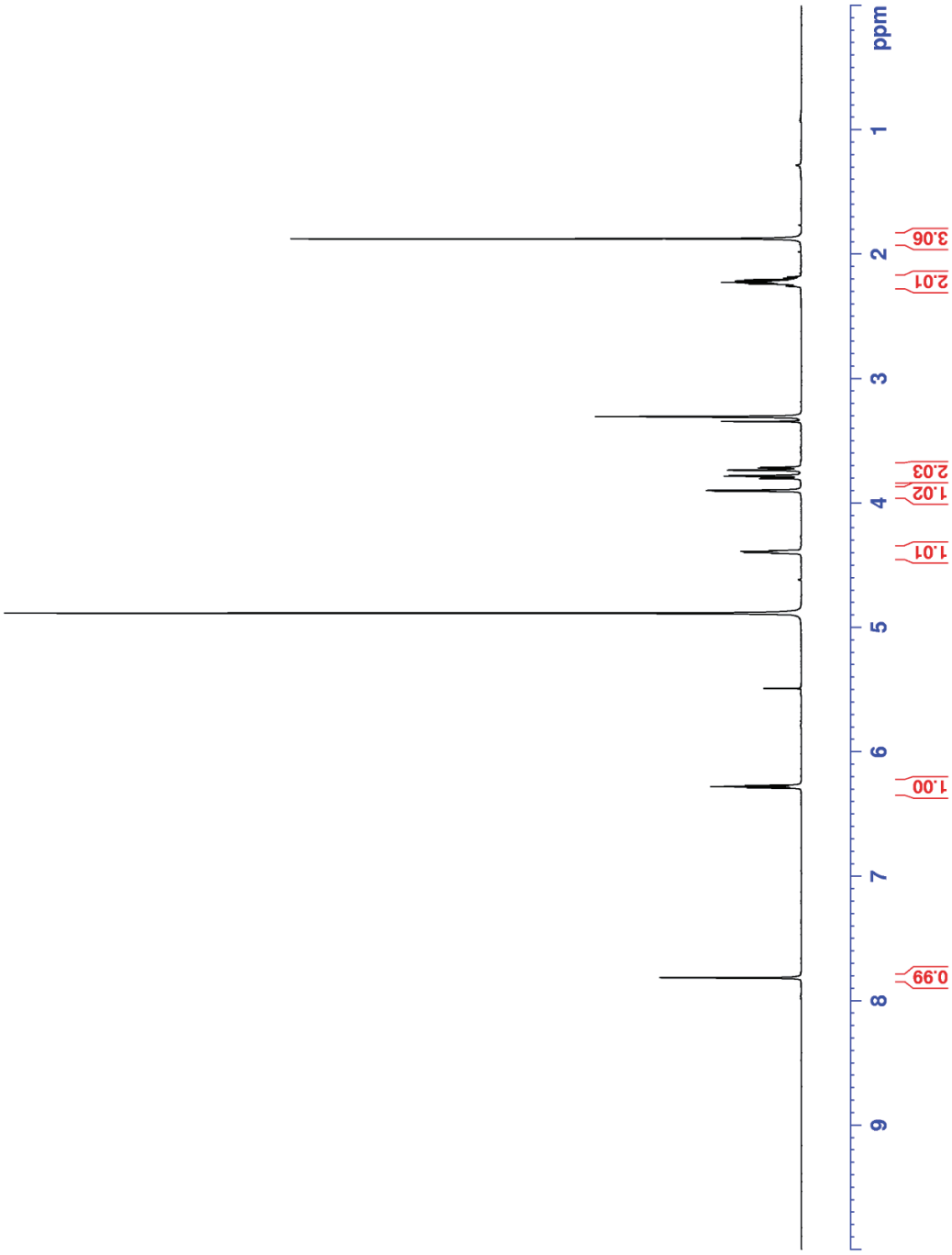


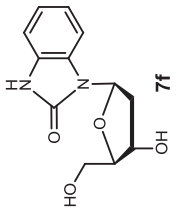
^{1}H NMR of **5d** in $CDCl_3$



