Chemical Synthesis of Cross-Linked Purine Nucleosides

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SUPPORTING INFORMATION

General. All reagents and solvents were of commercial grade and used as such unless specified. NMR (^1H and ^{13}C) spectra were recorded on a Bruker AC-250 spectrometer. Samples prepared for NMR analysis were dissolved in $CDCl_3$ or C_5D_5N. Chemical shifts are reported in ppm relative to TMS in the proton spectra and to the deuterated solvent in the carbon spectra. UV spectra were recorded on a Beckman DU-600 using a 0.1 M Na_2HPO_4/NaH_2PO_4 buffer (pH=5.7) and a 0.3 M tris(hydroxymethyl)aminomethane buffer (pH=10.5). Mass spectra were recorded on a Micromass Trio 2000 in Fast Atom Bombardment (FAB) mode. High resolution FAB MS spectra were performed by the Mass Spectrometry Laboratory of the School of Chemical Sciences, University of Illinois at Urbana - Champaign. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, 56-19, 37th Avenue, Woodside, NY. Thin layer chromatography (TLC) was performed on silica gel sheets (Riedel-deHaën, Sleeze, Germany) containing a fluorescent indicator. Components were visualized by UV light (λ=254 nm) or by spraying with a solution of phosphomolybdic acid. Flash column chromatographic separations were carried out on 60Å (230-400-mesh) silica gel (TSI Chemical Company, Cambridge, MA). All experiments dealing with moisture or air sensitive-compounds were conducted under dry nitrogen. The starting materials and reagents, unless otherwise specified, were the commercially available best grade (Aldrich, Fluka), and were used without further purification. All products showed a single spot on TLC analysis, after purification.

General Procedure for the Coupling: An oven-dried reaction vial was charged with the aryl amine (0.17 mmol), cesium carbonate (0.078 g, 0.24 mmol, 1.4 eq.), palladium acetate (0.004 g, 0.017 mmol, 0.1 eq.), BINAP (0.016 g, 0.025 mmol, 0.15 eq.), the aryl bromide or iodide (0.20 mmol, 1.2 eq.) and toluene (1.5 mL). The vial was flushed with argon prior to sealing. The reaction mixture was stirred for 30 minutes at room temperature, heated at 90 °C for 16 h, then diluted with ethyl acetate. Centrifugation and concentration *in vacuo* of the supernant liquid afforded a residue, which was purified by flash chromatography (silica gel, 5-30% ethyl acetate in hexane) to afford the desired compound.

Compound (7):[11] light-yellow oil (0.177 g, 90%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.09 (s, 2H), 7.89 (s, 1H), 7.51 (m, 4H), 7.32-7.28 (m, 6H), 6.45 (t, *J*=6.2 Hz, 2H), 5.71 (s, 4H), 4.57 (m, 2H), 3.88 (m, 2H), 3.82 (dd, *J*=10.4, 3.8 Hz, 2H), 3.75 (dd, *J*=10.4, 2.7 Hz, 2H), 2.58 (m, 2H), 2.33 (m, 2H), 0.89 (s, 36H), 0.06 (s, 12H), 0.05 (s, 12H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 160.4, 153.2, 152.9, 139.0, 136.1, 128.4 (× 2), 128.2 (× 2), 127.9, 117.5, 87.4, 83.6, 71.3, 68.0, 62.3, 41.1, 25.8 (× 3), 25.6 (× 3), 18.3, 17.8, –4.8 (× 2), –5.5 (× 2); FABMS *m/z* 1154 $[M+1]^+$; Anal. Calcd for $C_{58}H_{91}N_9O_8Si_4$: C, 60.33; H, 7.94; N, 10.92. Found: C, 60.02; H, 8.04; N, 10.88.

Compound (9): light-yellow oil (0.107 g, 60% or, based on unreacted recovered **5** (0.020 g), 75%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.73 (s, 1H), 8.48 (bs, 1H), 8.27 (s, 1H), 8.10 (s, 1H), 7.55 (m, 4H), 7.32-7.28 (m, 6H), 6.51 (t, *J*=6.4 Hz, 2H), 5.68 (s, 2H), 4.61 (m, 2H), 4.02 (m, 2H), 3.99-3.76 (m, 4H), 2.70 (m, 2H), 2.50 (m, 2H), 0.90 (s, 36H), 0.09 (s, 12H), 0.05 (s, 12H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 160.6, 152.6, 152.5, 152.4, 150.5, 150.0, 140.1, 139.7, 136.2, 128.6 (× 2), 128.3 (× 2), 128.0, 122.1, 118.2, 87.9, 87.8, 84.4 (× 2), 72.0, 71.9, 68.5, 62.7 (× 2), 41.3, 41.0, 25.9 (× 6), 25.7 (× 6), 18.3 (× 2), 17.9 (× 2), –4.7 (× 4), –5.4 (× 4); FABMS *m/z* 1048 $[M+1]^+$; Anal. Calcd for $C_{51}H_{85}N_9O_7Si_4$: C, 58.41; H, 8.17; N, 12.02. Found: C, 58.52; H, 8.24; N, 11.94.

Compound (4): light-yellow oil (0.043 g, 17% or, based on unreacted recovered **5** (0.020 g), 21%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.68 (s, 2H), 8.23 (s, 1H), 8.01 (s, 2H), 7.20-7.16 (m, 5H), 6.48 (t, *J*=6.5 Hz, 1H), 6.17 (t, *J*=6.0 Hz, 1H), 5.22 (s, 2H), 4.60 (m, 2H), 4.43 (m, 1H), 4.02 (m, 2H), 3.85 (m, 1H), 3.73-3.80 (m, 6H), 2.69 (m, 2H), 2.42 (m, 2H), 2.30-2.15 (m, 2H), 0.92-2.82 (s, 54H), 0.10-0.01 (s, 36H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 160.6, 154.5, 153.1 (× 2), 152.2 (× 3), 152.0 (× 2), 141.4 (× 2), 140.2, 136.1, 128.2 (× 2), 128.1 (× 2), 127.7, 127.1 (× 2), 120.1, 88.0 (× 2), 87.5, 84.6 (× 2), 84.2, 72.2 (× 2), 71.0, 68.4, 62.9 (× 2), 62.4, 42.0, 40.8 (× 2), 25.7 (× 18), 18.3 (× 3), 18.0 (× 3), –4.7 (× 6), –5.5 (× 6); FABMS *m/z* 1510 $[M+1]^+$; Anal. Calcd for $C_{73}H_{123}N_{13}O_{10}Si_6$: C, 58.01; H, 8.20; N, 12.05. Found: C, 57.91; H, 8.27; N, 11.93.

