Supporting Information for "Synthesis of a New Class of 5'-Functionalized Adenosine Using a Rh(II) Catalyzed 1,3-dipolar Cycloaddition"

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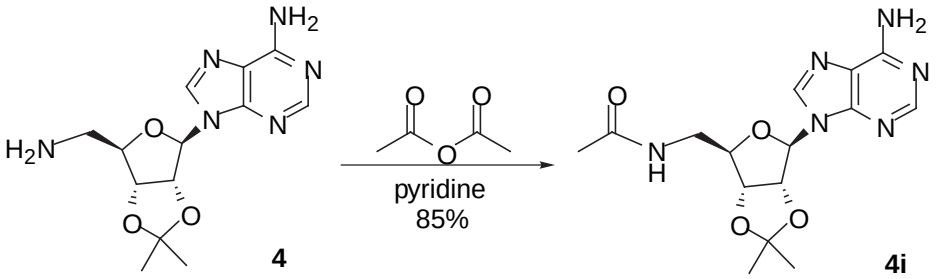
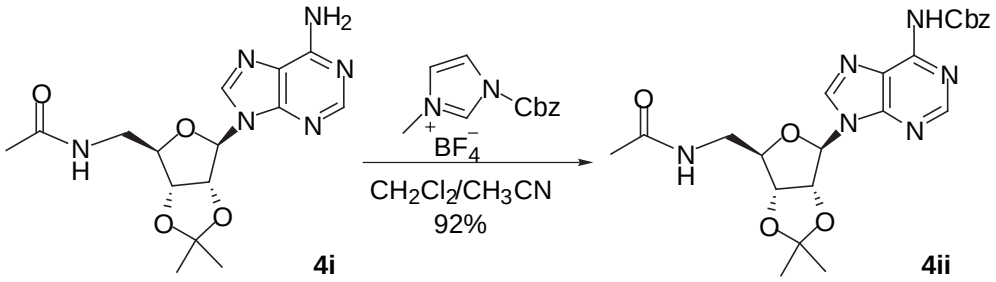
Materials and Methods. Unless otherwise specified, reactions were performed under a nitrogen atmosphere with exclusion of moisture in freshly distilled solvents. Pyridine, triethyl amine, and methylene chloride (CH_2Cl_2) were distilled from calcium hydride (CaH_2). Toluene was distilled from sodium/benzophenone. Chlorobenzene was distilled from potassium hydroxide (KOH). Dry dioxane was purchased from Aldrich. All other commerically available reagents were used as received. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using Si250F pre-coated plates from J.T. Baker (0.25mm). Flash column chromatography was performed on 32-63 D 60 Å silica gel from ICN SiliTech (ICN Biomedicals GmbH). ^{1}H and ^{13}C NMR spectra were taken on Bruker Avance DPX-500 or DPX-400 and GE Omega 300 FT spectrometers. Chemical shifts are reported using the following internal references: chloroform (^{1}H, δ 7.26 ppm, ^{13}C δ 77.5 ppm), or methanol (^{1}H, δ 3.30 ppm, ^{13}C δ 49.9 ppm). Infrared spectra were taken on a Midac M-1200 FTIR spectrometer. All optical rotation data were acquired on a Perkin-Elmer 341 Polarimeter (Na lamp, 589 nm, 20 °C). High resolution mass analysis was obtained at The University of Illinois Mass Spectrometry Center.

Preparation of 5'-acetamido-5'-deoxy-2',3'-isopropylideneadenosine 4i.



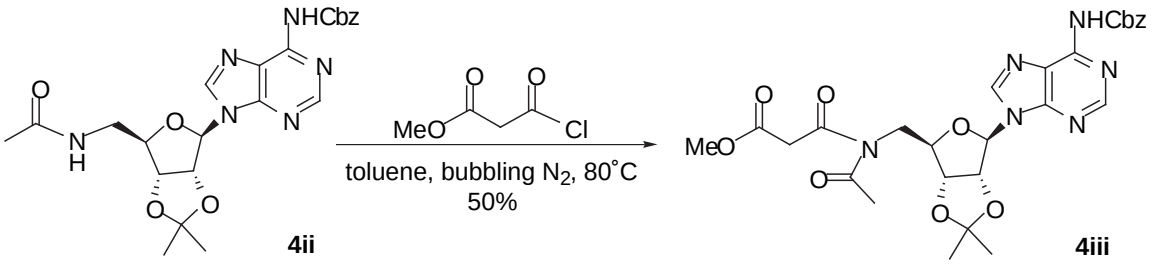
To a solution of 5'-amino-5'-deoxy-2',3'-isopropylideneadenosine **4** (5.0 g, 16.3 mmol) in dry pyridine was added acetic anhydride (1.67 mL, 15.0 mmol) at 0 ˚C. The mixture was stirred and warmed to room temperature until TLC indicated the complete disappearance of **4**. The solvent was then dried *in vacuo* and co-evaporated with toluene. The crude mixture was purified by silica gel column chromatography (MeOH:EtOAc, 0:1 then 1:3) to give 5'-acetamido-5'-deoxy-2',3'-isopropylideneadenosine **4i** (4.7 g, 85% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.62 (s, 3H), 2.15 (s, 3H), 3.29 (d, J = 13.6 Hz, 1H), 4.12 (m, 1H), 4.49 (br s, 1H), 4.84 (d, J = 6.2 Hz, 1H), 5.29 (t, J = 5.2 Hz, 1H), 5.83 (d, J = 4.8 Hz, 1H), 6.15-6.75 (br s, 2H), 7.86 (s, 1H), 8.24 (br s, 1H), 8.33 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 23.6, 25.7, 27.9, 41.5, 81.8, 82.6, 83.9, 92.9, 115.1, 121.4, 140.8, 149.2, 153.1, 156.6, 171.2; **IR** (thin film/NaCl) 3319 (br w), 3184, 2989, 2936, 1652, 1600, 1576, 1557, 1477, 1426, 1376, 1333, 1298, 1272, 1253, 1156, 1099, 1080, 913, 855, 732 cm^{-1}; $[\alpha]_D^{20}$ –209.9° (*c* 1.258, $CHCl_3$).

Preparation of 5'-acetamido-5'-deoxy-2',3'-isopropylidene-N^6-[phenylmethoxycarbonyl] adenosine 4ii.



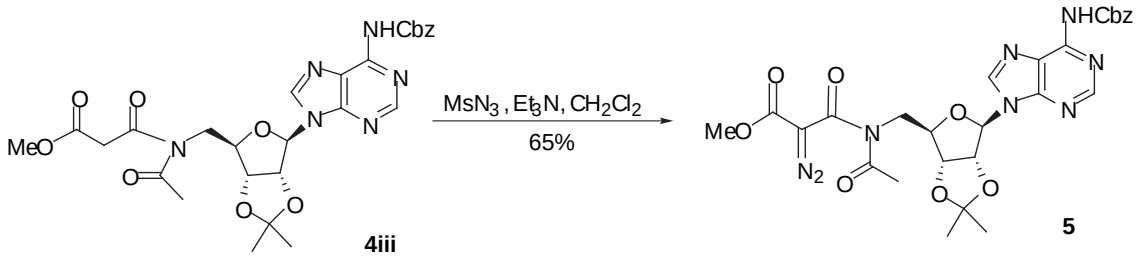
To a solution of 5'-acetamido-5'-deoxy-2',3'-isopropylideneadenosine **4i** (0.6 g, 1.7 mmol) in dry dichloromethane was added a solution of Rappaport's Cbz-transfering agent (1-((benzyloxy)carbonyl)-3-methlyimidazolium tetrafluoroborate, 2.1 g, 6.9 mmol) in dry acetonitrile at room temperature. The mixture was stirred for 20 hrs until TLC indicated the complete disappearance of **4i**. The solvent was then dried *in vacuo*, and the crude was purified by silica gel column chromatography (100% EtOAc) to give **4ii** (0.76 g, 92% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.62 (s, 3H), 2.10 (s, 3H), 3.33 (dt, J = 2.9, 14.4Hz, 1H), 4.04 (ddd, J = 2.9, 8.2, 14.4 Hz, 1H), 4.47 (dd, J = 2.9, 5.8 Hz, 1H), 4.86 (dd, J = 2.9, 6.2 Hz, 1H), 5.27 (dd, J = 4.2, 6.2 Hz, 1H), 5.30 (dd, J =12.3, 25.0 Hz, 1H), 5.78 (d, J = 4.2 Hz, 1H), 7.35-7.44 (m, 5H), 7.64 (d, J = 5.8 Hz, 1H), 7.96 (s, 1H), 8.76 (s, 1H), 9.25 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.1, 23.2, 25.4, 38.9, 65.9, 79.3, 80.4, 81.8, 90.2, 112.9, 121.3, 126.7, 133.2, 140.8, 148.2, 148.9, 150.5, 168.7; **IR** (thin film/NaCl) 3276, 3199, 3067, 3034, 2986, 2937, 1753, 1661, 1615, 1585, 1540, 1465, 1374, 1214, 1157, 1098, 1077, 733 cm^{-1}; $[\alpha]_D^{20}$ –122.3° (*c* 2.06, $CHCl_3$).

Preparation of imide adenosine 4iii.



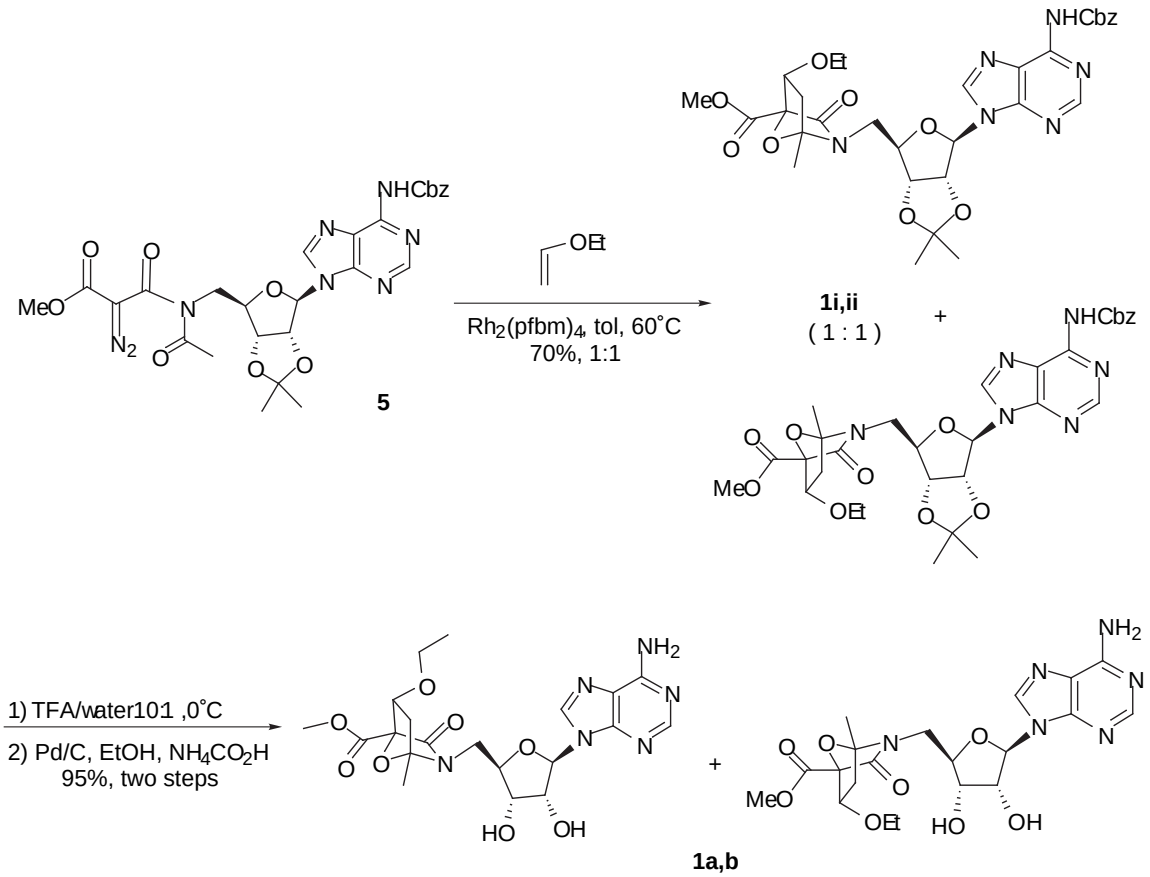
A solution of 5'-acetamido-5'-deoxy-2',3'-isopropylidene-N^6-[phenylmethoxycarbonyl] adenosine **4ii** (700 mg, 1.5 mmol) in dry toluene (50 mL) was brought to reflux. Methyl malonylchloride (0.39 mL, 3.6 mmol) was added dropwise while N_2 was bubbled through the reaction mixture. The reaction was continued for 45 minutes until TLC indicated the disappearance of **4ii**. The reaction was cooled to room temperature and 150 mL of dichloromethane was added. The mixture was washed with sat. $NaHCO_3$ (2 x 100 mL) and dried over Na_2SO_4. The crude mixture was purified by silica gel column chromatography (hexanes:EtOAc, 1:1 then 0:1) to give a mixture of overacylated product and **4iii**. The mixture was stirred in THF/water overnight and purified by silica gel column chromatography to give **4iii** (438 mg, 50% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.61 (s, 3H), 2.02 (s, 3H), 3.68 (s, 3H), 3.76 (dd, J = 16.3, 42.1 Hz, 2H), 3.97 (dt, J = 7.6, 15.1 Hz, 1H), 4.28 (dd, J = 3.4, 15.1 Hz, 1H), 4.42 (dt, J = 3.7, 7.6 Hz, 1H), 5.11 (dd, J = 4.5, 6.5 Hz, 1H), 5.31 (s, 2H), 5.32 (m, 1H), 6.00 (d, J = 2.9 Hz, 1H), 7.35-7.44 (m, 5H), 8.00 (s, 1H), 8.76 (s, 1H), 8.93 (br s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 25.1, 25.4, 27.2, 45.7, 46.8, 52.3, 67.9, 82.0, 83.8, 85.3, 90.0, 115.2, 122.5, 128.6, 135.3, 142.3, 149.9,150.5, 150.8, 153.0, 167.7, 168.7, 173.5; **IR** (thin film/NaCl) 3253, 3197, 3187, 3118, 3032, 2988, 2954, 2849, 1747, 1709, 1613, 1586, 1546, 1530, 1464, 1374, 1328, 1214, 1157, 1095, 1076, 733 cm^{-1}; $[\alpha]_D^{20}$ –45.9° (*c* 0.44, $CHCl_3$).

Preparation of diazo adenosine 5.



To a solution of **4iii** (70 mg, 0.12 mmol) in dry dichloromethane was added mesyl azide (75 mg, 0.6 mmol) and triethyl amine (22 µL, 0.15 mmol). The reaction was stirred at room temperature until TLC indicated the complete disappearance of **4iii**. The solvent was then dried *in vacuo*, and the crude mixture was purified by silica gel column chromatography (hexanes:EtOAc, 1:3 then 1:1) to give **5** (48 mg, 65% yield) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.49 (s, 3H), 1.69 (s, 3H), 2.23 (s, 3H), 3.80 (s, 3H), 3.85 (dd, J = 9.1, 14.9 Hz, 2H), 4.27 (dd, J = 3.4, 14.8 Hz, 1H), 4.66 (dt, J = 3.2, 14.8 Hz, 1H), 5.22 (dd, J = 3.2, 6.3 Hz, 1H), 5.42 (dd, J = 12.1, 25.1 Hz, 2H), 5.55 (dd, J = 1.8, 6.3 Hz, 1H), 6.12 (d, J = 1.8 Hz, 1H), 7.47-7.57 (m, 5H), 8.08 (s, 1H), 8.81 (s, 1H), 8.85 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 24.2, 25.8, 27.5, 31.3, 48.8, 53.0, 68.4, 82.7, 84.5, 87.0, 91.1, 115.1, 122.9, 129.1, 135.7, 143.0, 149.9,150.2, 150.6, 151.1, 153.3, 160.5, 167.0, 172.2; **IR** (thin film/NaCl) 3253, 3197, 3187, 3118, 3032, 2988, 2958, 2143, 1755, 1723, 1692, 1665, 1612, 1586, 1462, 1365, 1329, 1309, 1214, 1156, 1094, 1069 cm^{-1}; $[\alpha]_D^{20}$ +85.4° (*c* 0.328, $CHCl_3$).