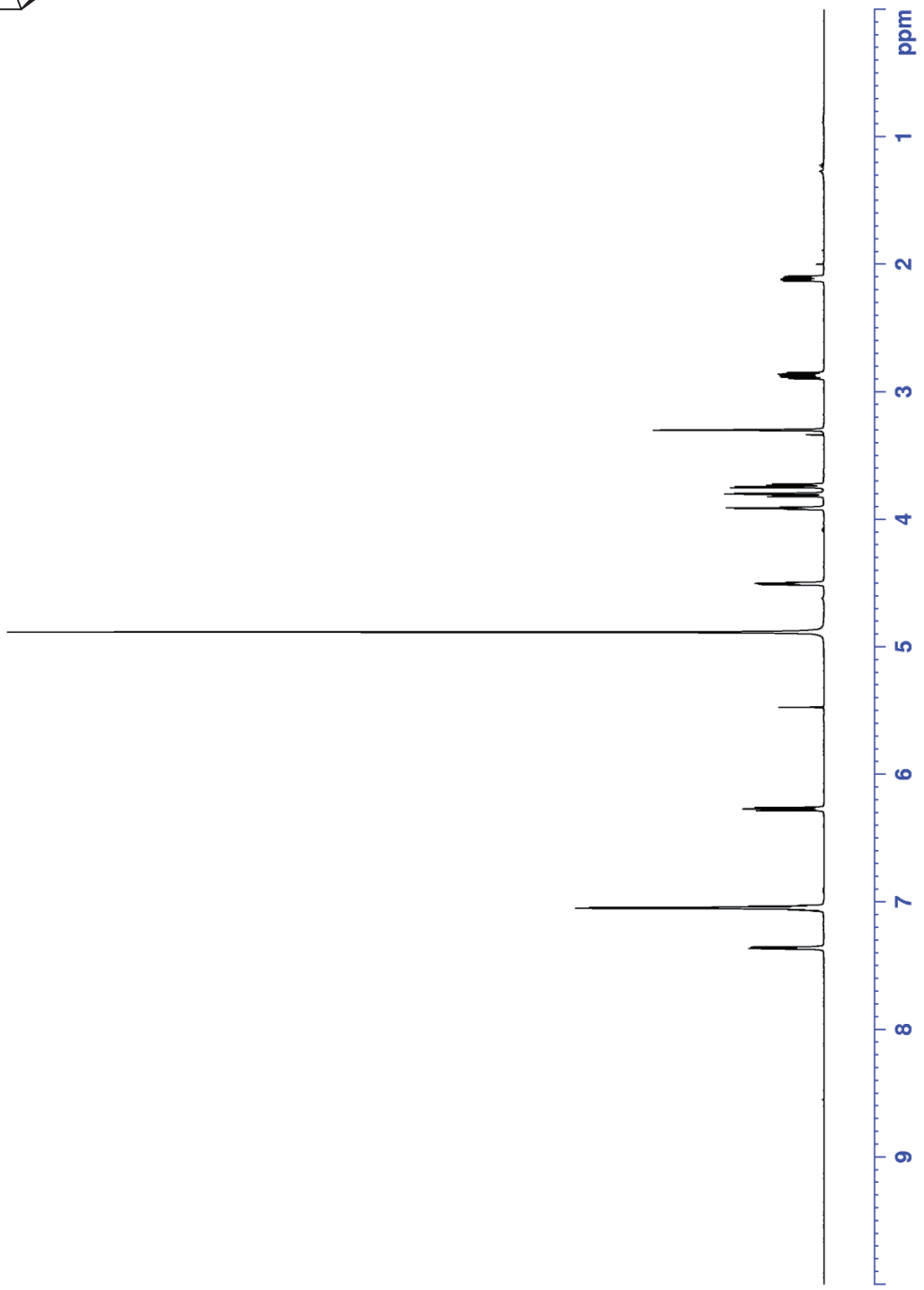


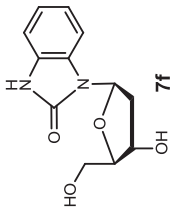
^{1}H NMR of **7a** in MeOD



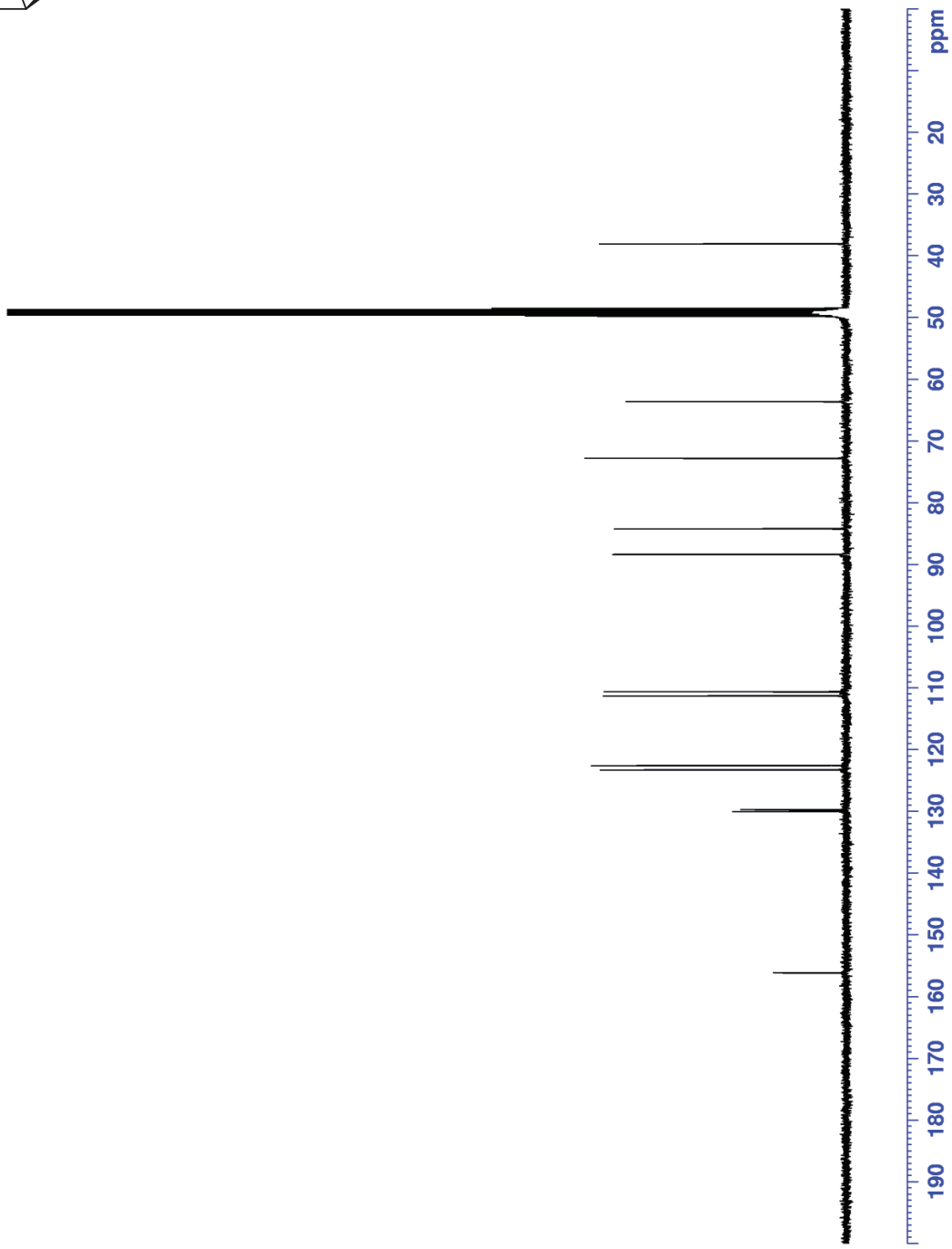