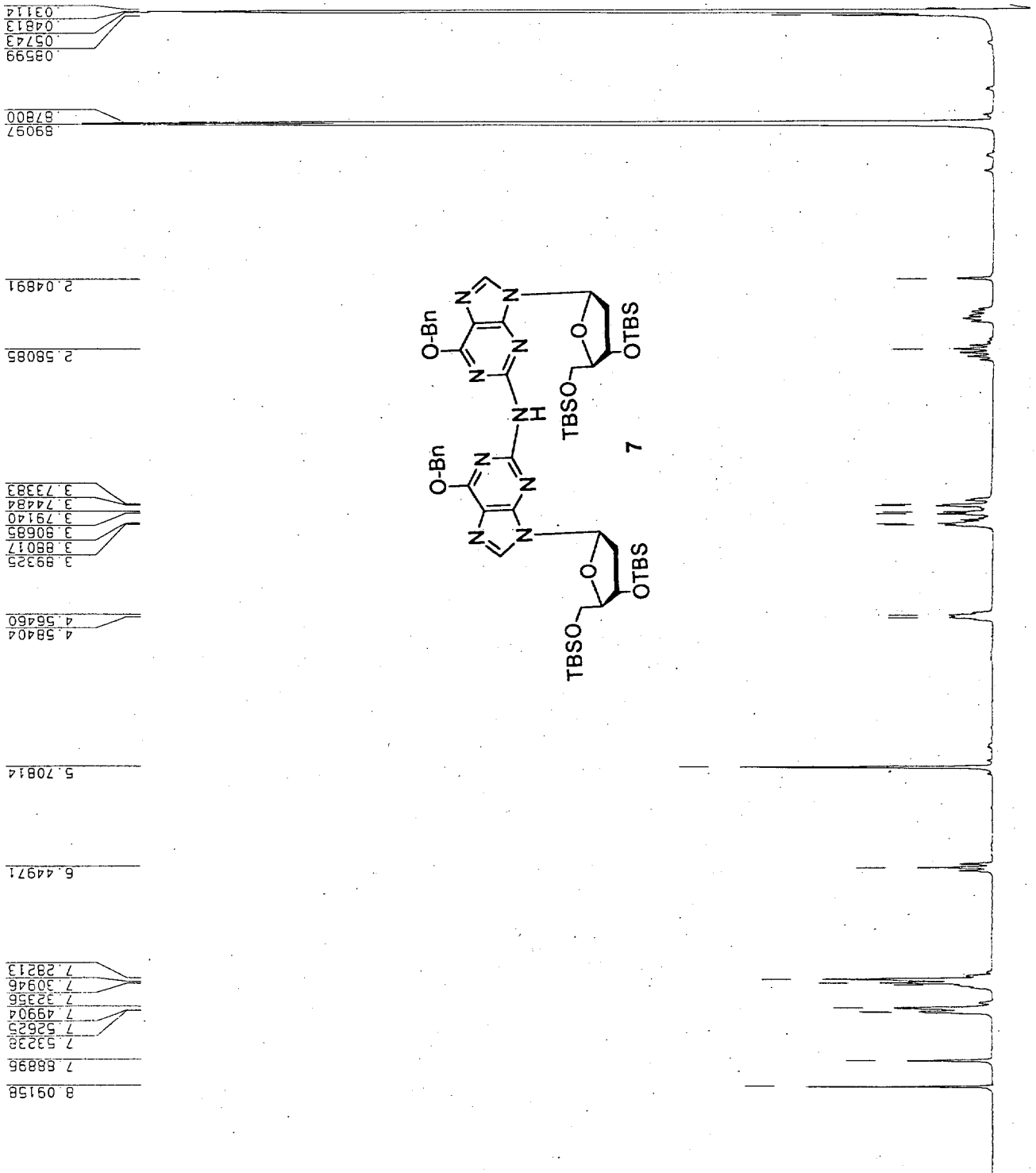
Compound (12): light-yellow oil (0.082 g, 51%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.88 (s, 2H), 8.32 (s, 2H), 6.50 (t, *J*=6.3 Hz, 2H), 4.62 (m, 2H), 4.02 (m, 2H), 3.88 (dd, *J*=11.2, 4.0 Hz, 2H), 3.78 (dd, *J*=11.2, 3.1 Hz, 2H), 2.68 (m, 2H), 2.47 (m, 2H), 0.91 (s, 36H), 0.10 (s, 12H), 0.08 (s, 12H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 152.7, 150.5, 149.6, 141.0, 122.5, 88.0, 84.6, 71.9, 62.7, 41.4, 25.9 (× 3), 25.7 (× 3), 18.4, 18.0, –4.8 (× 2), –5.5 (× 2); FABMS *m/z* 942 $[M+1]^+$; Anal. Calcd for $C_{44}H_{79}N_9O_6Si_4$: C, 56.07; H, 8.45; N, 13.38. Found: C, 56.20; H, 8.48; N, 13.47.