Preparation of 1a,b.

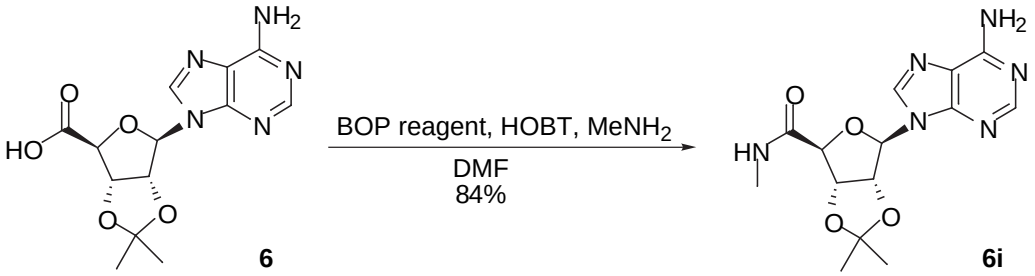


To a solution of diazo adenosine **5** (40 mg, 0.066 mmol) in dry toluene was added ethyl vinyl ether (excess), $Rh_2(pfbm)_4$ (1mg, 1mol%), and 4Å molecular sieves under nitrogen with exclusion of moisture. The reaction was stirred at 70 ˚C until TLC indicated the complete disappearance of **5**. The solvent was then dried *in vacuo*, and the crude mixture was purified by silica gel column chromatography (hexanes:EtOAc, 1:3, 1:1, and 0:1) to give cycloadducts **1i,ii** (30 mg, 70% yield) as an inseparable mixture of diastereomers. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.10-1.14 (m, 3H), 1.34 (2 s, 3H), 1.56 (s, 3H), 1.71-1.91 (2 dd, J = 2.1, 12.4 Hz, 1H), 2.06-2.12 (m, 1H), 2.13 (s, 3H), 3.32-3.35 (m, 1H), 3.46-3.51 (m, 1H), 3.65-3.90 (m, 2H), 3.85 (s, 3H), 4.34-4.38 (m, 2H), 5.04-5.10 (m, 1H), 5.27 (s, 2H), 5.35-5.41 (2 dd, J = 2.3, 2.8, 6.3, 6.5 Hz, 1H), 5.97-5.98 (2 d, J = 2.8, 2.3 Hz, 1H), 7.31-7.40 (m, 5H), 8.02 (2 s, 1H), 8.75 (s, 1H), 9.18 (2 s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 15.3, 17.6, 18.2, 42.3, 42.4, 43.4, 43.8, 53.2, 66.7, 66.8, 68.0, 78.8, 79.4, 82.3,

82.6, 83.6, 83.8, 85.3, 85.7, 87.7, 87.8, 90.6, 91.2, 95.5, 95.6, 114.8, 115.2, 122.7, 122.9, 135.5, 142.4, 142.4, 150.0, 150.1, 150.8, 151.0, 151.2, 153.1, 153.2, 166.1, 168.0, 168.8; **IR** (thin film/NaCl) 3253, 3197, 3187, 3118, 3032, 2984, 2958, 1756, 1731, 1613, 1586, 1527, 1463, 1410, 1376, 1329, 1306, 1259, 1213, 1156, 1076, 996, 869, 738 cm^{-1}; **HRMSFAB** [M+H$^+$]: 653.2569, calcd for $C_{31}H_{37}N_6O_{10}$: 653.2571.

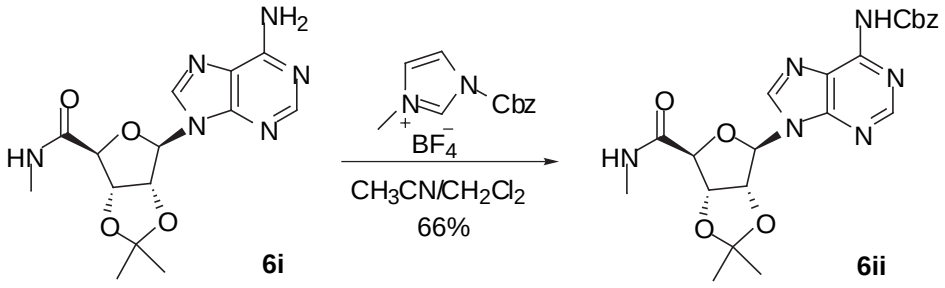
A solution of **1i,ii** (98 mg, 0.15 mmol) in 500 µL of 10:1 TFA/water was stirred at 0°C until TLC indicated the disappearance of the starting material. The mixture was dried and purified by reverse-phase HPLC. The fractions containing the two separated products were lyophilized to give the acetonide-deprotected intermediates as white solids. Both intermediates were then mixed in separate reaction vials with ammonium formate (47 mg, 0.75 mmol) and palladium on carbon in 500 µL of EtOH and stirred until TLC indicated the disappearance of the starting material. Both reaction mixtures were dried and purified by silica gel column chromatography (EtOH:EtOAc 1:5) to give **1a,b** as white solids. The mixture **1a,b** was further separated by reverse-phase HPLC on a Rainin C_{18} column (Varian, #R0089200C5) using a MeOH/water eluent system. **1a** (first on reverse-phase HPLC) **^{1}H NMR** (d_4-MeOH, 400 MHz) δ 0.93 (t, J = 7.2 Hz, 3H), 1.48 (s, 3H), 1.74 (dd, J = 2.3 Hz, 12.4 Hz, 1H), 2.11 (q, J = 8.2 Hz, 12.4 Hz, 1H), 3.36-3.66 (m, 4H), 3.74(dd, J = 3.5 Hz, 5.5 Hz, 1H), 4.04-4.08 (m, 1H); 4.19-4.22 (br. s, 1H), 4.34 (dd, J = 2.3 Hz, J = 8.2 Hz, 1H), 4.75 (m, 1H), 5.87 (d, J = 5.5 Hz, 1H), 8.10 (s, 1H), 8.21 (s, 1H); **^{13}C NMR** (d_4-MeOH, 100 MHz) δ 15.8, 18.8, 43.8, 43.9, 53.7, 68.0, 73.4, 74.8, 80.0, 84.3, 89.1, 90.4, 97.9, 142.1, 144.9, 151.1, 154.3, 157.8, 171.7; **HRMSFAB** [M+H$^+$]: 479.1891, calcd for $C_{20}H_{27}N_6O_8$: 479.1812; $[\alpha]_D^{20}$ +25° (*c* 0.48, MeOH). **1b** (second on reverse-phase HPLC) **^{1}H NMR** (d_4-MeOH, 400 MHz) δ 1.40 (t, J = 7.2 Hz, 3H), 1.74 (s, 3H), 2.26 (dd, J = 2.3 Hz, 12.7 Hz, 1H), 2.41 (dd, J = 8.2 Hz, 12.7 Hz, 1H), 3.76-3.95 (m, 3H), 4.11 (s, 3H), 4.18 (dd, J = 3.2 Hz, 14.8 Hz, 1H), 4.38-4.42 (m, 1H), 4.64 (t, J = 5.2 Hz, 1H), 4.69 (dd, J = 2.3 Hz, J = 8.2 Hz, 1H), 5.06 (t, J = 5.1 Hz, 1H), 6.26 (d, J = 5.1 Hz, 1H), 8.48 (s, 1H), 8.58 (s, 1H); **^{13}C NMR** (d_4-MeOH, 100 MHz) δ 15.9, 18.4, 44.1, 44.1 53.7, 68.0, 73.6, 74.9, 80.5, 84.8, 89.2, 91.1, 98.1, 121.1, 142.2, 151.0, 154.4, 157.8, 167.8, 171.1; **HRMSFAB** [M+H$^+$]: 479.1891, calcd for $C_{20}H_{27}N_6O_8$: 479.1812; $[\alpha]_D^{20}$ +5.3° (*c* 0.38, MeOH).

Preparation of amide adenosine 6i.



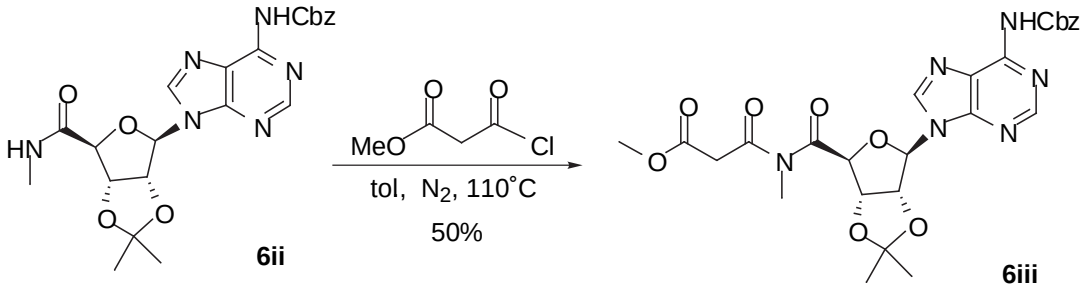
To a solution of 5'-carboxy-2',3'-isopropylideneadenosine **6** (6.2 g, 19.3 mmol) in DMF was added methyl amine (7 mL, 81.3 mmol), BOP reagent (11.0 g, 24.9 mmol), and 1-hydroxybenzyltriazole hydrate (3.0 g, 22.2 mmol) at room temperature. The mixture was stirred for 4 hrs. After solvent removal, the residue was combined with 200 mL of 1:1 dichloromethane:ether. The resulting solution was filtered to give **6i** (5.4g, 84% yield) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 1.33 (s, 3H), 1.54 (s, 3H), 2.29 (d, J = 4.5 Hz, 2H), 4.55 (s, 1H), 5.34 (s, 2H), 6.31 (s, 1H), 7.33 (br s, 2H), 7.59 (br s, 1H), 8.08 (s, 1H), 8.27 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 25.4, 25.4, 27.0, 83.4, 383.6, 86.1, 89.9, 113.3, 119.2, 140.6, 149.2, 152.8, 156.4, 169.2; **IR** (KBr pellet) 3452, 3341, 3226, 3104, 2985, 2940, 2590, 2432, 1671, 1644, 1615, 1601, 1584, 1551, 1482, 1428, 1412, 1374, 1339, 1295, 1270, 1252, 1231, 1212, 1156, 1088, 1059, 864 cm^{-1}; $[\alpha]_D^{20}$ –45.9° (*c* 0.44, DMSO).

Preparation of *exo*-Cbz amide adenosine 6ii.



To a solution containing **6i** (5.2 g, 15.6 mmol) and $NaHCO_3$ (4 g, 47.6 mmol) in 100 mL dry dichloromethane was added the Rappaport's Cbz-transfering agent (18.7 g, 61.6 mmol) in 25 mL dry acetonitrile at room temperature with exclusion of moisture. The mixture was stirred for 22 hrs until TLC indicated the complete disappearance of **6i**. The solvent was then dried *in vacuo*, and the crude mixture was purified by silica gel column chromatography (100% EtOAc then 1:10 MeOH:EtOAc) to give **6ii** (4.8 g, 66% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.56 (s, 3H), 2.48 (d, J = 4.9 Hz, 2H), 4.66 (d, J = 1.9 Hz, 1H), 5.24 (m, 2H), 5.28 (dd, J = 3.0 , 6.3 Hz, 1H), 5.36 (dd, J = 1.9, 6.3 Hz, 1H), 5.98 (d, J = 3.0 Hz, 1H), 6.59 (br m, 1H), 7.29-7.39 (m, 5H), 7.92 (s, 1H), 8.66 (s, 1H), 8.78 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 25.5, 26.1, 27.5, 68.5, 83.1, 84.0, 86.7, 92.5, 115.1, 123.0, 129.1, 129.2, 135.6, 142.8, 150.4, 150.9, 151.3, 153.4, 169.5; **IR** (thin film/NaCl) 3302, 3245, 3093, 3032, 2986, 2938, 1754, 1672, 1613, 1588, 1535, 1500, 1463, 1411, 1383, 1326, 1303, 1213, 1156, 1090, 972, 911, 869, 852, 796, 748, 736 cm^{-1}; $[\alpha]_D^{20}$ –31.6° (*c* 0.76, $CHCl_3$).

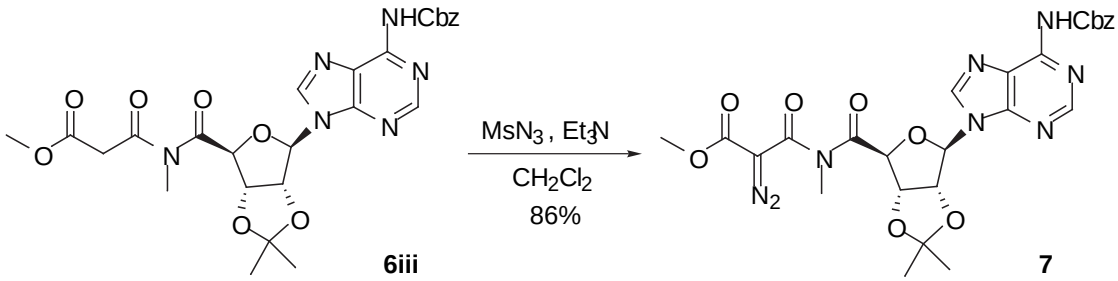
Preparation of imide adenosine 6iii.



To a refluxing solution of **6ii** (1.0g, 2.14 mmol) in dry toluene with nitrogen bubbling through the reaction mixture was added methyl malonylchloride (0.46 mL, 4.27 mmol). The reaction was stirred until TLC indicated the complete disappearance of **6ii**. The solvent was then dried *in vacuo*, and the crude mixture was purified by silica gel column chromatography (hexanes:EtOAc, 1:1 then 0:1) to give a mixture of over-acylated product and mono-acylated **6iii**. The mixture was dissolved in wet THF and stirred for 6