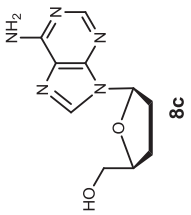
^{1}H NMR of **7f** in MeOD





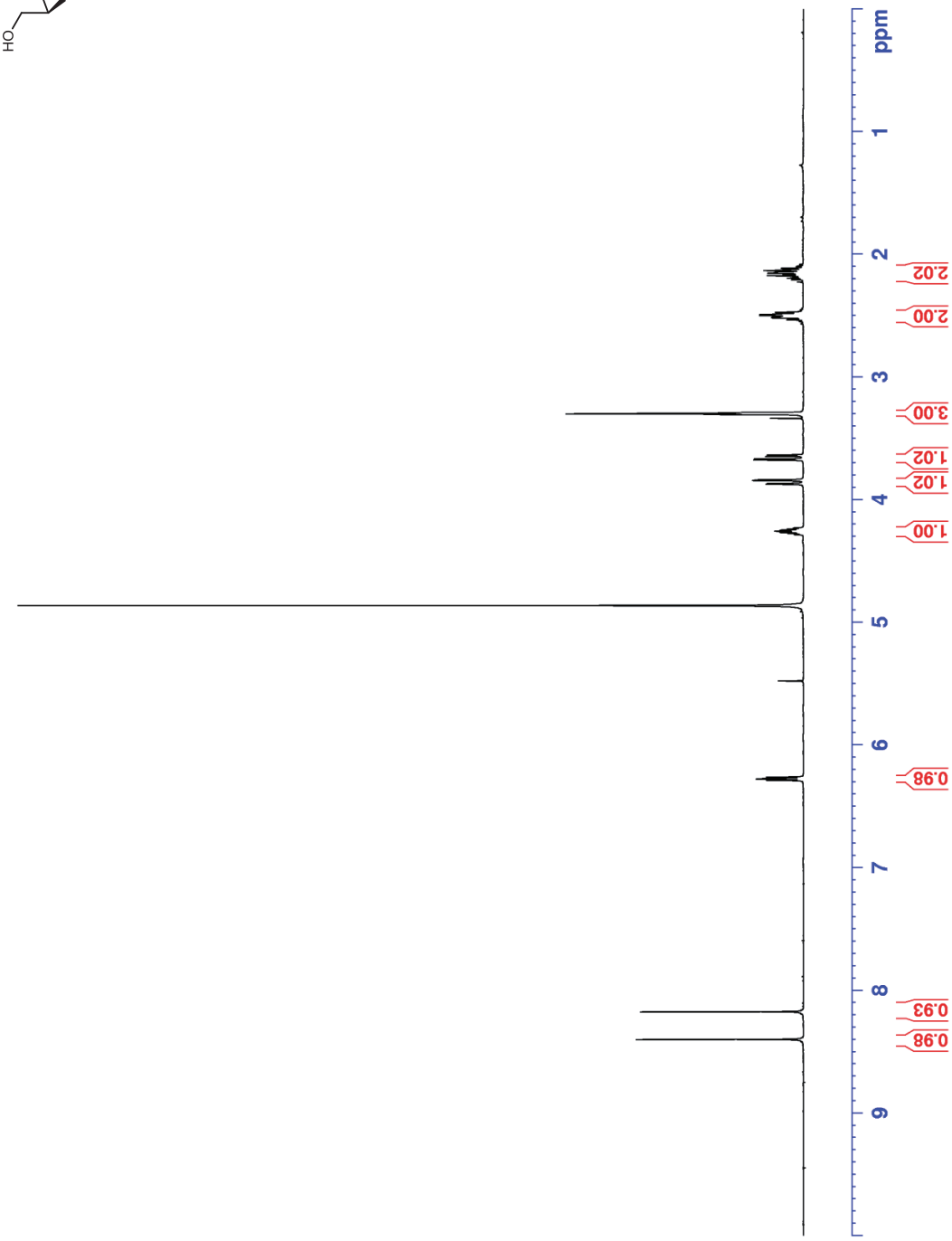
^{13}C NMR of **7f** in MeOD

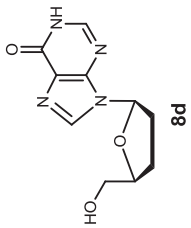




8c

^{1}H NMR of **8c** in MeOD





^{1}H NMR of **8d** in MeOD