Compound (14): To a solution of **9** (0.050 g, 0.048 mmol) in ethanol (10 mL) was added a 10% palladium on activated-carbon catalyst (0.010 g). The flask was evacuated (50 Torr) and

flushed with hydrogen three times. The reaction mixture was hydrogenated for 24 h at 60 psi with stirring, then was filtered through a pad of celite and concentrated under reduced pressure to give **14** as a white solid, (0.046 g, 100%). An analytically pure sample was obtained by recrystallization from ethanol; m.p. 135–137° C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 13.49 (s, 1H), 8.95 (bs, 1H), 8.61 (s, 1H), 8.39 (s, 1H), 7.94 (s, 1H), 6.48 (t, *J*=6.1 Hz, 1H), 6.24 (t, *J*=6.5 Hz, 1H), 4.59 (m, 2H), 4.01 (m, 2H), 3.85 (m, 1H), 3.78-3.72 (m, 3H), 2.67 (m, 1H), 2.50-2.37 (m, 3H), 0.89 (s, 36H), 0.09 (s, 12H), 0.06 (s, 12H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 156.2, 151.0, 150.2, 149.5, 148.4, 141.8, 135.6, 120.8, 120.6, 88.1, 87.8, 84.4, 83.7, 71.7 (× 2), 62.7 (× 2), 41.3 (× 2), 25.9 (× 6), 25.7 (× 6), 18.3 (× 2), 17.9 (× 2), –4.7 (× 4), –5.5 (× 4); FABMS *m/z* 958 $[M+1]^+$; Anal. Calcd for $C_{44}H_{79}N_9O_7Si_4$: C, 55.14; H, 8.31; N, 13.15. Found: C, 55.28; H, 8.26; N, 13.05.

Compound (2): To a solution of **14** (0.030 g, 0.031 mmol) in pyridine (0.25 mL) at 0 °C in a polypropylene vial, HF/Pyridine (70%, 0.040 mL) was added. The vial was warmed at r.t. for 3 h and then concentrated under a stream of argon. The residue was washed with ethyl acetate to afford pure **2** as a beige solid (0.015 g, 97%); m.p. 160–163° C; UV (pH=5.7 buffer): λ_{max} 302 (ε=34,000); (pH=10.5 buffer): λ_{max} 257, 300, 340 (ε=10,000, 13,100, 7,000), ^{1}H NMR (250 MHz, C_5D_5N): δ 9.04 (s, 1H), 8.75 (bs, 1H), 8.54 (s, 1H), 6.97 (t, *J*=6.4 Hz, 1H), 6.84 (t, *J*=6.5 Hz, 1H), 5.22 (m, 1H), 5.14 (m, 1H), 4.60 (m, 2H), 4.28-4.13 (m, 4H), 3.15 (m, 1H), 2.98 (m, 1H), 2.90-2.77 (m, 2H); ^{13}C NMR (62.5 MHz, C_5D_5N): δ 156.9, 151.1, 150.7, 149.8 (× 3, overlapping with the solvent peak), 142.5, 137.2, 121.7, 121.0, 89.6, 89.4, 85.2, 84.3, 71.8, 71.6, 62.6, 62.5, 41.6, 41.5; FABMS *m/z* 502 $[M+1]^+$; Anal. Calcd for $C_{20}H_{23}N_9O_7$: C, 47.90; H, 4.62; N, 25.14. Found: C, 48.01; H, 4.72; N, 25.70.

Compound (3): To a solution of **12** (0.030 g, 0.032 mmol) in pyridine (0.25 mL) at 0 °C in a polypropylene vial, HF/Pyridine (70%, 0.040 mL) was added. The vial was warmed at r.t. for 3 h and then concentrated under a stream of argon. The residue was washed with ethyl acetate to afford pure **3** as an amorphous beige solid (0.015 g, 100%); ^{1}H NMR (250 MHz, C_5D_5N): δ 8.91 (s, 2H), 8.90 (s, 2H), 6.95 (t, *J*=6.5 Hz, 2H), 5.17 (m, 2H), 4.57 (m, 2H), 4.22 (dd, *J*=12.1, 2.8 Hz, 2H), 4.12 (dd, *J*=12.1, 3.1 Hz, 2H), 3.10 (m, 2H), 2.73 (m, 2H); ^{13}C NMR (62.5 MHz, C_5D_5N): δ 152.3, 151.8, 144.7, 142.0, 125.2, 89.6, 85.5, 71.8, 62.8, 41.3; FABMS *m/z* 486 $[M+1]^+$; Anal. Calcd for $C_{20}H_{23}N_9O_6$: C, 49.48; H, 4.78; N, 25.97. Found: C, 49.40; H, 4.72; N, 25.86.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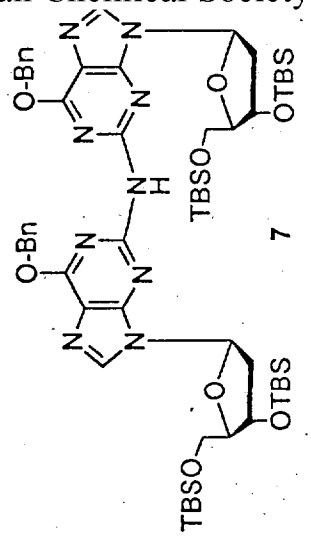