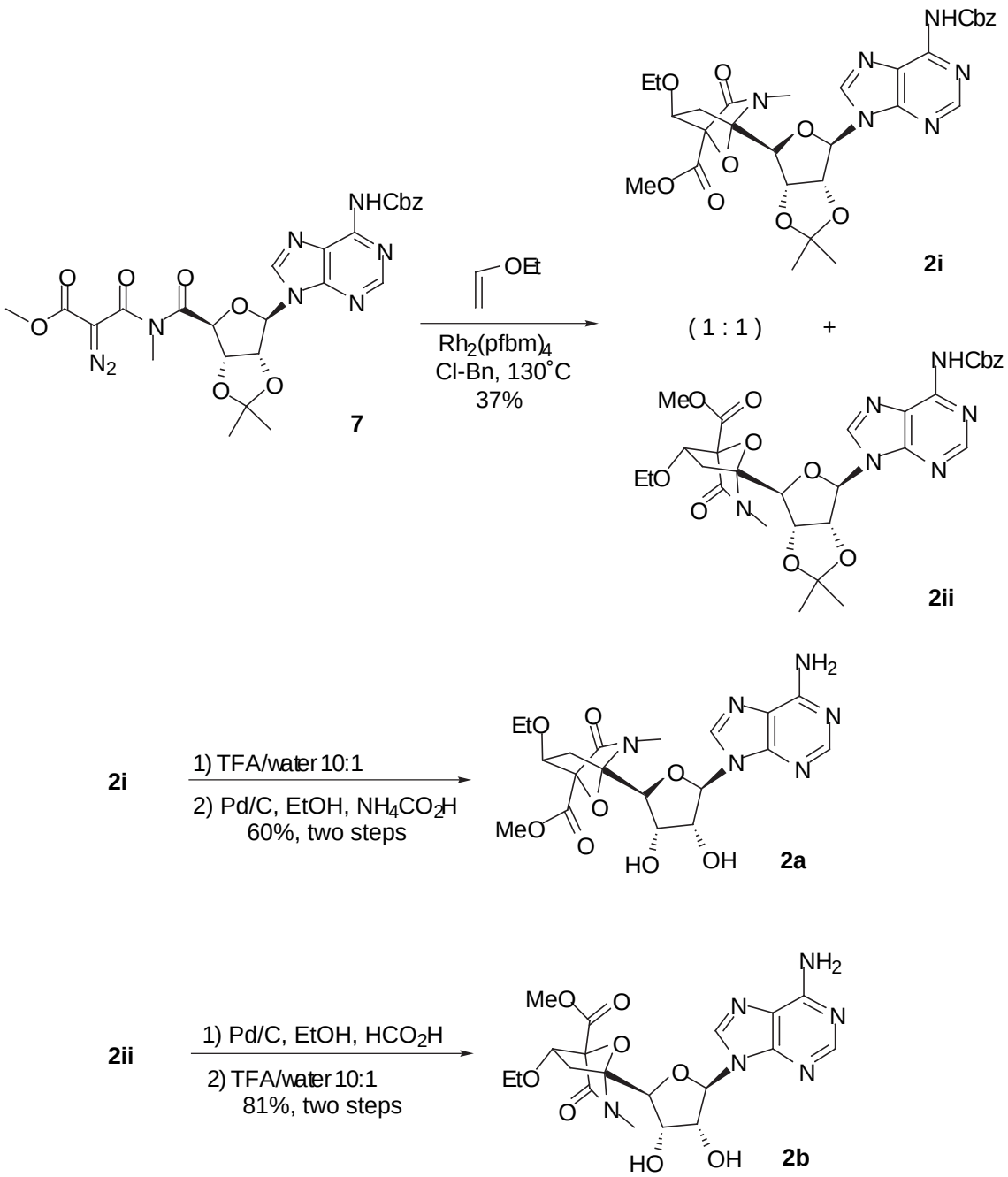
hrs. The solvent was then removed, and the crude mixture was purified by silica gel column chromatography to give **6iii** (0.8 g, 50% yield) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.43 (s, 3H), 1.64 (s, 3H), 3.11 (s, 3H), 3.52-3.68 (dd, J = 16.3, 26.1 Hz), 3.68 (s, 3H), 5.28 (s, 2H), 5.32 (d, J = 1.5 Hz, 1H), 5.48-5.50 (2 d, J = 6, 7.1 Hz, 2H), 6.25 (s, 1H), 7.33-7.42 (m, 5H), 8.12 (s, 1H), 8.67 (s, 1H), 8.86 (br s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 25.4, 27.2, 32.1, 45.3, 53.0, 68.3, 84.0, 84.3, 89.3, 92.0, 114.6, 122.4, 129.1, 135.7, 142.9, 150.0, 151.0, 151.4, 153.1, 167.4, 169.0, 172.2; **IR** (thin film/NaCl) 2987, 1748, 1702, 1614, 1587, 1532, 1464, 1437, 1384, 1376, 1336, 1303, 1213, 1157, 1085, 1056, 974, 871, 734 cm^{-1}; $[\alpha]_D^{20}$ –27.7° (*c* 0.92, $CHCl_3$).

Preparation of diazo adenosine 7.



6iii **7**

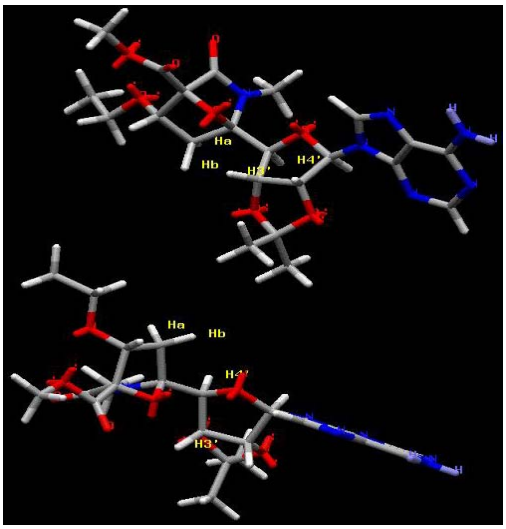
To a solution of **6iii** (0.77 g, 1.31 mmol) in dry dichloromethane was added mesyl azide (0.92 g, 7.88 mmol) and triethyl amine (0.18 mL, 1.31 mmol). The reaction was stirred at room temperature until TLC indicated the complete disappearance of **6iii**. The solvent was then dried *in vacuo*, and the crude mixture was purified by silica gel column chromatography (hexanes:EtOAc, 1:3 then 1:1) to **7** (0.67 g, 86% yield) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.56 (s, 3H), 2.83 (s, 3H), 3.61 (s, 3H), 5.23-5.24 (m, 3H), 5.33 (dd, J = .9, 5.9 Hz, 1H), 5.52 (dd, J = 1.3, 5.9 Hz, 1H), 6.18 (s, 1H), 7.27-7.37 (m, 5H), 8.03 (s, 1H), 8.63 (s, 1H), 8.70 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 25.6, 27.2, 34.1, 53.0, 68.2, 72.0, 77.2, 77.4, 77.7, 84.1, 85.0, 88.1, 92.1, 114.5, 122.6, 129.0, 129.1, 135.8, 142.4, 150.0, 151.2, 151.4, 153.3, 160.2, 167.1, 172.2; **IR** (thin film/NaCl) 2990, 2146, 1754, 1723, 1656, 1613, 1589, 1528, 1463, 1437, 1383, 1376, 1331, 1298, 1212, 1156, 1073, 973, 869, 791, 756 cm^{-1}; $[\alpha]_D^{20}$ –55.0° (*c* .6, $CHCl_3$).

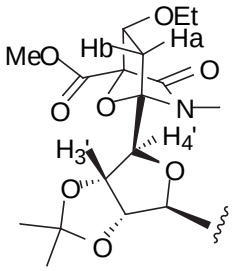


Preparation of 2a and 2b.

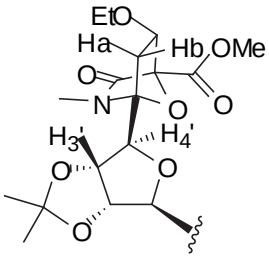
To a solution of diazo adenosine **7** (133 mg, 0.224 mmol) in dry chlorobenzene was added ethyl vinyl ether (807 mg, 11.2 mmol), $Rh_2(pfbm)_4$ (1 mg, 0.4 mol%), and 4Å molecular sieves under nitrogen with exclusion of moisture. The reaction was stirred at

130 ˚C until TLC indicated the complete disappearance of **7**. The solvent was then dried *in vacuo*, and the crude mixture was purified by silica gel column chromatography (hexanes:EtOAc, 1:3, 1:1, and 0:1) to give **2i** and **2ii** (56 mg, 37% combined yield) as white solids. **2i** eluted first. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.04 (t, J = 6.8 Hz, 3H), 1.32 (s, 3H), 1.54 (d, J = 12.4 Hz, 1H), 1.59 (s, 3H), 2.41 (dd, J = 8.0, 12.4 Hz, 1H), 2.82 (s, 3H), 3.36-3.40 (m, 1H), 3.61-3.66 (m, 1H), 3.84 (s, 3H), 4.120 (d, J = 8.0 Hz, 1H), 4.59 (d, J= 2.3 Hz, 1H), 5.10 (dd, J = 2.3, 6.2 Hz, 1H), 5.21 (dd, J = 2.8, 6.2 Hz, 1H), 5.24 (s, 2H), 6.38 (d, J = 2.8 Hz, 1H), 7.28-7.39 (m, 5H), 8.11 (s, 1H), 8.20 (s, 1H), 8.71 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 15.4, 25.6, 26.6, 27.0, 29.7, 36.9, 53.6, 67.3, 68.3, 78.8, 79.4, 80.5, 83.3, 84.6, 87.7, 90.7, 95.8, 114.6, 115.5, 122.1, 129.0, 135.7, 141.5, 149.7, 151.1, 151.7, 153.6, 165.7, 168.1; **IR** (thin film/NaCl) 3032, 2980, 2957, 2899, 1756, 1734, 1614, 1588, 1532, 1463, 1386, 1331, 1212, 1155, 1074, 993, 944, 866, 734 cm^{-1}; **HRMSFAB** [$M+H^+$]: 639.2413, calcd for $C_{31}H_{37}N_6O_{10}$: 639.2415; $[\alpha]_D^{20}$ –86.3° (*c* 1.02, $CHCl_3$). **2ii** eluted second. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.16 (t, J = 6.8 Hz, 3H), 1.42 (s, 3H), 1.68 (s, 3H), 1.79 (dd, J = 2.2, 12.5 Hz, 1H), 2.47 (dd, J = 8.2, 12.5 Hz, 1H), 2.90 (s, 3H), 3.53-3.56 (m, 1H), 3.75-3.79 (m, 1H), 3.88 (s, 3H), 4.44 (dd, J = 8.0, 12.5 Hz, 1H), 4.64 (d, J= 3.3 Hz, 1H), 5.06 (dd, J = 3.3, 6.3 Hz, 1H), 5.28 (dd, J = 2.3, 6.3 Hz, 1H), 5.31 (s, 2H), 6.42 (d, J = 2.3 Hz, 1H), 7.36-7.47 (m, 5H), 8.06 (br s, 1H), 8.28 (s, 1H), 8.79 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 15.1, 25.3, 26.1, 27.2, 29.3, 38.2, 53.2, 67.0, 67.9, 78.2, 79.8, 83.1, 84.9, 87.5, 90.7, 96.2, 115.3, 122.0, 128.6, 128.7, 135.4, 141.2, 149.3, 150.6, 150.8, 153.1, 165.3, 167.1; **IR** (thin film/NaCl) 3032, 2981, 2957, 2900, 1756, 1614, 1588, 1530, 1463, 1383, 1332, 1214, 1156, 1075, 987, 913, 867, 732 cm^{-1}; **HRMSFAB** [$M+H^+$]: 639.2413, calcd for $C_{31}H_{37}N_6O_{10}$: 639.2415; $[\alpha]_D^{20}$ +4.8° (*c* 0.42, $CHCl_3$). The absolute stereochemistry is determined by NOESY and Monte-Carlo conformational search (3000 steps, MM2* forcefield, chloroform solvent set) in MACROMODEL 5.0





2i

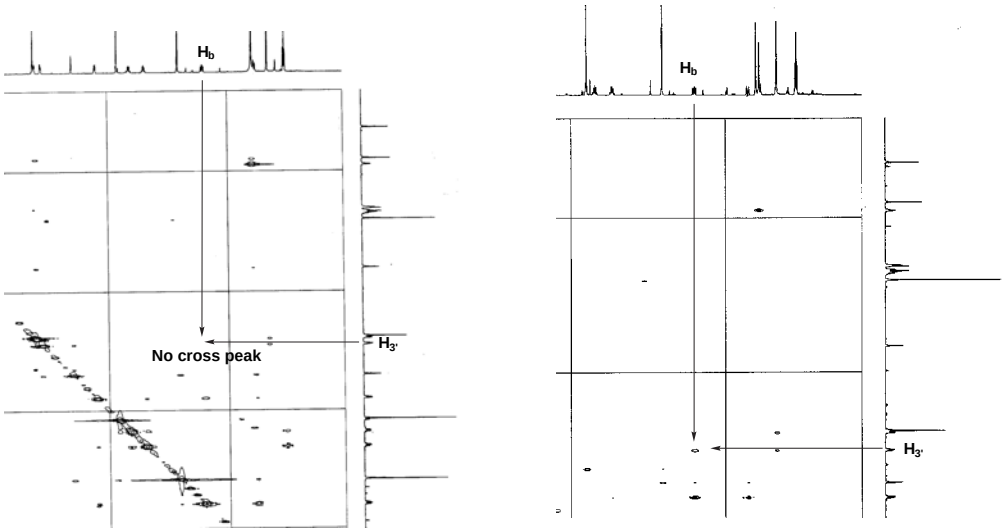


2ii

Table 1. Atom distances from the two global minima found for the **2i** and **2ii**.

	Distance to H4' (Å)	Distance to H3' (Å)
2i (bottom)	$H_aH_{4'}$ = 2.938	$H_aH_{3'}$ = 4.798
	$H_bH_{4'}$ = 3.017	$H_bH_{3'}$ = **4.618**
2ii (top)	$H_aH_{4'}$ = 2.925	$H_aH_{3'}$ = 4.088
	$H_bH_{4'}$ = 3.008	$H_bH_{3'}$ = **2.693**

In both isomers **2i** and **2ii**, the distances $H_aH_{4'}$, $H_aH_{3'}$, and $H_bH_{4'}$ are comparable. However, the distance H_bH_3 of **2ii** is significantly shorter than that of **2i**, indicating that the noe in **2ii** would be stronger than that of **2i**. In the NOESY spectrum, **2ii** indeed showed cross peaks between H_b and H_3, while for **2i** this crossing was missing.

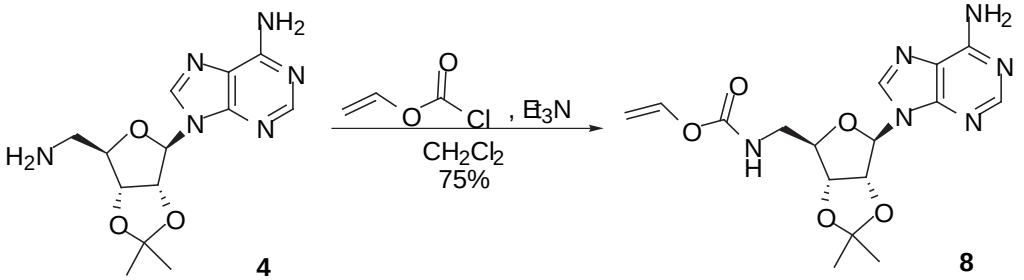


2i **2ii**

To deprotect, **2i** (5 mg, 0.0078mmol) was dissolved in 500 μL of 10:1 TFA/water solution at 0 °C and warmed to room temperature until TLC indicated the disappearance of the starting material. The crude mixture was then dried *in vacuo*, and purified by silica gel column chromatography (EtOAc 100% and then EtOH:EtOAc 1:5). The intermediate was combined with ammonium formate (2.1 mg, 0.033 mmol) and palladium on carbon in 500 μL of EtOH and stirred until TLC indicated the disappearance of the starting material. The mixture was dried and purified by reverse-phase HPLC to give **2a** as a white solid (2.2 mg, 60% yield). **2ii** (4 mg, 0.0062 mmol) was deprotected similarly to give **2b** (2.1 mg, 81% yield), except that the order of removal was reversed while using formic acid as the source of hydrogen. **2a** ^{1}H NMR (d_4-MeOH, 500 MHz) δ 1.00 (t, J = 7.0 Hz, 3H), 1.64 (dd, J = 2.1 Hz, 12.7 Hz, 1H), 2.52 (dd, J = 8.4 Hz, 12.7 Hz, 1H), 2.81 (s, 3H), 3.39-3.43 (m, 2H), 3.58-3.61 (m, 2H), 3.81 (s, 3H), 4.35 (dd, J = 2.1 Hz, 8.4, 1H), 4.44 (dd, J= 3 Hz, 5 Hz, 1H), 4.56 (t. J = 5.6 Hz, 1H), 6.08 (d, J = 5.6 Hz, 1H), 7.4-7.35 (m, 5H), 8.11 (s, 1H), 8.20 (s, 1H); **^{13}C NMR** (d_4-MeOH, 100 MHz) δ 15.8, 27.1, 37.8, 53.9, 68.2, 71.7, 76.3, 80.8, 82.8, 89.0, 89.1, 97.8, 120.4, 140.7, 151.5, 154.5, 157.8, 167.4, 170.7; **HRMSFAB** [M+H$^+$]: 465.1736, calcd for $C_{19}H_{25}N_6O_8$: 465.1734; $[\alpha]_D^{20}$ -84.6° (*c* 0.26, $CHCl_3$). **2b ^{1}H NMR** (d_4-MeOH, 500 MHz) δ 1.22 (t, J = 7.3 Hz, 3H), 1.84 (d, J = 12.5 Hz, 1H), 2.50(dd, J = 8.1 Hz, 12.5 Hz, 1H), 3.02 (s, 3H), 3.43-3.46 (m, 1H), 3.60-3.63 (m, 1H), 4.02 (s, 3H), 4.56 (d, 8.5 Hz, 1H), 4.61 (m, 1H), 4.69 (m, 1H),

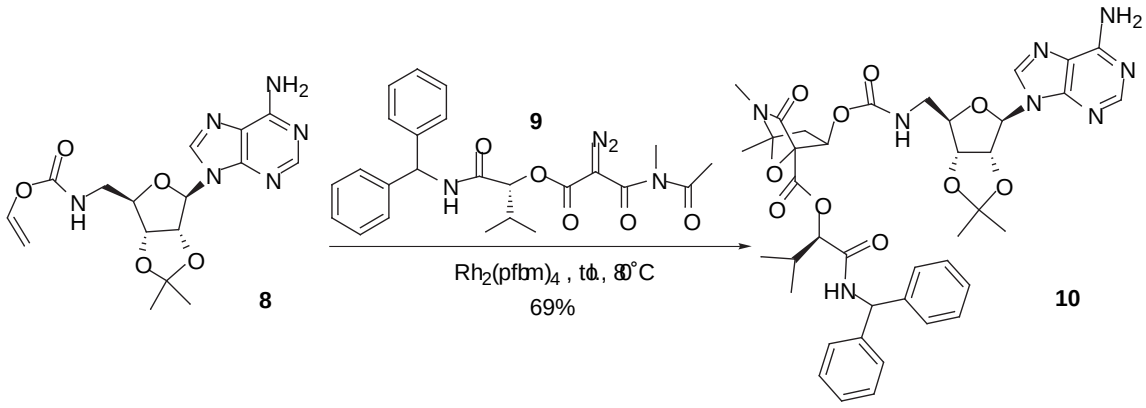
4.76 (t, J = 5.9 Hz, 1H), 6.27 (d, J = 5.9 Hz, 1H), 8.32 (s, 1H), 8.40 (s, 1H); **^{13}C NMR** (d_4-MeOH, 100 MHz) δ 15.9, 26.6, 39.0, 54.0, 68.3, 71.7, 77.1, 79.9, 81.8, 89.0, 89.4, 90.1, 98.9, 141.1, 153.3, 167.3, 170.2; **HRMSFAB** [M+H$^+$]: 465.1736, calcd for $C_{19}H_{25}N_6O_8$: 465.1734; $[\alpha]_D^{20}$ -75° (*c* 0.12, MeOH).

