Efficient Synthesis of 2′-*C*-α-Aminomethyl-2′-deoxynucleosides

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Experimental

Methyl 3,5-di-*O*-benzyl-2-deoxy-2-α-hydroxymethyl-α-D-ribofuranoside (2): Under an argon atmosphere, *sec*-BuLi in cyclohexane (4.29 mL, 1.4 M, 6.0 mmol) was added to a suspension of triphenylmethylphosphonium bromide (2.14 g, 6.0 mmol) in THF (20 mL) at –78 ^{o}C. After the reaction mixture was stirred at –78 ^{o}C for 1 h, a solution of methyl 3,5-di-*O*-benzyl-2-keto-α-D-ribofuranoside (**1**) (1.18 g, 3.44 mmol) in THF (10 mL) was transferred slowly into the reaction mixture. The reaction mixture was allowed to warm to room temperature and stirred for 72 h. The reaction was quenched with *t*-butanol (5 mL), and stirred at room temperature for 24 h. The solid was filtered away and rinsed with ether. The filtrate was washed sequentially with saturated ammonium chloride and brine and dried over anhydrous $MgSO_4$. After solvent was removed, the residue was purified by silica gel chromatography, eluting with 10% ethyl acetate in hexane to give methyl 3,5-di-*O*-benzyl-2-methylene-α-D-ribofuranoside: (714 mg, 61% yield): ^{1}H NMR ($CDCl_3$/TMS) δ 7.30 (m, 10H), 5.44 (s, 1H), 5.39 (s, 1H), 5.25 (s, 1H), 4.63 (d, 1H, J = 12.0 Hz), 4.56-4.50 (m, 3H), 4.30 (m, 2H), 3.57 (m, 2H), 3.43 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 146.9, 138.0, 137.8, 128.2, 128.1, 127.7, 127.62, 127.56, 127.4, 114.0, 104.0, 81.0, 78.3, 73.3, 70.8, 69.6, 54.7. Under argon, 9-BBN dimer (774 mg, 3.17 mmol) was added to a solution of methyl 3,5-di-*O*-benzyl-2-methylene-α-D-ribofuranoside (1.079 g, 3.17 mmol) in THF (15 mL) at room temperature. After the reaction mixture was stirred at room temperature for 24 h, sodium perborate tetrahydrate (2.93 g, 19.0 mmol) and water (6 mL) were added and the mixture was stirred at room temperature for 2 h. The organic layer was separated, and the aqueous was extracted with

ethyl acetate (3x10mL). The organic layers were combined and dried over $MgSO_4$. The solvent was removed and the product was purified by silica gel chromatography, eluting with hexane/ethyl acetate (v/v=6/4) to give **2** (976 mg, 86% yield): ^{1}H NMR ($CDCl_3$/TMS) δ 7.35-7.20 (m, 10H), 5.00 (d, 1H, *J* = 5.2 Hz), 4.62-4.43 (m, 4H), 4.28 (m, 1H), 3.94 (dd, 1H, *J* = 7.6, 2.8 Hz), 3.87 (d, 2H, *J* = 7.2 Hz), 3.45-3.35 (m, 2H), 3.40 (s, 3H), 2.41 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 137.9, 137.8, 128.4, 128.3, 128.0, 127.78, 127.68, 105.3, 83.0, 78.4, 73.4, 71.9, 70.3, 57.8, 55.5, 49.0; HRMS calcd for $C_{21}H_{26}NaO_5$ [MNa^+] 381.1678, found 381.1689.

Methyl 3,5-di-*O*-benzyl-2-deoxy-2-α-phthalimidomethyl-α-D-ribofuranoside (3): To a solution of **2** (1.24 g, 3.47 mmol), phthalimide (614 mg, 4.17 mmol) and PPh_3 (1.10 g, 4.19 mmol) in dry THF (25 mL), was added DEAD (0.73 g, 4.2 mmol) at room temperature under argon. TLC showed the reaction was complete in 4 h. Methanol (4 mL) was added to the reaction mixture and the mixture was stirred at room temperature for 15 min. The solvent was removed, and the residue was isolated by silica gel chromatography, eluting with 20% ethyl acetate in hexane to give **3** (1.528 g, 90% yield): ^{1}H NMR ($CDCl_3$/TMS) δ 7.76 (dd, 2H, *J* = 5.1, 3.1 Hz), 7.63 (d, 2H, *J* = 3.1 Hz), 7.30-7.18 (m, 10H), 4.95 (d, 1H, *J* = 4.7 Hz), 4.60-4.42 (m, 4H), 4.31 (m, 1H), 4.01 (m, 2H), 3.94 (dd, 1H, *J* = 7.3, 2.0 Hz), 3.43 (s, 3H), 3.34 (m, 2H), 2.73 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 167.6, 137.6, 137.5, 133.4, 131.5, 127.8, 127.7, 127.1, 122.5, 104.7, 83.0, 78.4, 72.8, 71.7, 70.0, 55.1, 45.6, 32.5; HRMS calcd for $C_{29}H_{33}N_2O_6$ [MNH_4^+] 505.2339, found 505.2319.