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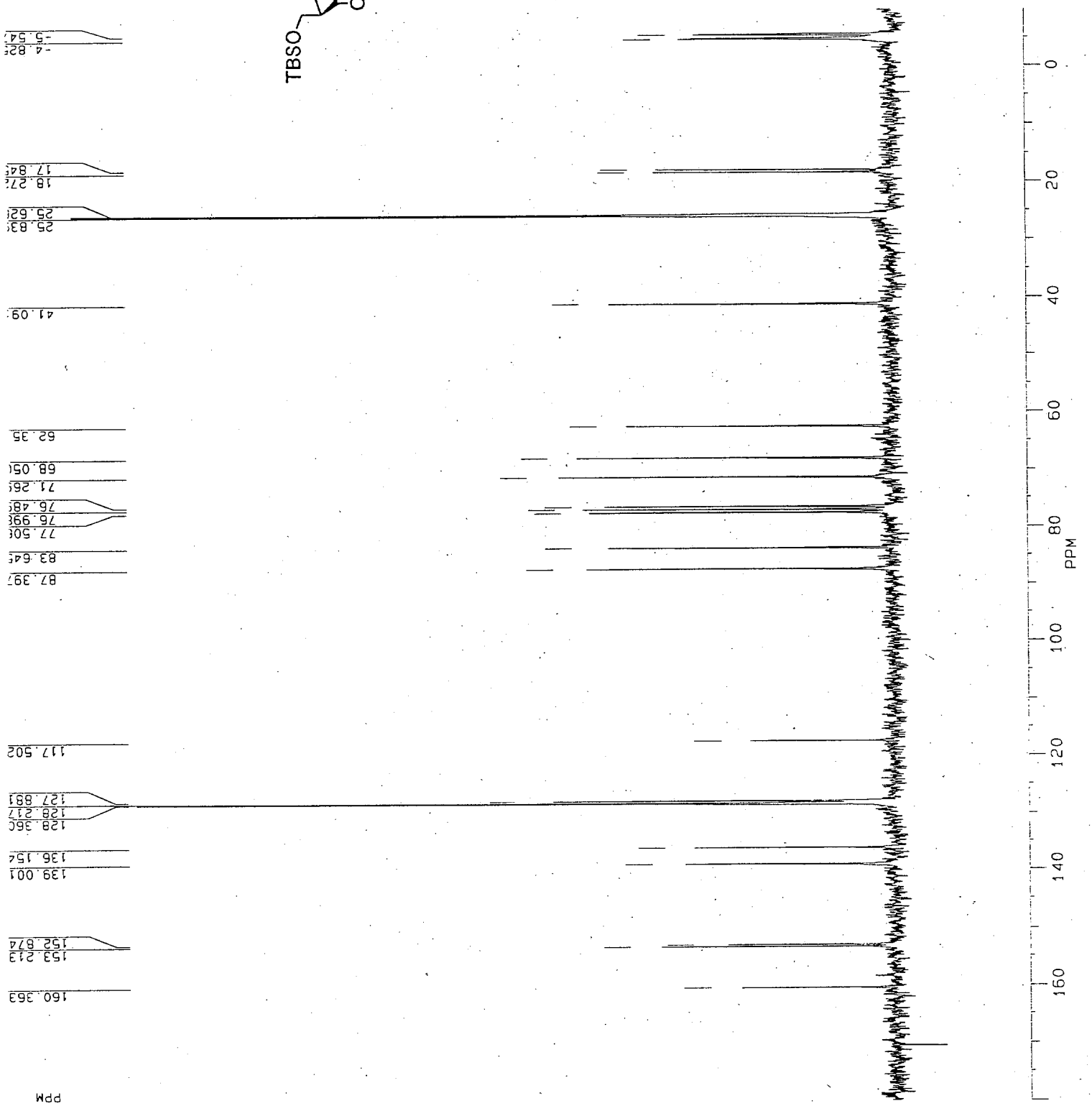