Preparation of vinylcarbamate adenosine 8.



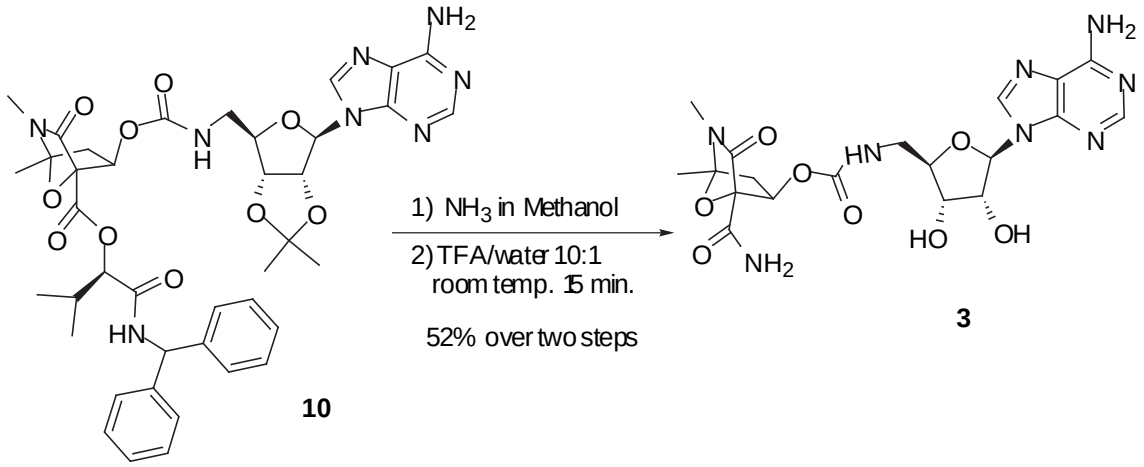
To a solution of **4** (0.59 g, 1.9 mmol) in 100 mL dry dichloromethane was added vinyl chloroformate (0.15 mL, 1.8 mmol) and dry triethyl amine (0.74 mL, 5.3 mmol) at -78 ˚C with exclusion of moisture. The mixture was allowed to warm to room temperature and stirred for 10 hrs until TLC indicated the complete disappearance of **4**. The reaction mixture was then washed with sat. $NaHCO_3$ (3 x 50 mL) and dried over Na_2SO_4. The crude mixture was then dried *in vacuo*, and purified by silica gel column chromatography (100% EtOAc then 1: 10 MeOH:EtOAc) to give **8** (0.49 g, 75% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.56 (s, 3H), 3.39 (dd, J = 2.5, 14.4 Hz, 1H), 3.80 (ddd, J = 2.5, 8.6, 14.4 Hz, 1H), 4.40 (d, J = 6.3 Hz, 1H), 4.45 (dd, J = 2.5 , 4.9 Hz, 1H), 4.74 (d, J = 14.2 Hz, 1H), 4.87 (dd, J = 2.5, 6.5 Hz, 1H), 5.22 (dd, J = 4.4, 6.5 Hz, 1H), 5.78 (d, J = 4.4 Hz, 1H), 6.05 (br s, 2H), 7.23 (dd, J = 6.3, 14.2 Hz, 1H), 7.78 (s, 1H), 8.38 (s, 1H), 8.50 (d, J = 8.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 25.7, 27.8, 43.4, 81.7, 83.2, 84.1, 93.0, 95.2, 115.3, 121.2, 140.5, 142.7, 149.1, 153.4, 155.0, 156.5, 171.5; **IR** (thin film/NaCl) 3327, 3181, 2990, 2938, 1733, 1646, 1600, 1581, 1549, 1576, 1457, 1426, 1375, 1332, 1296, 1243, 1214, 1173, 1129, 1096, 1079, 952, 923, 857, 799, 737, 703, 648 cm^{-1}; $[\alpha]_D^{20}$ –181.2° (*c* 2.34, $CHCl_3$).

Preparation of 10.



To a solution of diazo **9** (170 mg, 0.45 mmol) in dry chlorobenzene was added vinyl carbamate adenosine **8** (170 mg, 0.38 mmol), $Rh_2(pfbm)_4$ (1 mg, 0.2 mol%), and 4 Å molecular sieves under nitrogen with exclusion of moisture. The reaction was stirred at 80 ˚C overnight. The solvent was then dried *in vacuo*, and the crude mixture was purified by silica gel column chromatography (hexanes:EtOAc 1:1 and 0:1, then acetone:EtOAc 1:3) to give **10** (207 mg, 69% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ .95 (d, J = 6.8 Hz, 1H), 1.05 (d, J = 7.0 Hz, 1H), 1.35 (s, 3H), 1.46 (s, 3H), 1.67 (s, 3H), 1.80 (dd, J = 2.3, 13.1 Hz, 1H), 2.35 (dd, J = 8.7, 13.1 Hz, 1H), 2.38 (m, 1H), 2.84 (s, 3H), 2.98 (ddd, J =2.7, 7.6, 14.6 Hz), 3.04 (dt, J = 2.5, 14.5 Hz, 1H), 4.23 (dd, J = 2.9, x Hz, 1H), 4.87 (dd, J = 3.2, 7.3 Hz, 1H), 5.15 (dd, J = 3.8, 6.7 Hz, 1H), 5.32 (d, J = 3.5 Hz, 1H), 5.58 (dd, J = 2.3, 8.7 Hz, 1H), 5.57 (br s, 2H), 5.80 (d, J = 3.8 Hz, 1H), 6.42 (d, J = 9.1 Hz, 1H), 7.17-7.33 (m, 1H), 7.76 (s, 1H), 8.21 (s, 1H), 8.32 (d, J = x Hz, 1H), 8.32 (d, J = x Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 18.3, 19.4, 20.7, 27.1, 27.2, 29.3, 32.9, 43.3, 44.6, 58.0, 74.1, 82.3, 82.6, 85.2, 85.6, 88.1, 93.9, 96.5, 116.8, 128.8, 128.9, 129.6, 130.1, 130.2, 130.5, 130.6, 141.8, 157.6, 157.8, 166.3, 168.4, 170.3; **IR** (thin film/NaCl) 3320, 3193, 3060, 3030, 2986, 2937, 2878, 1725, 1645, 1599, 1538, 1496, 1474, 1455, 1424, 1407, 1376, 1332, 1262, 1212, 1159, 1097, 1079, 1030, 899, 860, 799, 759, 736, 701, 648 cm^{-1}; **HRMSFAB** [M+H$^+$]: 799.3414, calcd for $C_{40}H_{47}N_8O_{10}$: 799.3415; $[\alpha]_D^{20}$ –57.8° (*c* .2.32, $CHCl_3$).

Preparation of 3.

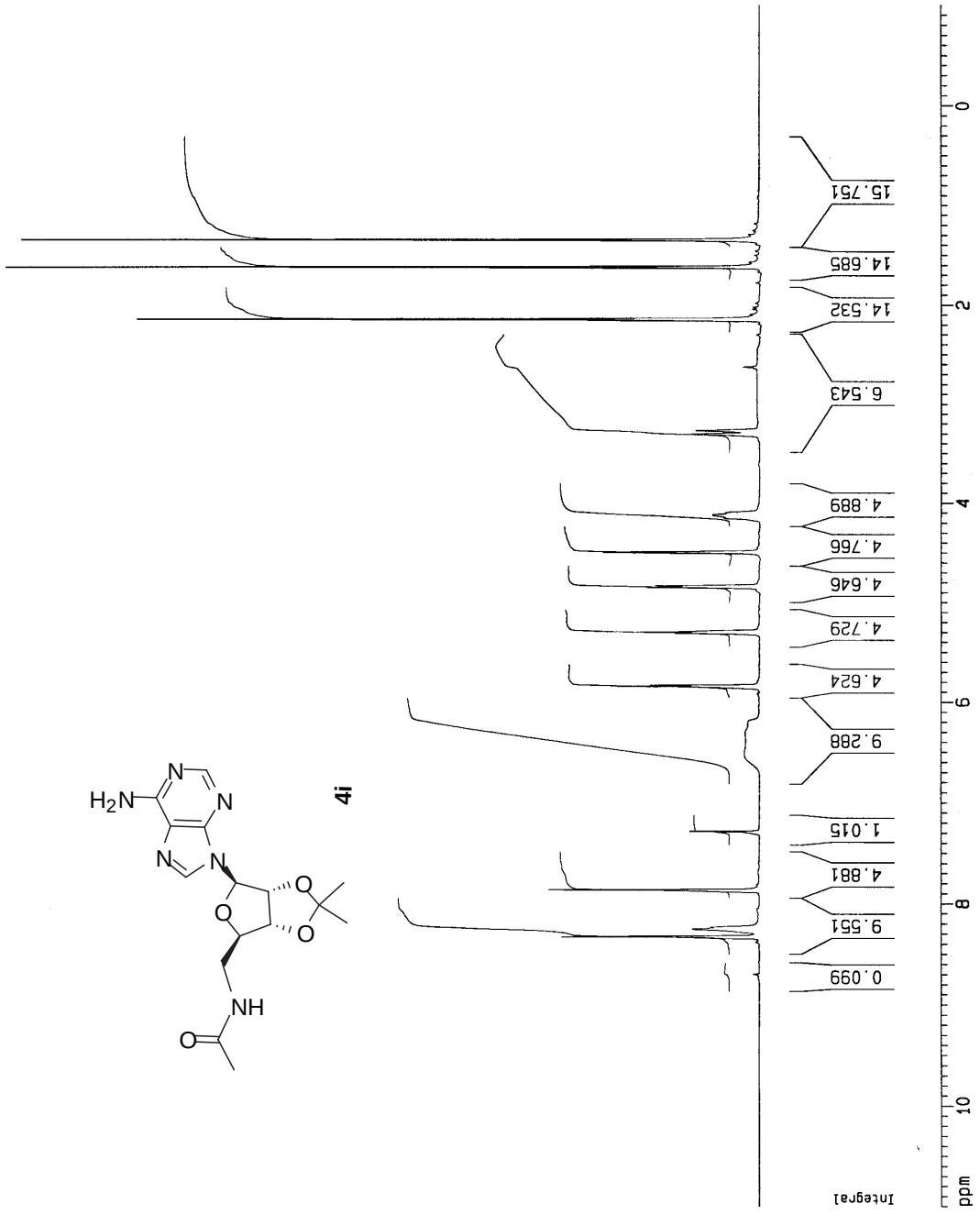


10 (25 mg, 0.031 mmol) was combined with 800 µL of methanolic NH_3 (2M solution). The reaction was stirred until TLC indicated the disappearance of the starting material. The crude mixture was then dried *in vacuo*, and purified by silica gel column chromatography (EtOAc 100% and then EtOH:EtOAc 1:5) to give the chiral-auxiliary cleaved product as a white solid. This intermediate was then dissolved in 500 µL of 10:1 TFA/water solution at 0 °C, allowed to warm up to room temperature, and stirred until TLC indicated the disappearance of the starting material (15 minutes). The mixture was dried and purified by reverse-phase HPLC. The fractions containing **3** were lyophilized to give the product (8 mg, 52% yield) as a white solid. **^{1}H** NMR (d_4-MeOH, 500 MHz) δ 1.60 (s, 3H), 1.81 (dd, J = 1.2 Hz, 13.0 Hz, 1H), 2.36 (dd, J = 8.6 Hz, 13.0 Hz, 1H), 2.76 (s, 3H), 3.21 (s, 3H), 3.59 (dd, J = 14.5 Hz, 14.1 Hz, 1H), 4.10-4.12 (m, 2H), 4.72 (t, J = 6.0 Hz, 1H), 5.41 (dd, J = 1.2 Hz, 8.6 Hz, 1H), 5.78 (d, J = 6.4 Hz, 1H), 8.13 (s, 1H), 8.14 (s, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 17.8, 25.9, 42.2, 44.3, 73.1, 74.8, 75.5, 86.0, 86.8, 91.4, 97.1, 121.5, 142.7, 150.5, 154.3, 157.9, 158.0, 169.0, 171.2; **HRMSFAB** [M+H$^+$]: 473.1796, calcd for $C_{20}H_{28}N_7O_7$: 492.1717; $[\alpha]_D^{20}$ –143.1° (*c* .23, MeOH).

Conformational analysis.

Monte-Carlo conformational search was performed for one of the diastereomers **1**, using the MM2* forcefield and water solvent set as implemented in MACROMODEL 5. The starting structures were generated in MACROMODEL, with the adenosine substructure fixed as in the x-ray structural conformation imported from PDB file 1B38, cyclin-dependent protein kinase 2 (CDK2). The search was stopped after 1000 steps, and all structures found within 50 $kJmol^{-1}$ of the global minimum were stored and examined. The search produced 73 minimized structures with good convergence that were within the 50 $kJmol^{-1}$ cutoff, 1 of which were within 1 $kcalmol^{-1}$ of the global minimum, 3 within 2 $kcalmol^{-1}$, and 10 within 3 $kcalmol^{-1}$.