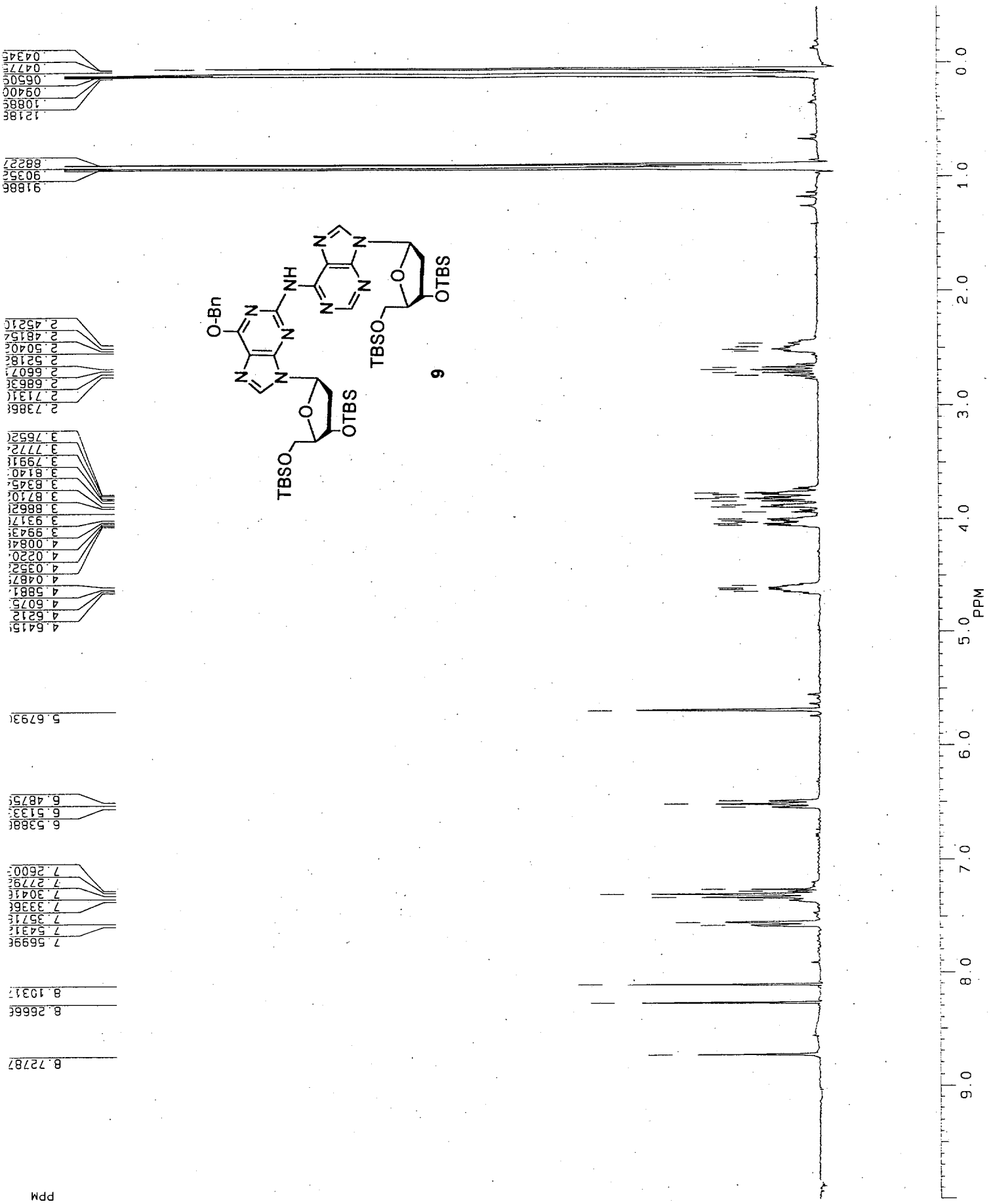

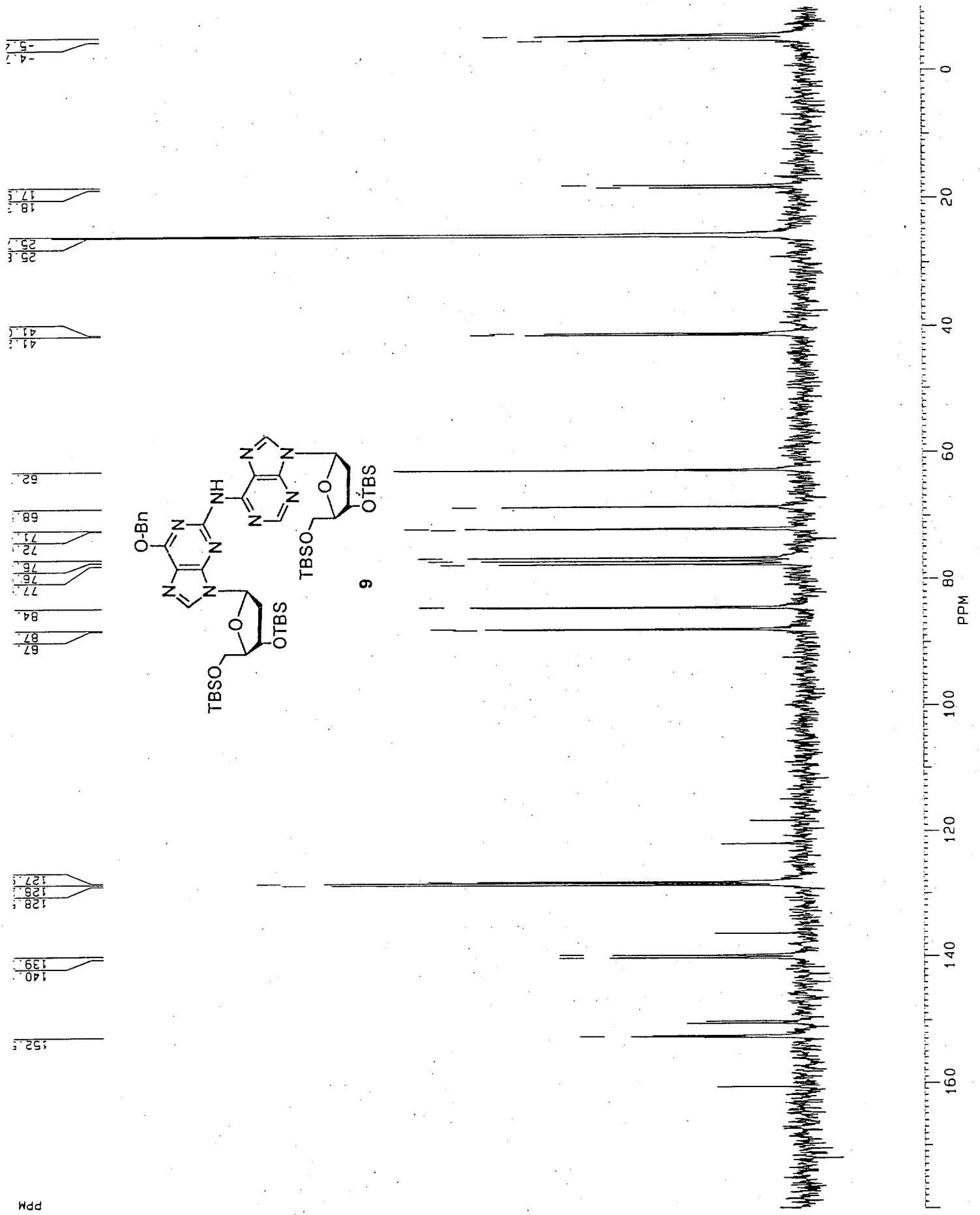
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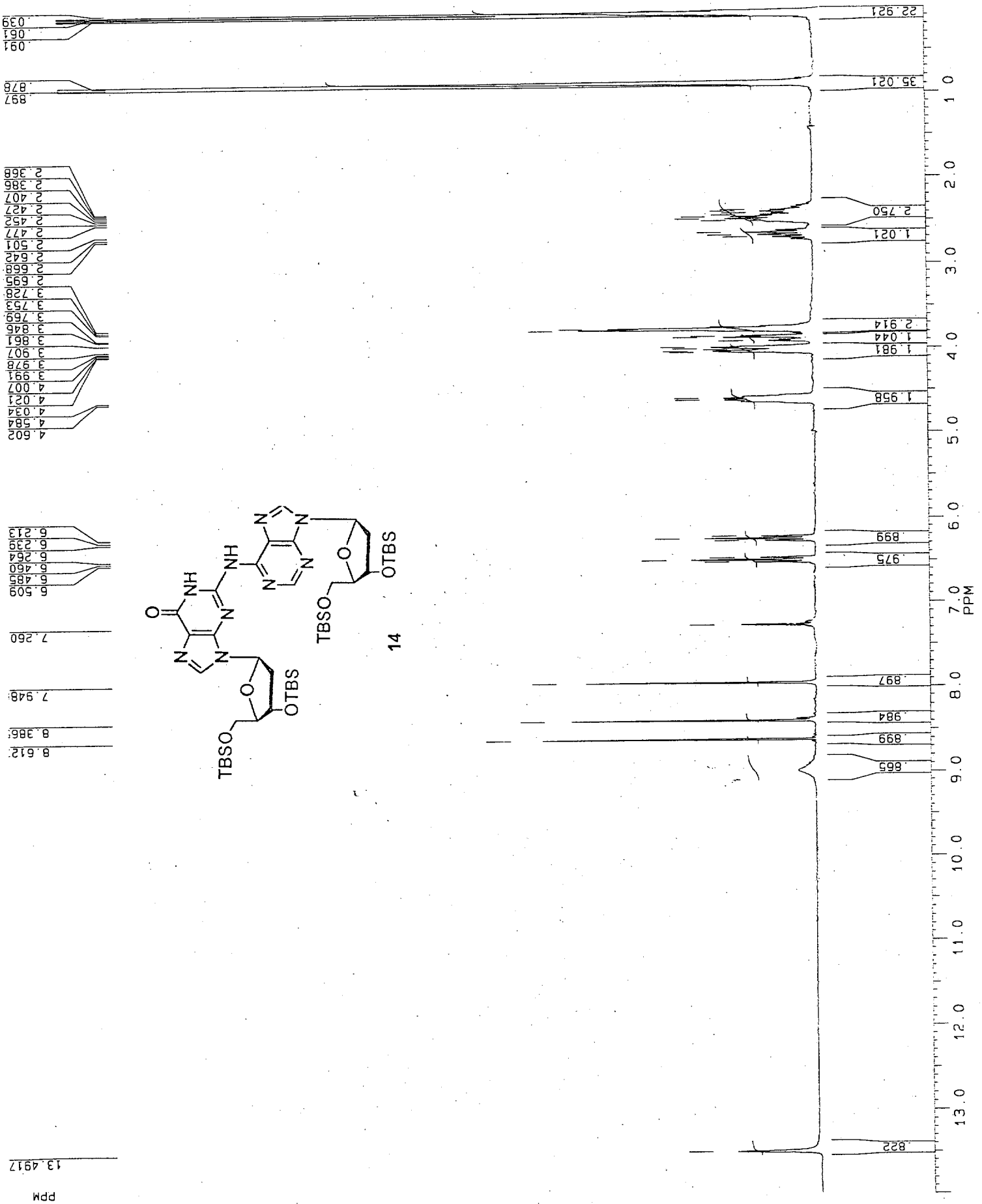
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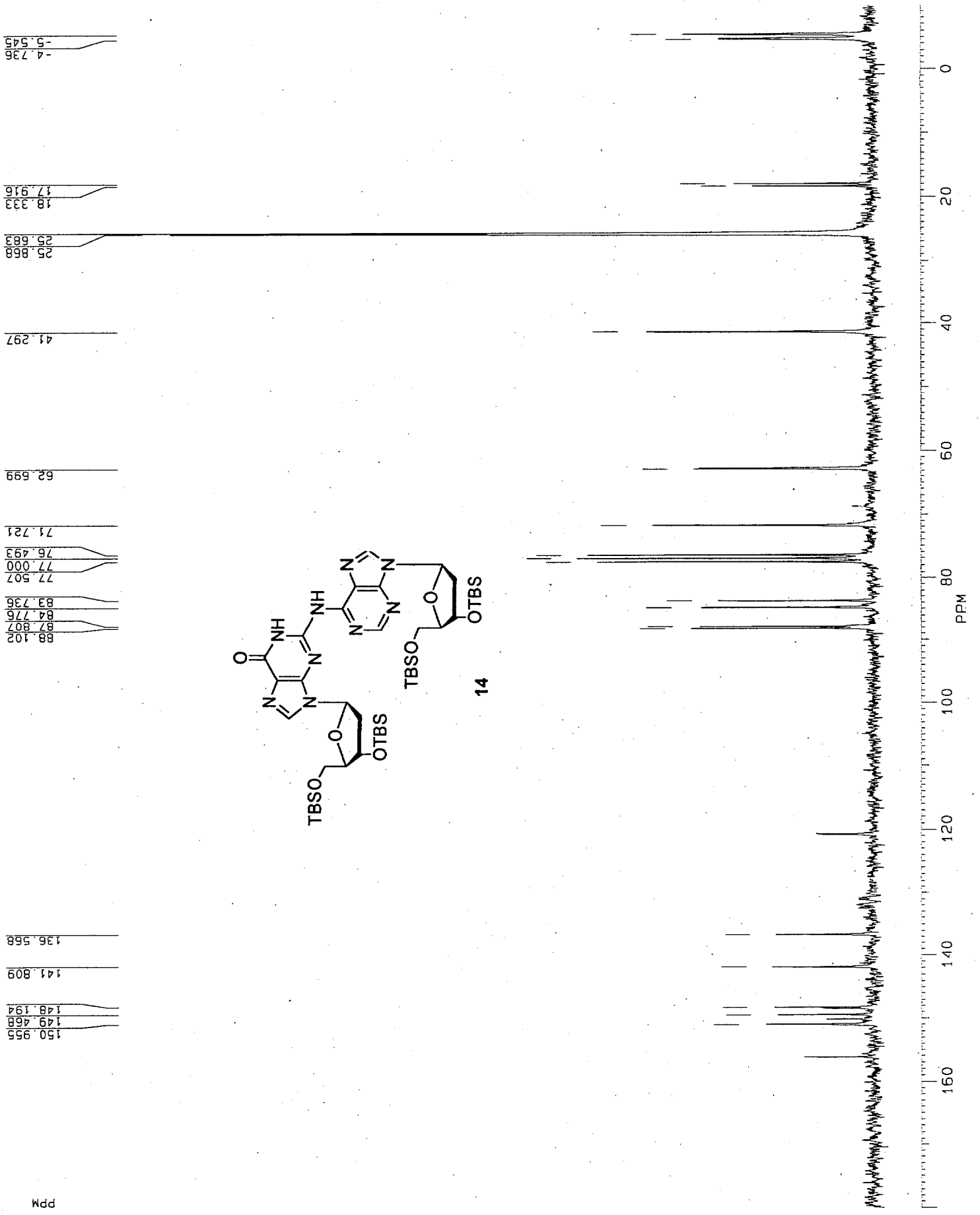