An unconstrained Monte-Carlo conformational search was also performed for diastereomer of **1** in the MM2* forcefield and water solvent set. The starting structure was generated in MACROMODEL, and no constraints were imposed. The search was stopped after 1000 steps, and all structures found within 50 $kJmol^{-1}$ of the global minimum were stored and examined. The search produced 438 minimized structures that were within the 50 $kJmol^{-1}$ cutoff, 17 of which were within 1 $kcalmol^{-1}$ of the global minimum, 53 within 2 $kcalmol^{-1}$, and 113 within 3 $kcalmol^{-1}$. The representative conformer shown in Figure 2 (the 73rd structure) was found to overlay closely to an enzyme-bound form of ATP (imported from 1JST, CDK2), was 2.3 $kcalmol^{-1}$ above the global minimum and found 4 times by the conformational search.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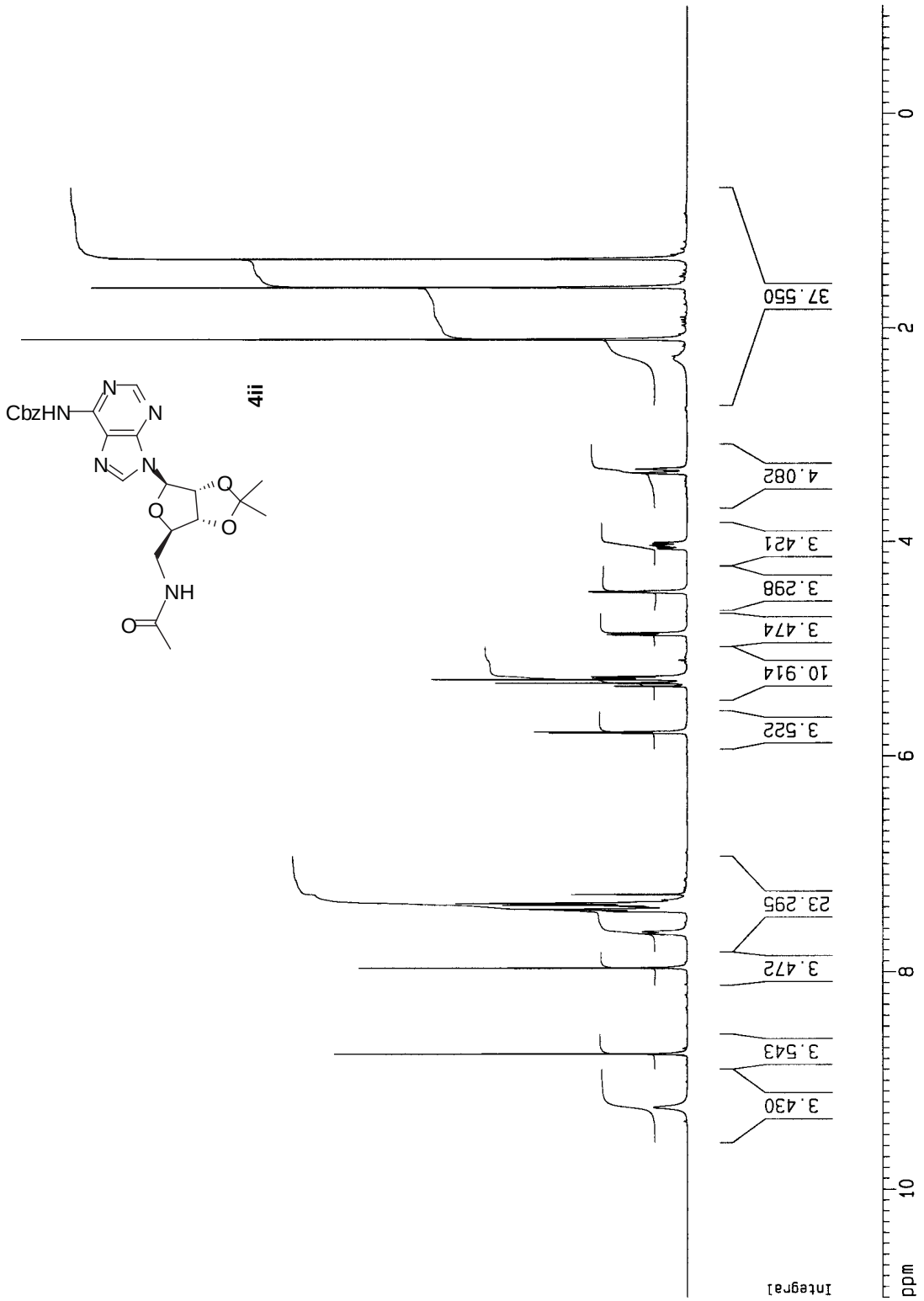
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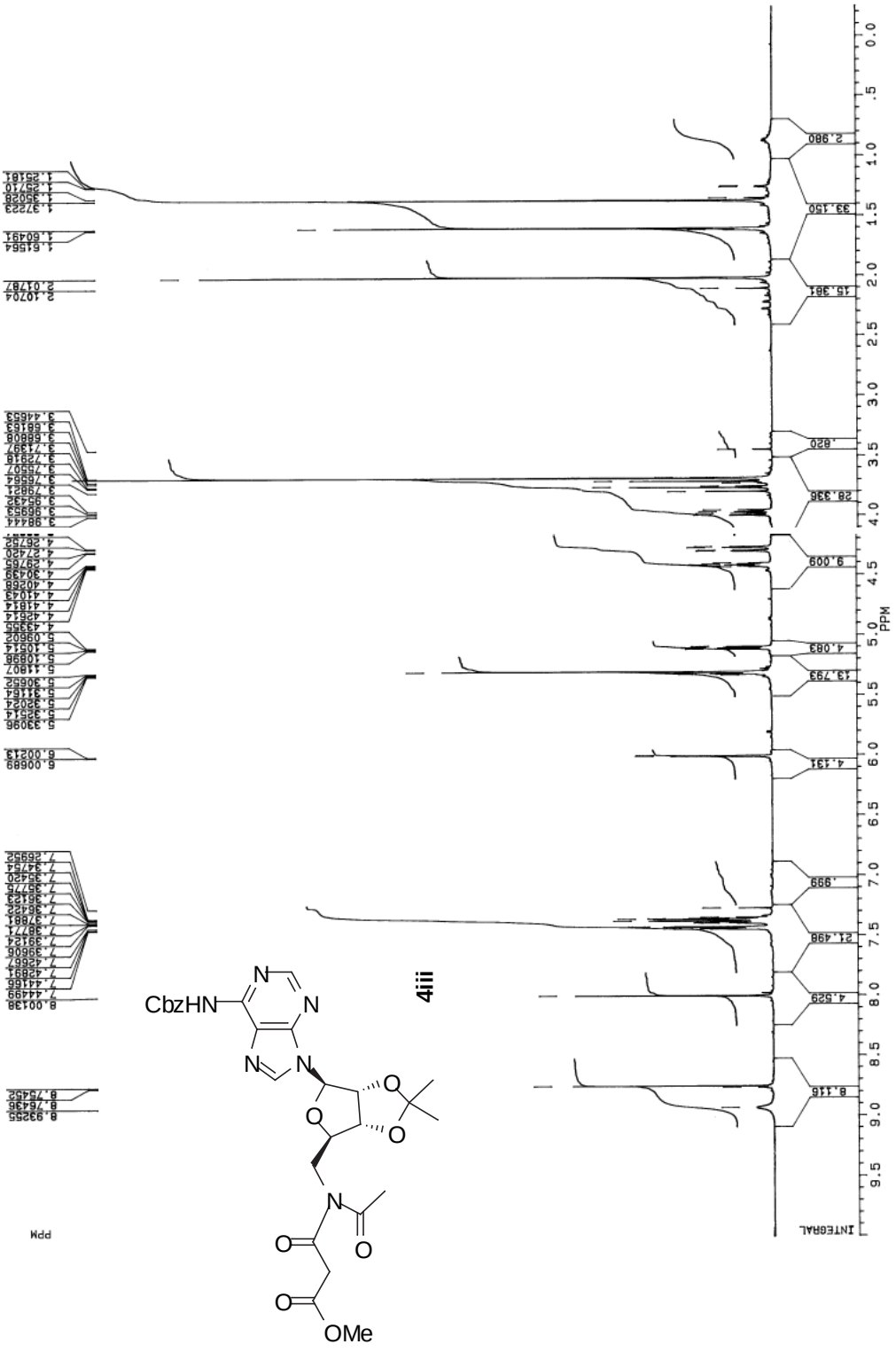
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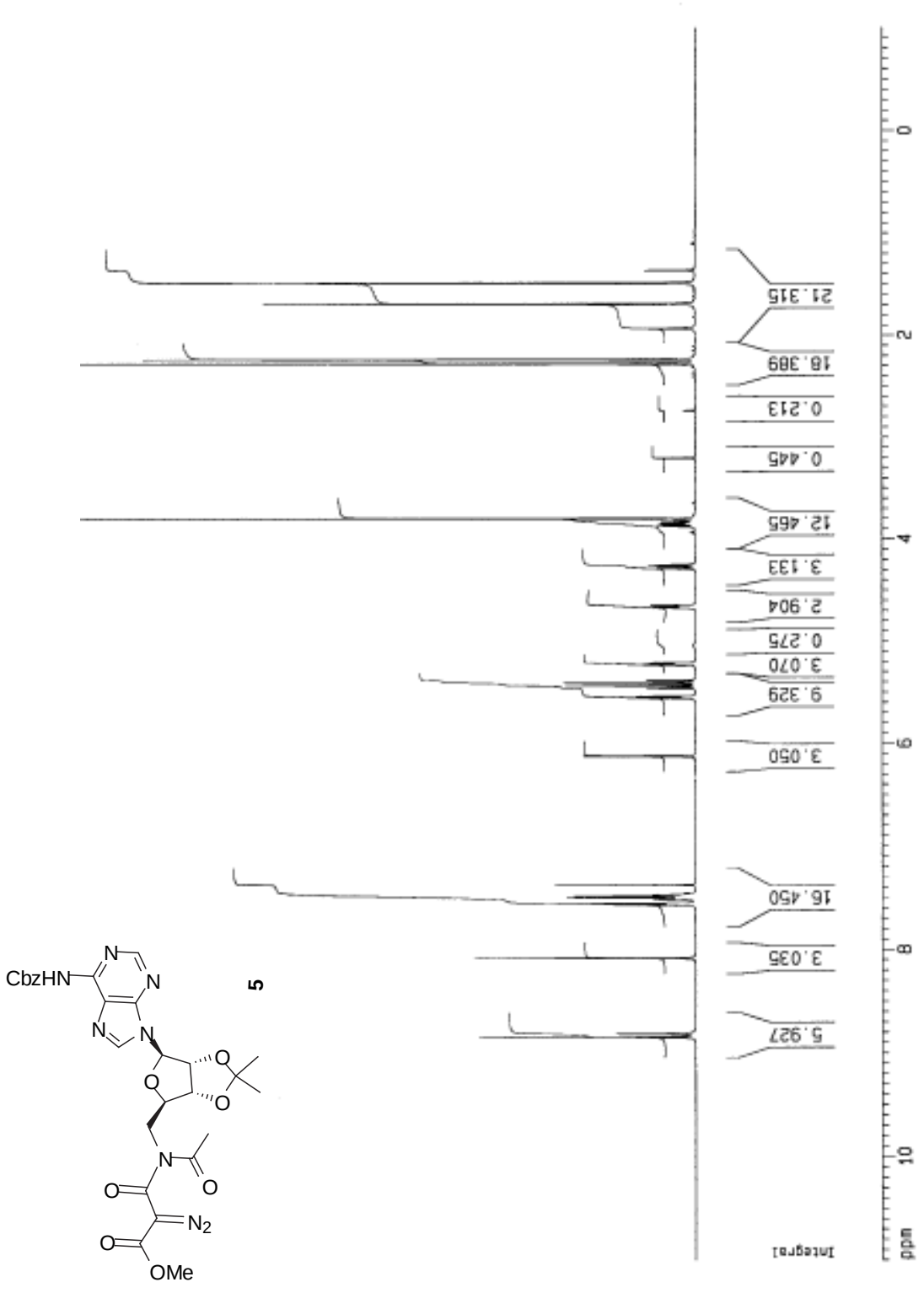
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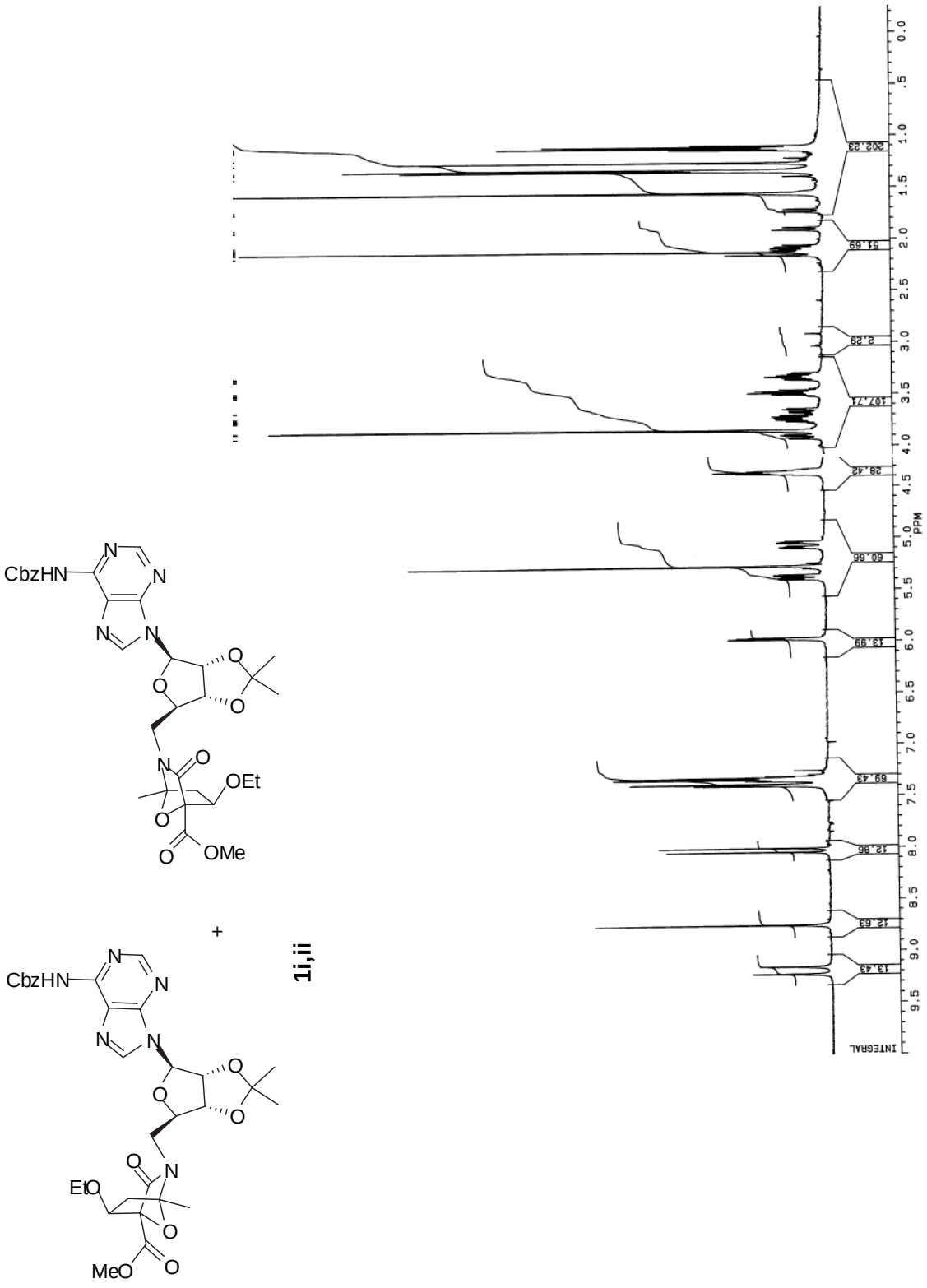
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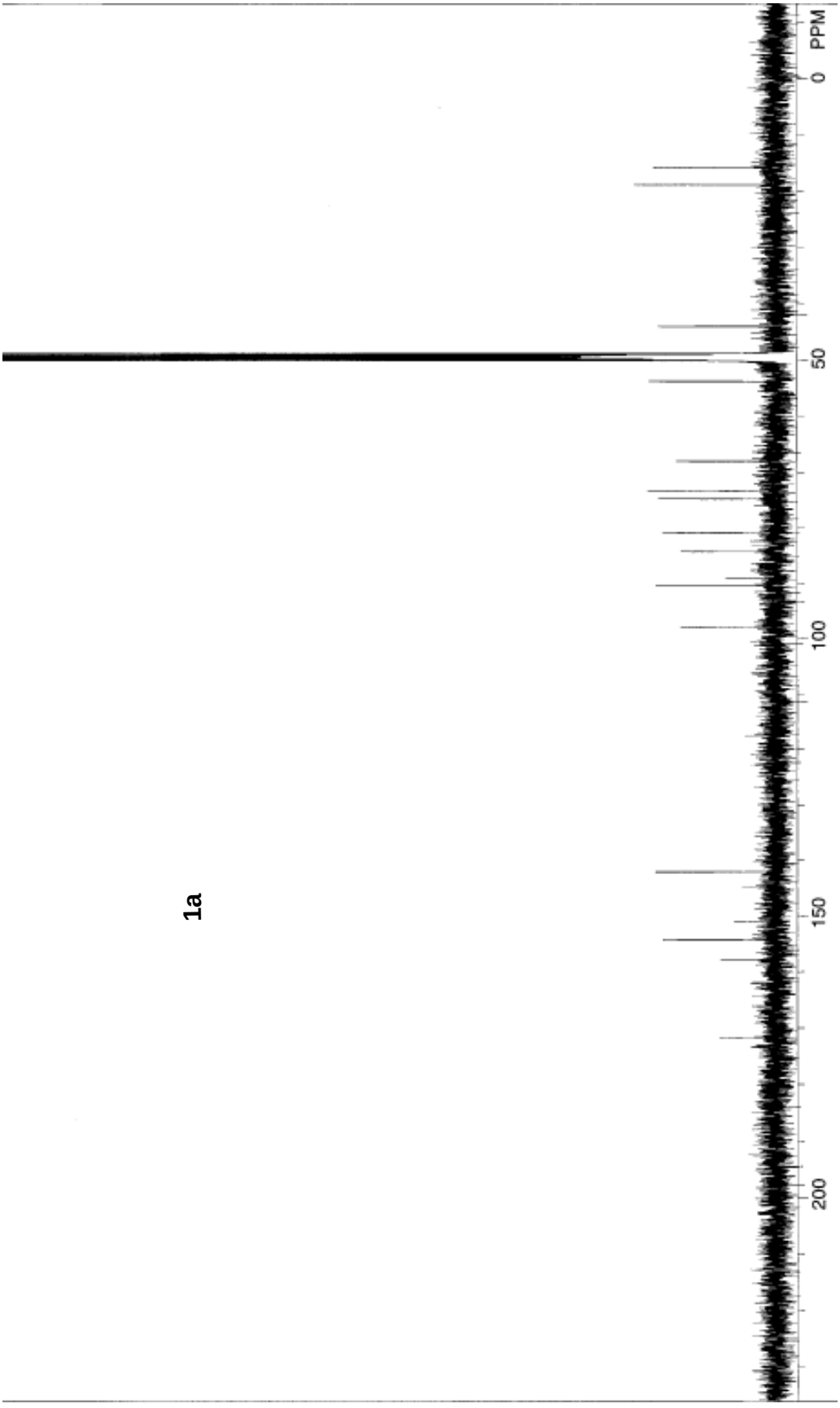