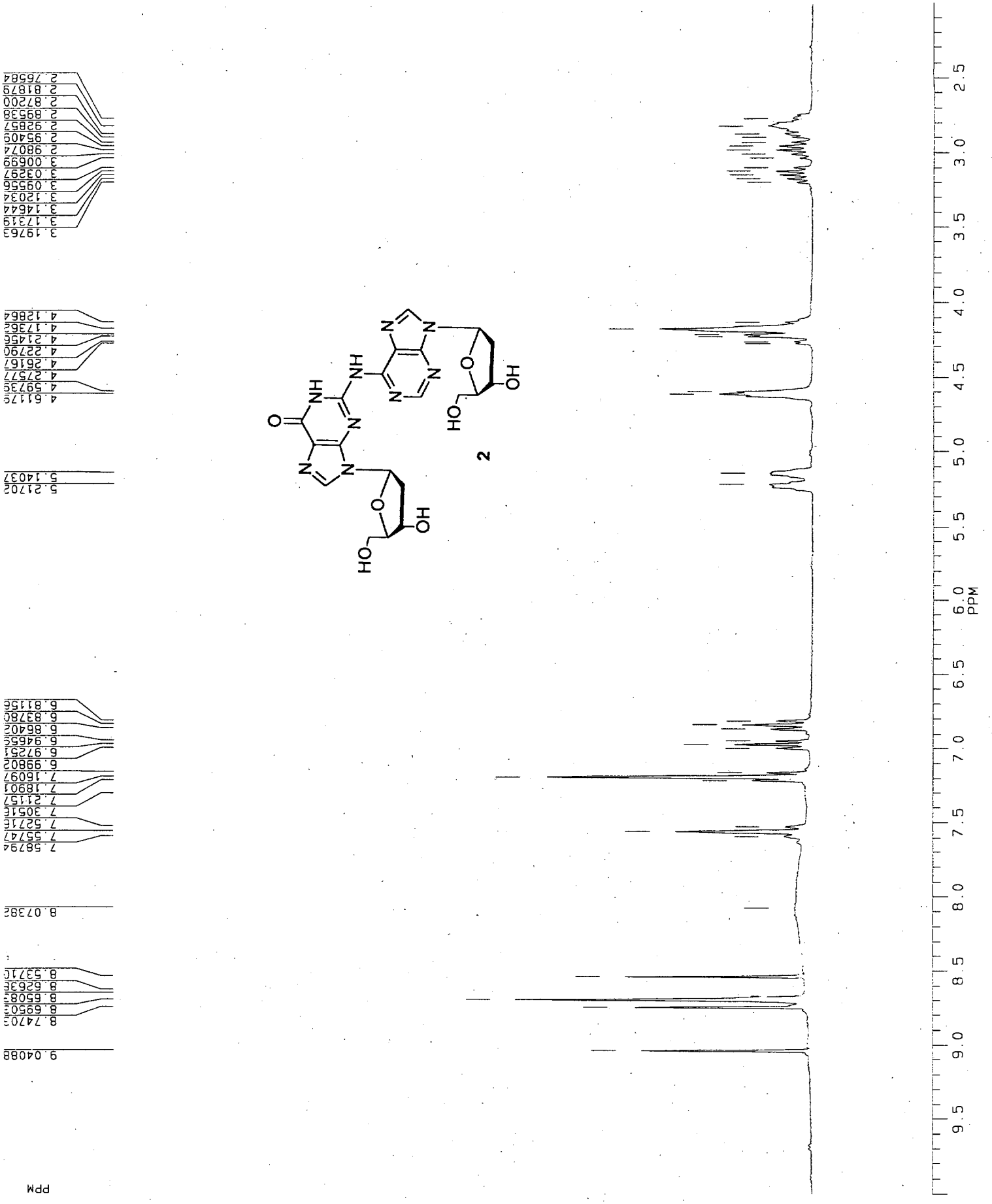

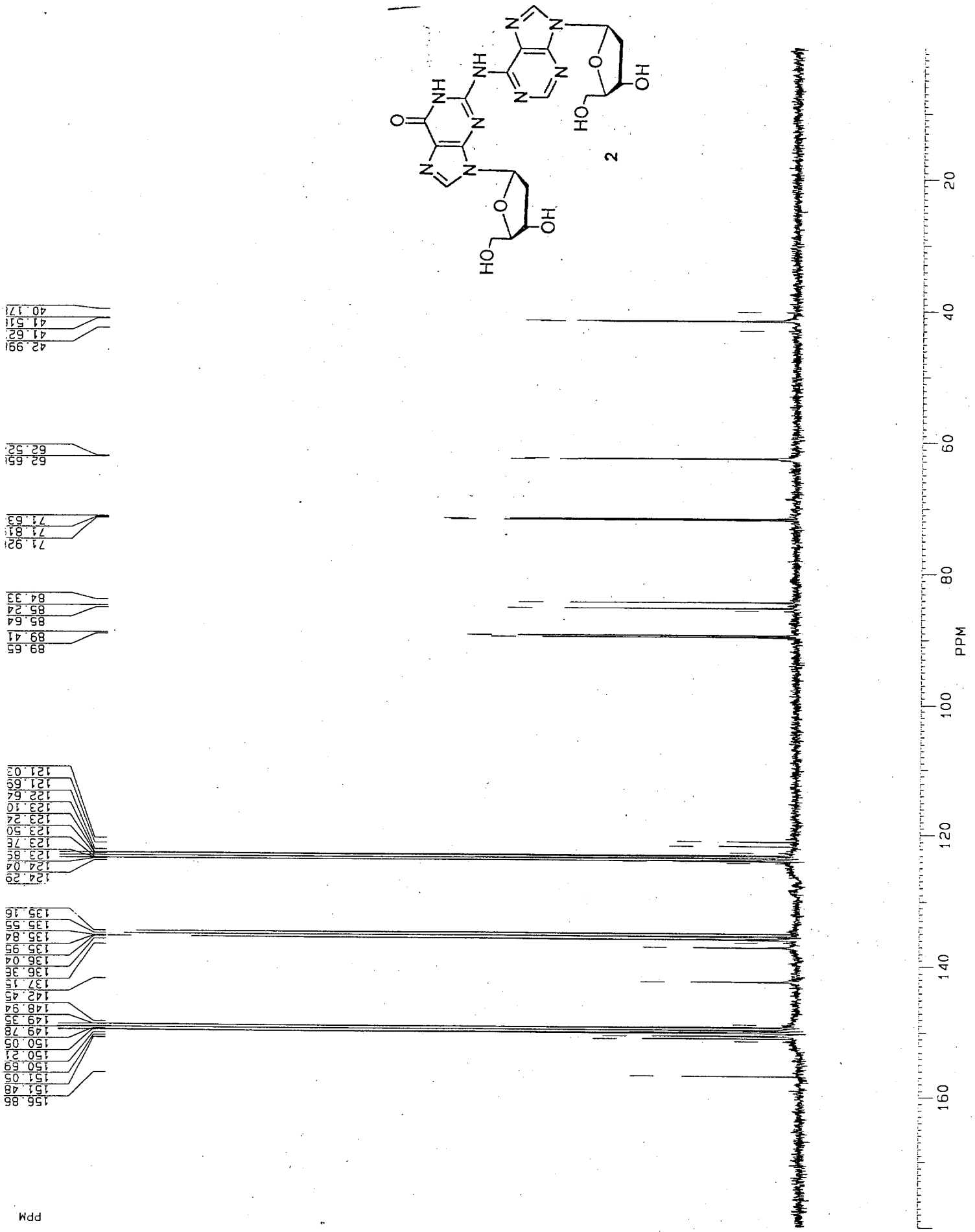

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