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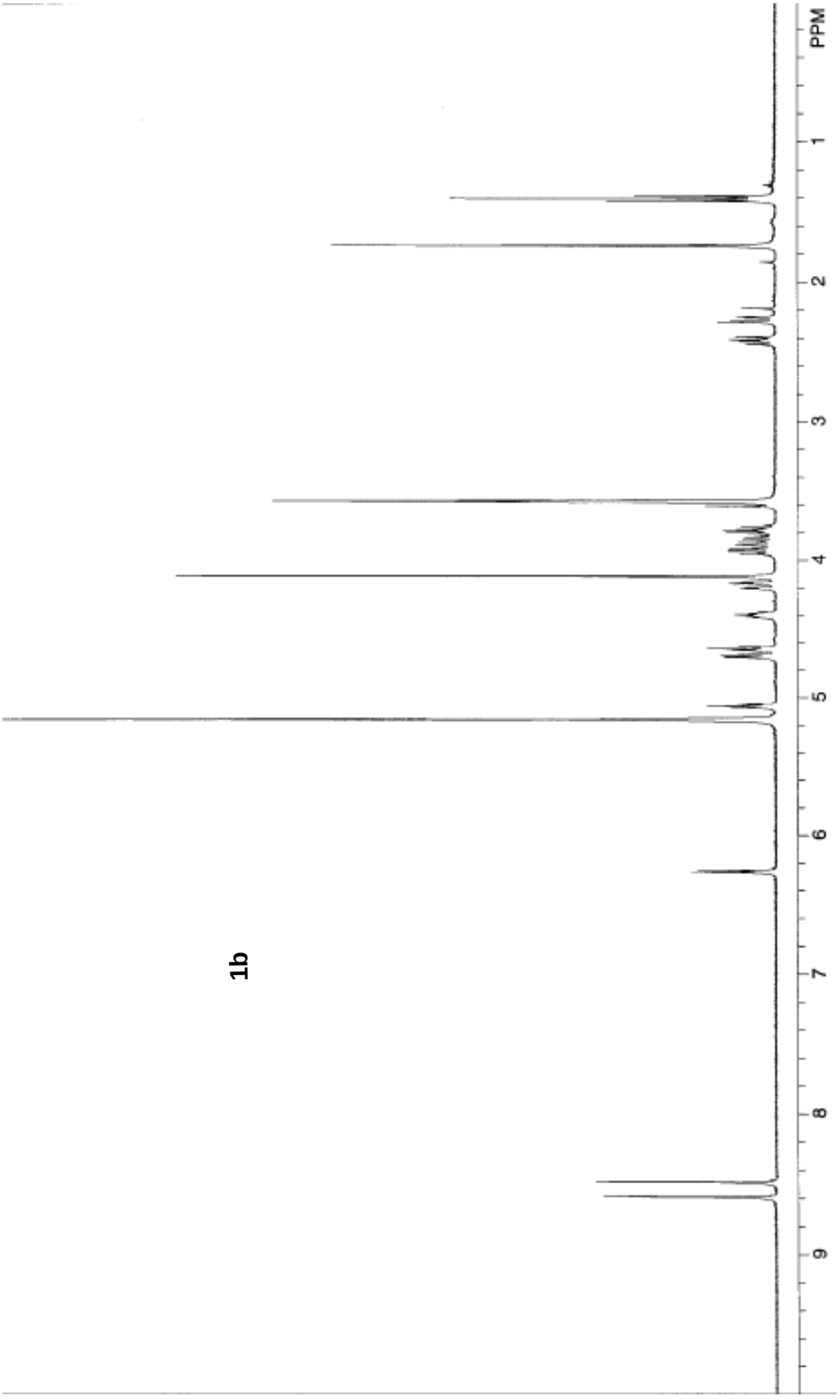
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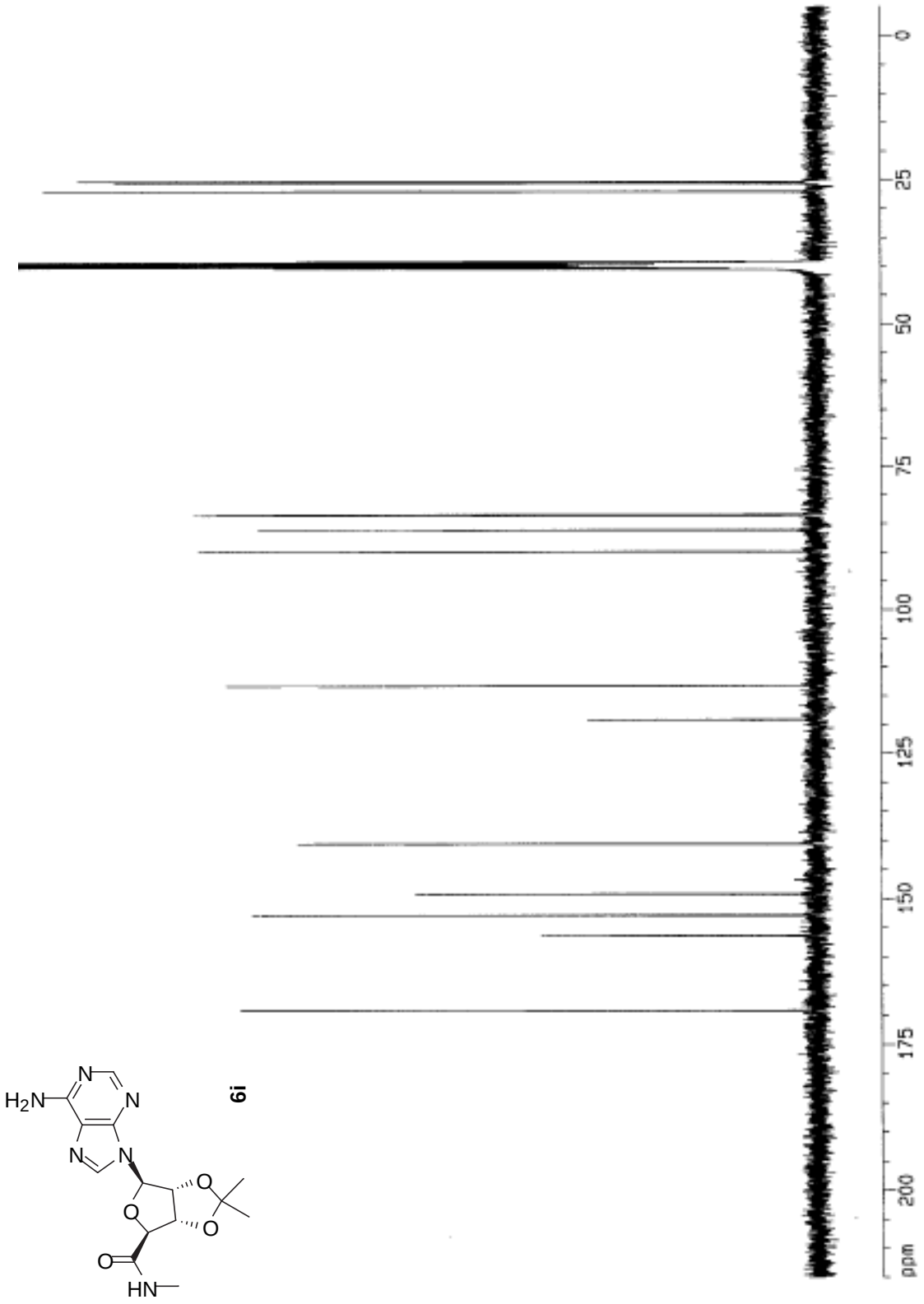
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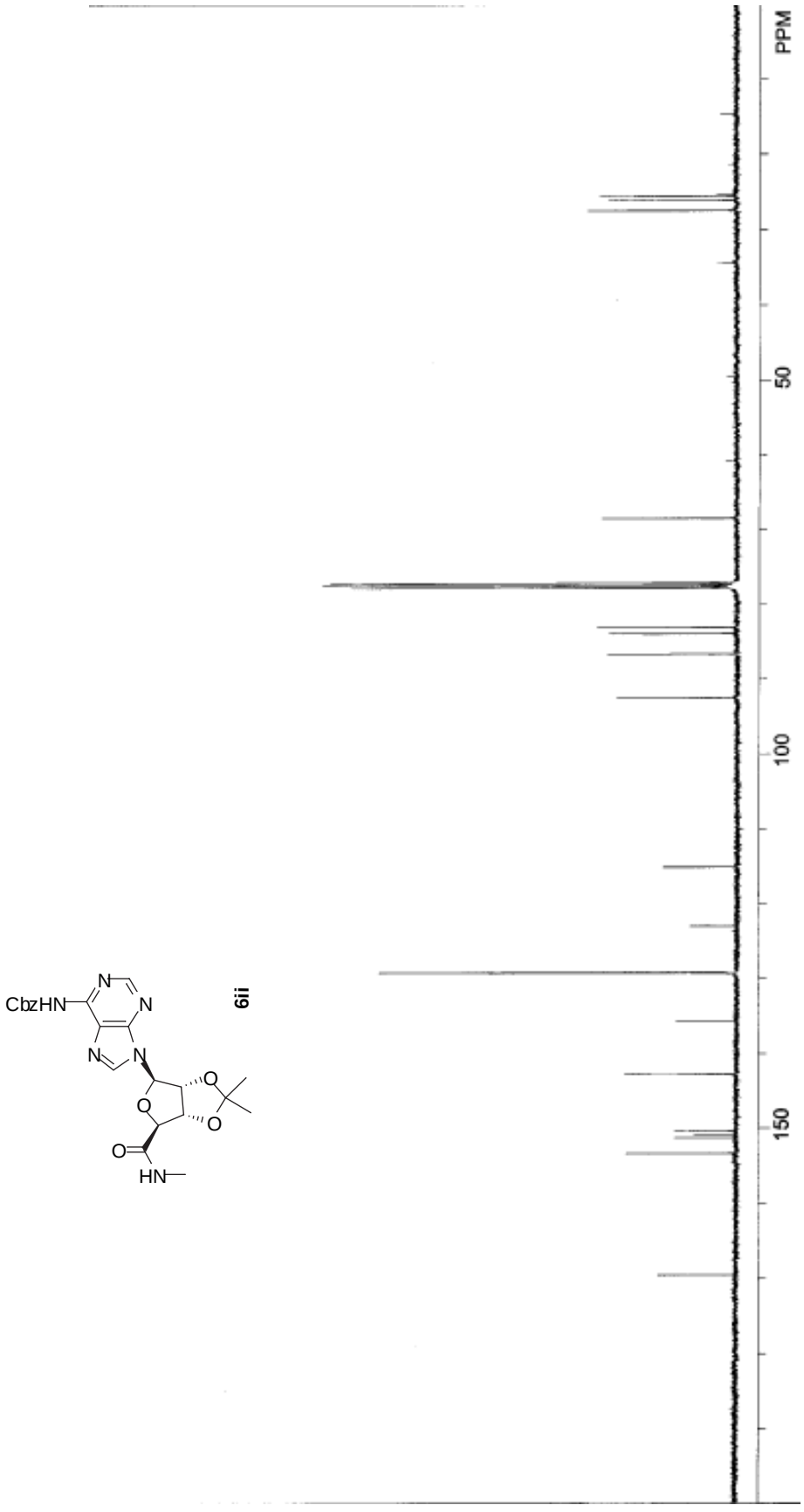
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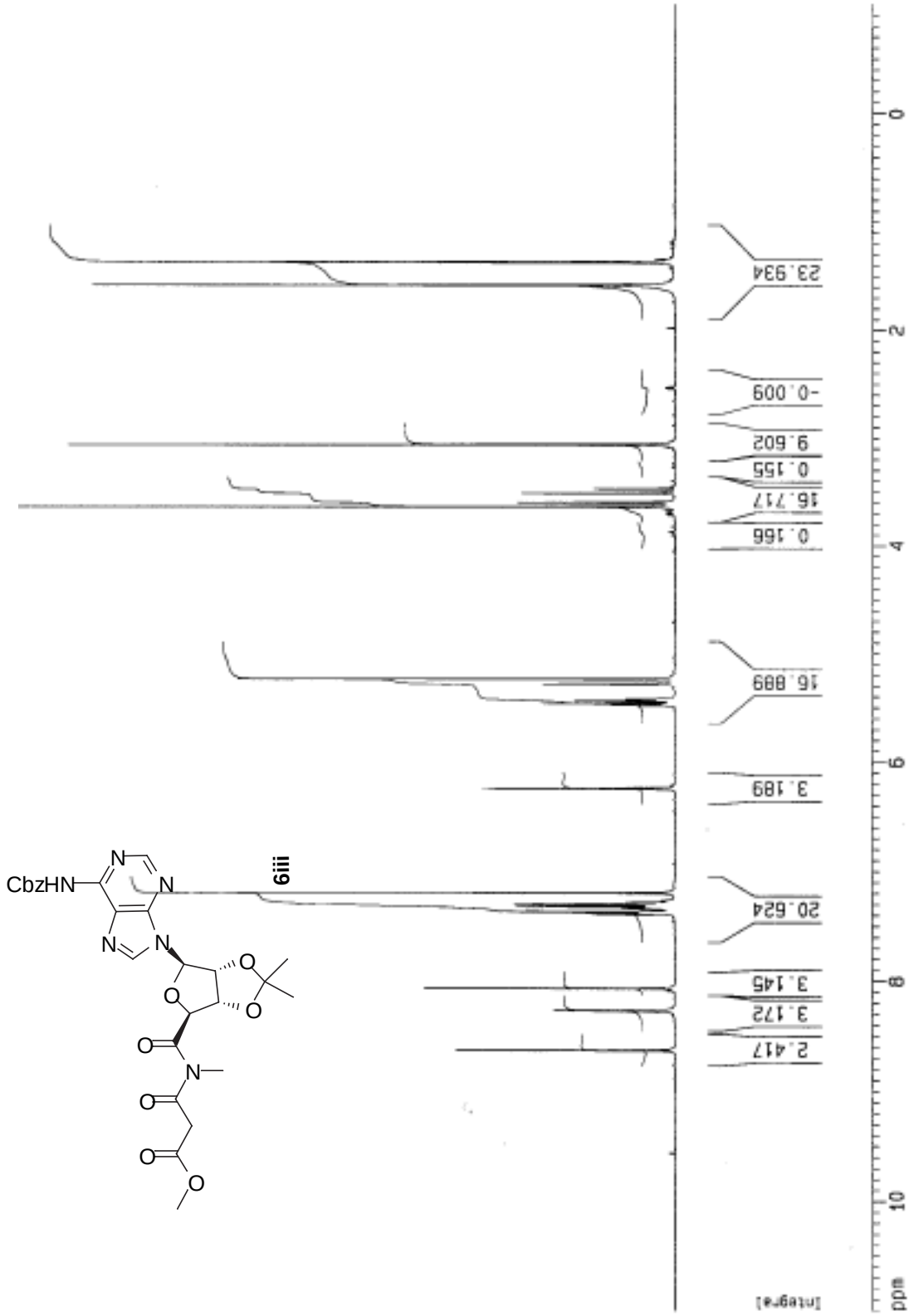
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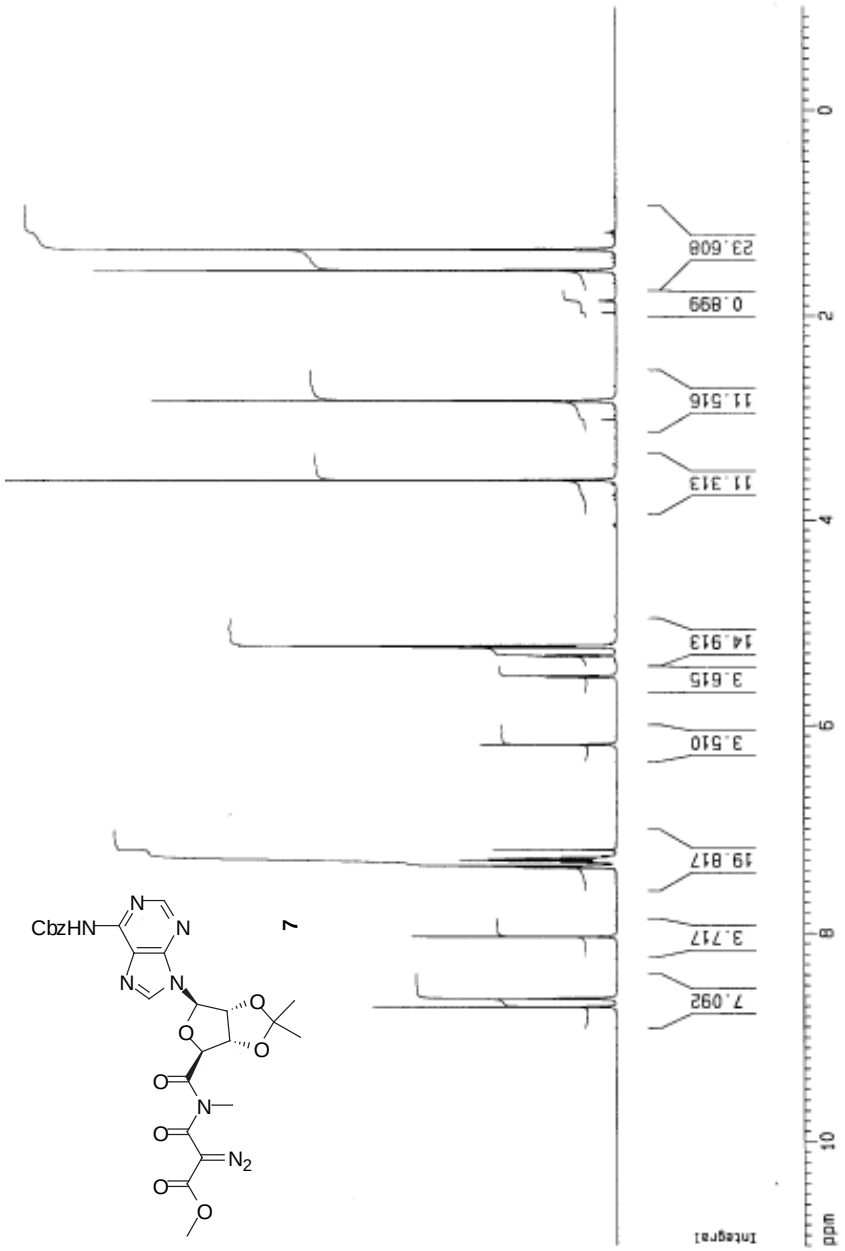
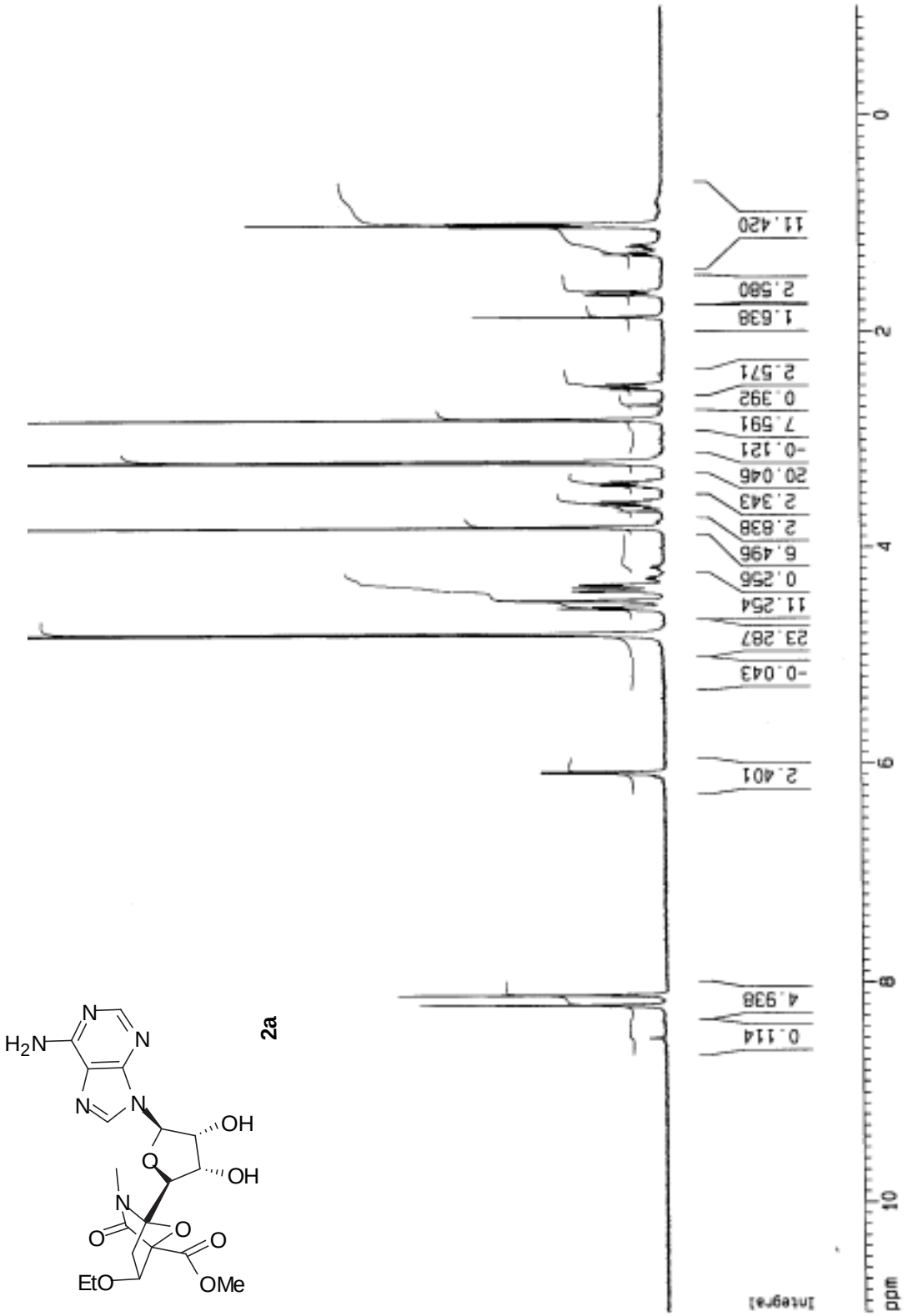
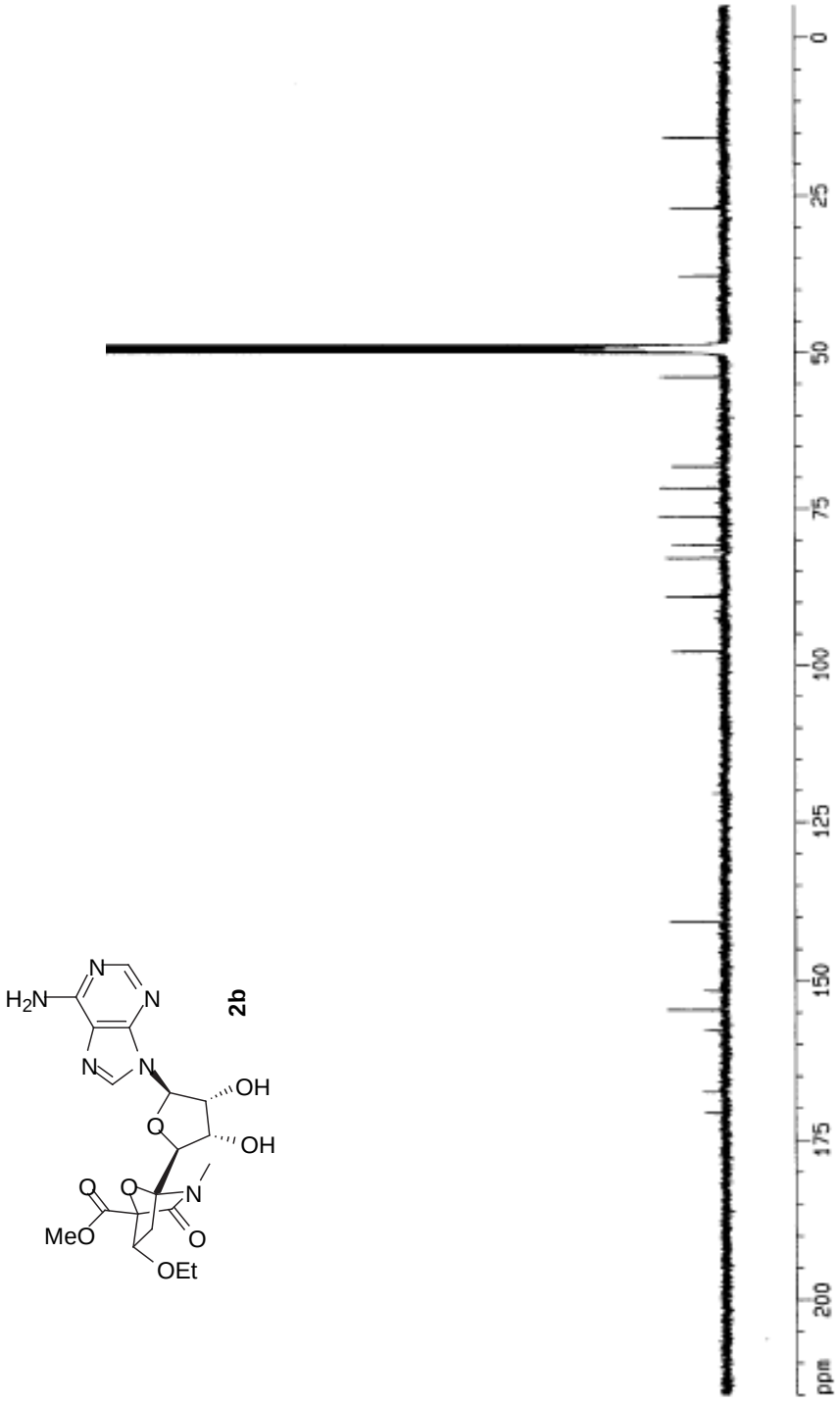
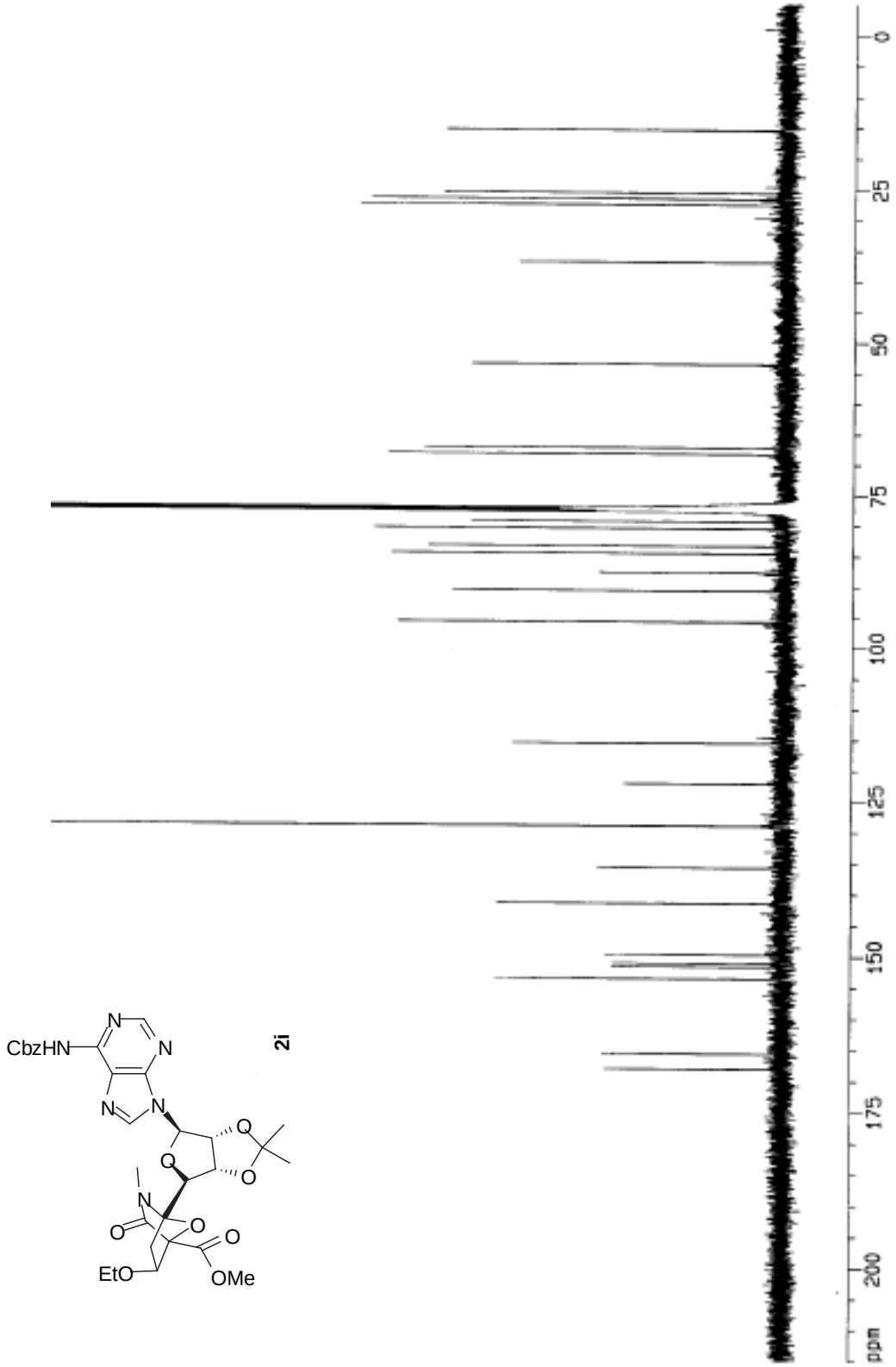
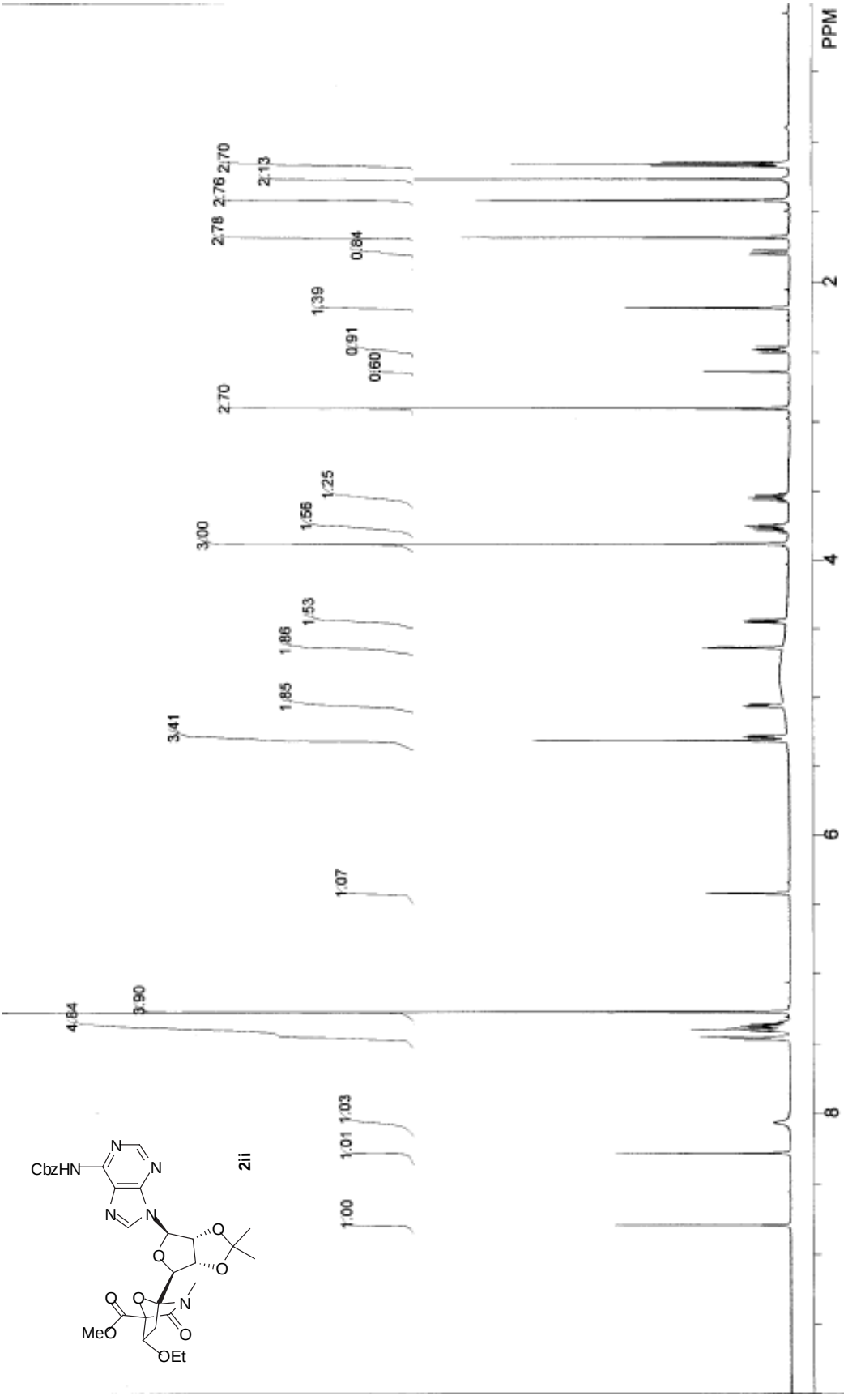

CbzHN
N
N
N
N
O
O
O
O
N
O
O
N_2
O
O
7
23.608
0.899
11.516
11.313
14.913
3.615
3.510
19.817
3.717
7.092
Integral
ppm
0
2
4
6
8
10

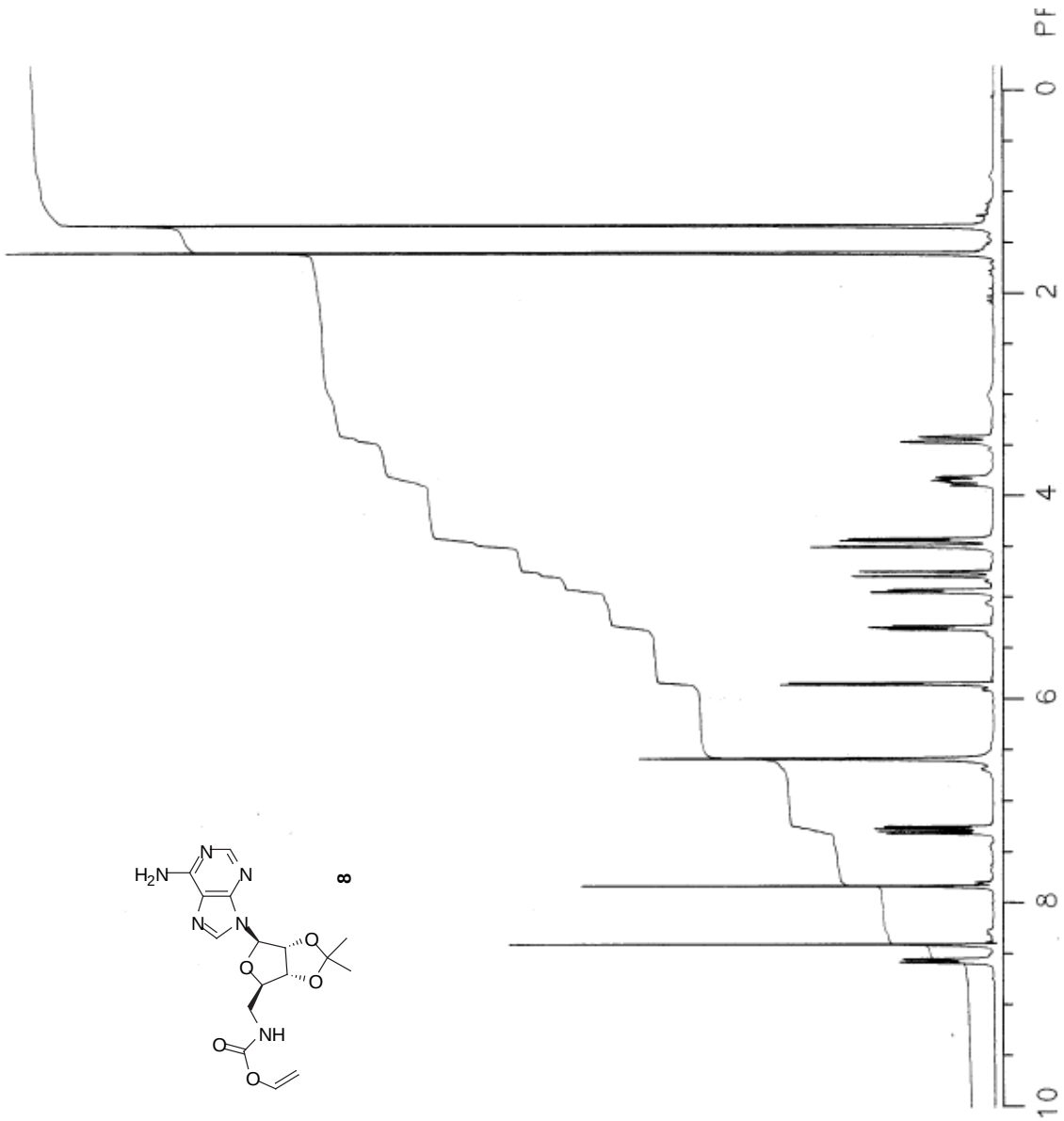

11.420
2.580
1.638
2.571
0.392
7.591
-0.121
20.046
2.343
2.838
6.496
0.256
11.254
23.287
-0.043
2.401
4.938
0.114
Integral
ppm
0
2
4
6
8
10
2a
H2N
N
N
N
N
OH
OH
O
N
O
O
O
EtO
OMe



2b


CbzHN
N
N
N
N
O
O
O
N
O
O
O
EtO
OMe
2i
0
25
50
75
100
125
150
175
200
ppm


PPM
2
4
6
8
2.70
2.13
2.76
2.78
0.84
1.39
0.91
0.60
2.70
1.25
1.56
3.00
1.53
1.86
1.85
3.41
1.07
3.90
4.84
1.03
1.01
1.00
CbzHN
N
N
N
N
O
O
O
O
O
N
MeO
O
OEt
2ii



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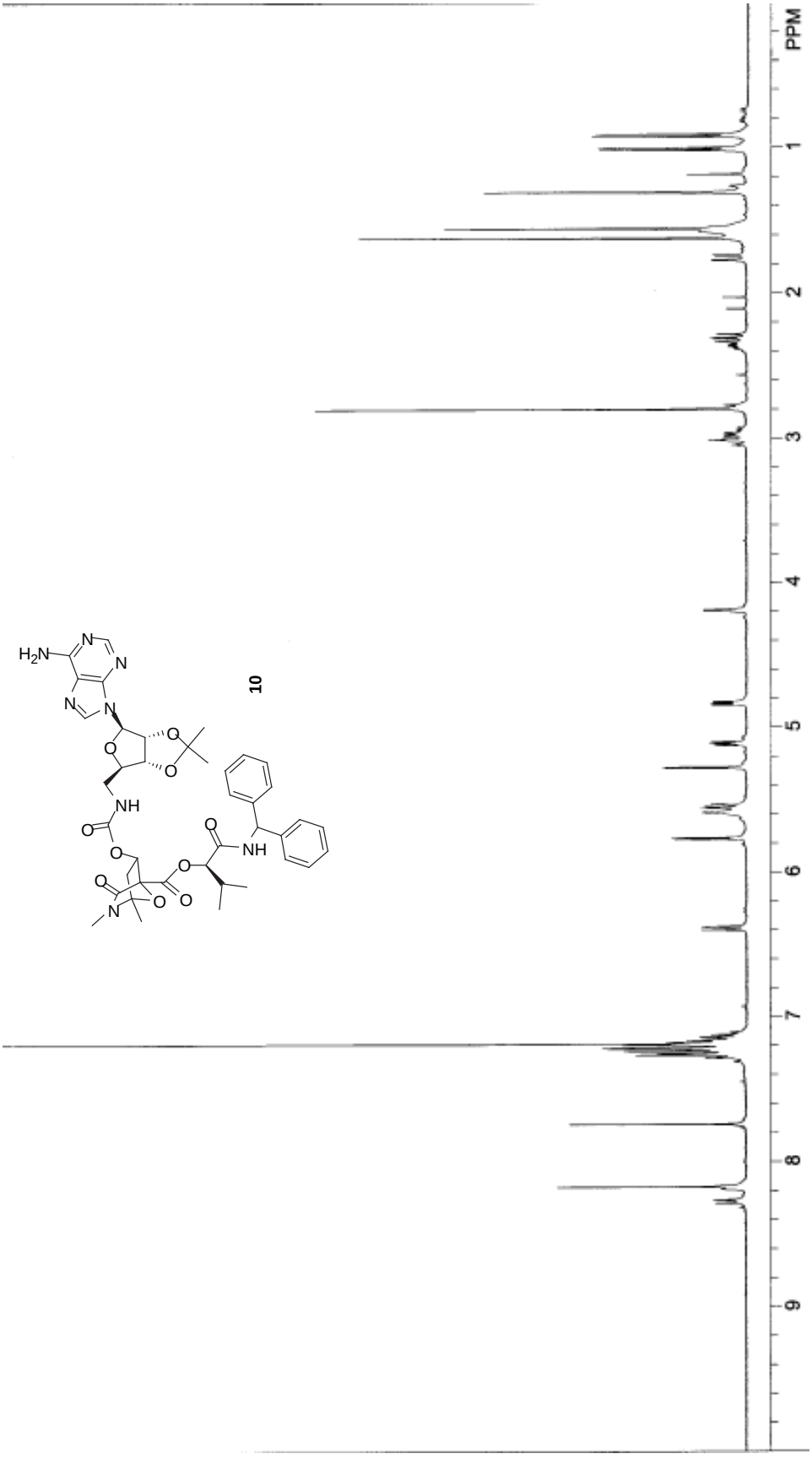
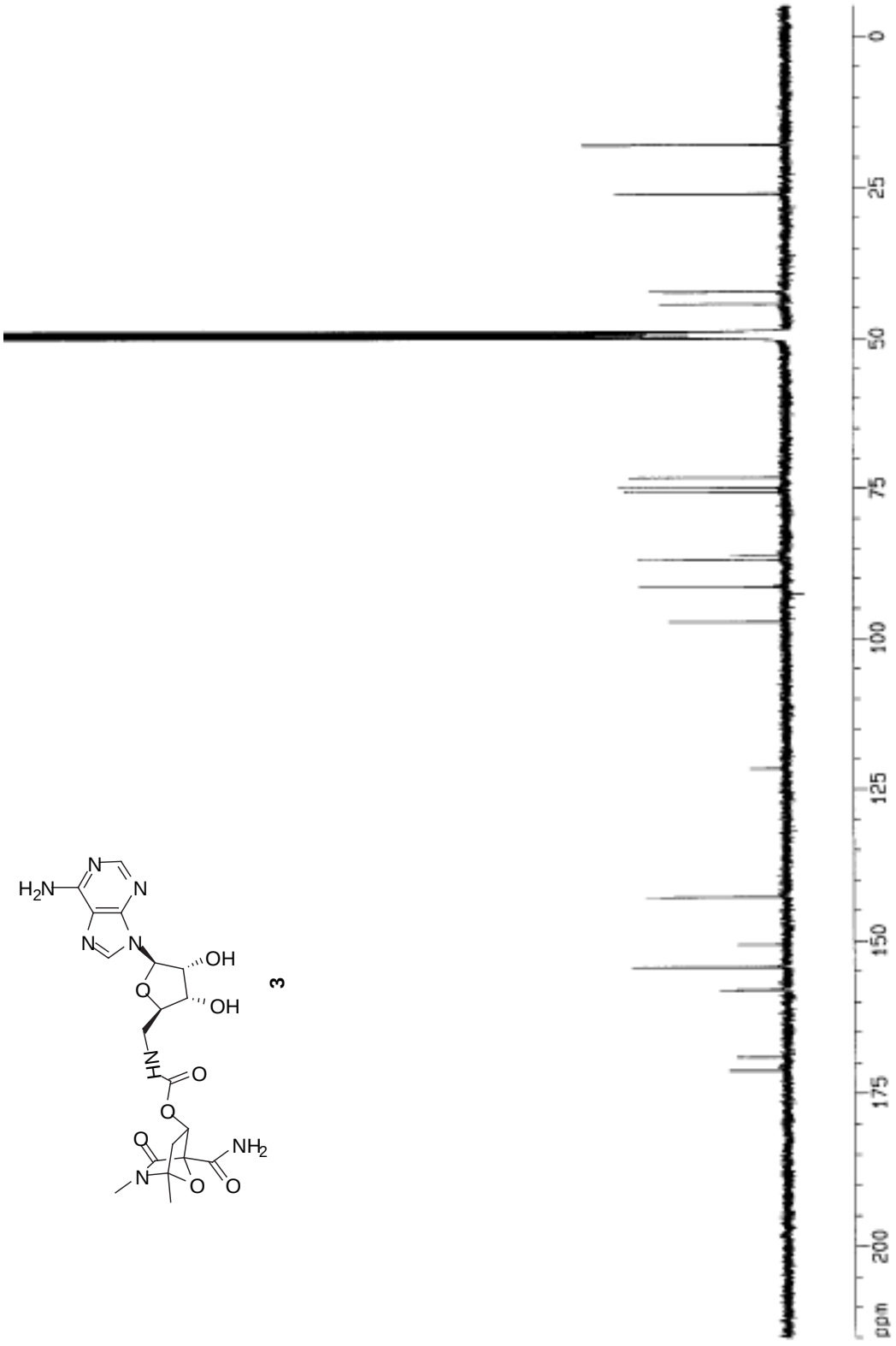

PPM
1
2
3
4
5
6
7
8
9
10



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