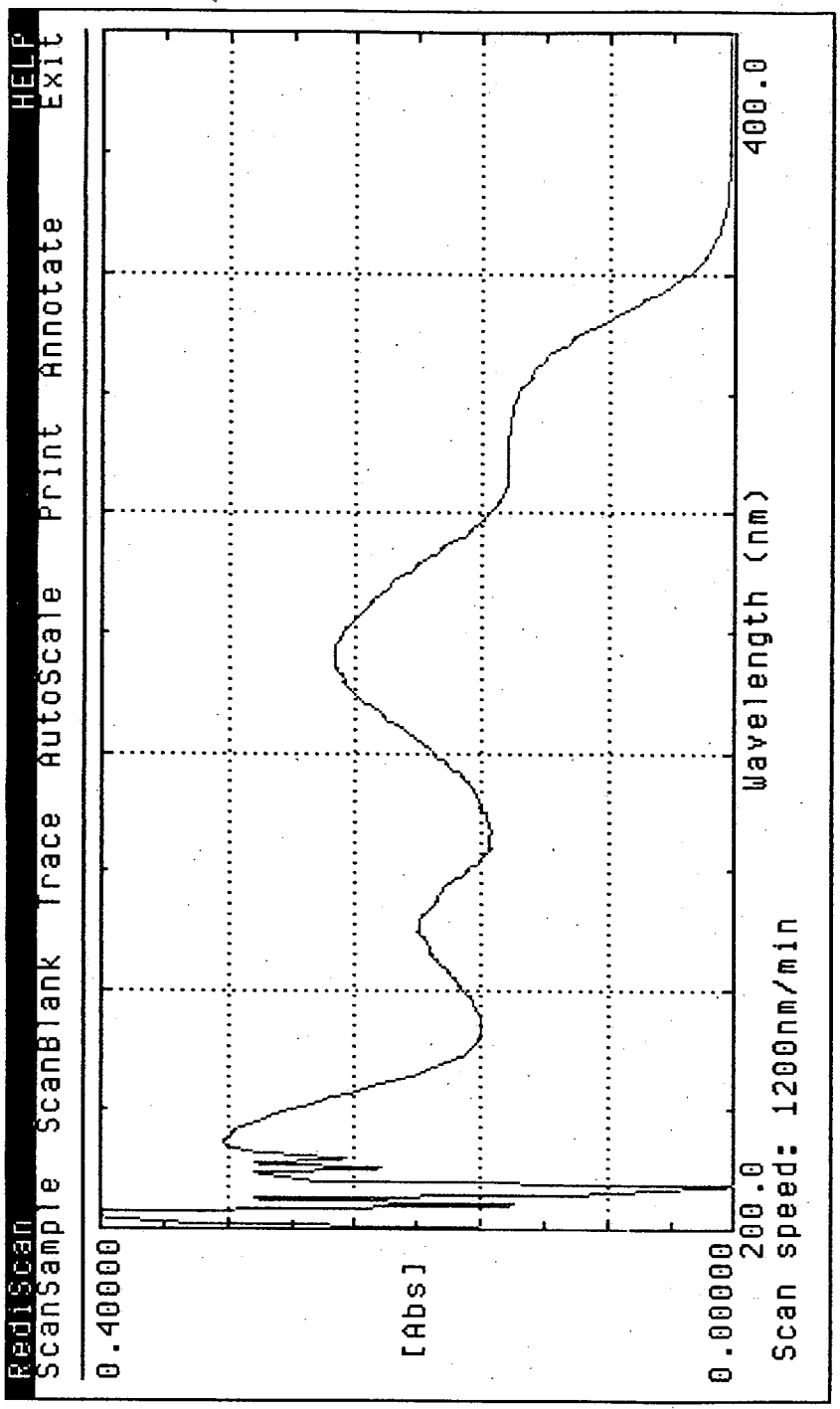

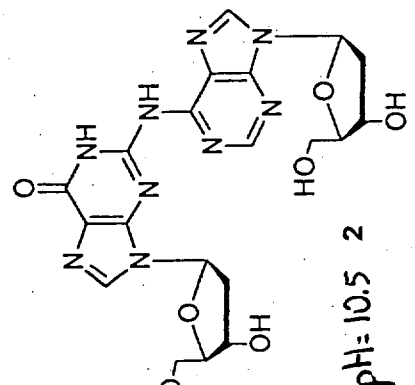

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