Methyl 3,5-di-*O*-benzyl-2-deoxy-2-α-[(α,α,α-trifluoroacetyl)aminomethyl]-α-D-ribofuranoside (4): The mixture of **3** (1.218 g, 2.50 mmol), 33% methylamine in EtOH (6.2 mL, 50 mmol), and EtOH (25 mL) were loaded in a sealed tube and stirred in an 80 ºC bath for 2.5 h. After it was cooled down, the solvent was removed, and the residue was dissolved into ether. The ether solution was washed with water, brine and dried over anhydrous $MgSO_4$. The solution was filtered and evaporated, and the residue was dried over vacuum for 30 min. The residue was then dissolved in a mixed solvent of dry dichloromethane and DMF (v/v 1:1). To the resulting solution, triethylamine (1.39 mL, 10.0 mmol) and *S*-ethyl trifluorothioacetate (0.79 g, 5.0 mmol) were added. The reaction mixture was stirred at room temperature for 1 h. TLC showed the reaction was complete. The solvent was removed, and the residue was isolated by silica gel chromatography, eluting with 20% ethyl acetate in hexane to give **4** (773 mg, 68% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 7.35-7.20 (m, 10H), 6.99 (brs, 1H), 4.92 (d, 1H, J = 4.9 Hz), 4.57 (d, 1H, J = 12.2 Hz), 4.50 (d, 1H, J = 12.1 Hz), 4.47 (d, 1H, J = 12.1 Hz), 4.36 (d, 1H, J = 12.2 Hz), 4.28 (m, 1H), 3.91 (dd, 1H, J = 7.4, 2.3 Hz), 3.59 (m, 2H), 3.43 (m, 1H), 3.37 (s, 3H), 3.39-3.33 (m, 1H), 2.45 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 156.8 (q), 137.5, 137.3, 128.2, 128.1, 127.74, 127.67, 127.45, 127.42, 115.6 (q), 104.7, 82.7, 78.3, 73.1, 71.5, 70.0, 55.0, 45.0, 34.8; HRMS calcd for $C_{23}H_{30}N_2O_5F_3$ [MNH_4^+] 471.2107, found 471.2097.

3′,5′-Di-*O*-benzyl-2′-deoxy-2′-*C*-α-phthalimidomethyluridine (5a): Bis(trimethylsilyl)uracil was prepared under an argon atmosphere by the reaction of uracil (224 mg, 2.00 mmol) with refluxing TMS_2NH (5 mL) in the presence of

$(NH_4)_2SO_4$ (5 mg) for 30 min. After the reaction mixture became clear, the excess TMS_2NH was evaporated under vacuum, and the residue was dried under vacuum for 1 h. Under argon, the persilylated base was dissolved into acetonitrile (10 mL), and the solution was transferred into the flask containing compound **3** (244 mg, 0.501 mmol). $SnCl_4$ (0.234 mL, 2.00 mmol) was added in one-portion with vigorous stirring and exclusion of moisture. The homogeneous pale yellow solution was stirred at room temperature for 20 h. TLC showed that no starting material remained. The reaction mixture was quenched carefully by addition of saturated aqueous $NaHCO_3$ (10 mL) and stirred for 15 min. The mixture was extracted with dichloromethane, and the organic phase was washed with brine and dried over $MgSO_4$. After evaporation of solvent, the product was purified by silica gel chromatography, eluting with hexane/ethyl acetate (v/v=4/6) to give compound **5a** (261 mg, 92% yield). The β/α selectivity is 98:2 based on the ^{1}H NMR spectra of **5a**. β-anomer: ^{1}H NMR ($CDCl_3$/TMS) δ 9.41 (s, 1H), 7.80-7.60 (m, 5H), 7.36-7.23 (m, 10H), 6.14 (d, 1H, *J* = 6.6 Hz), 5.26 (dd, 1H, *J* = 8.1, 1.7 Hz), 4.64 (d, 1H, *J* = 11.6 Hz), 4.56 (d, 1H, *J* = 11.6 Hz), 4.48 (s, 2H), 4.25 (m, 1H), 4.22 (m, 1H), 4.00 (m, 2H), 3.81 (dd, 1H, *J* = 10.8, 2.8 Hz), 3.59 (dd, 1H, *J* = 10.8, 2.0 Hz), 3.02 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 167.9, 163.2, 150.0, 139.8, 137.0, 136.9, 133.8, 131.6, 128.2, 127.82, 127.79, 127.5, 122.9, 101.7, 87.3, 82.0, 77.5, 73.2, 71.9, 69.2, 46.0, 33.4; HRMS calcd for $C_{32}H_{29}N_3O_7Na$ [MNa^+] 590.1903, found 590.1883.

3′,5′-Di-*O*-benzyl-2′-deoxy-2′-*C*-α-[(α,α,α-trifluoroacetyl)aminomethyl]uridine (5b): Bis(trimethylsilyl)uracil was prepared under an argon atmosphere by the reaction of uracil (112 mg, 1.00 mmol) with refluxing TMS_2NH (2.5 mL) in the presence of

$(NH_4)_2SO_4$ (5 mg) for 30 min. After the reaction mixture became clear, the excess TMS_2NH was evaporated under vacuum, and the residue was dried under vacuum. Under argon, the persilylated base was dissolved into acetonitrile (10 mL), and the solution was transferred into the flask containing compound **4** (109 mg, 0.24 mmol). $SnCl_4$ (0.12 mL, 1.0 mmol) was added in one-portion with vigorous stirring. The solution was stirred at room temperature for 3.5 h. TLC showed that no starting material remained. The reaction mixture was quenched carefully by addition of saturated aqueous $NaHCO_3$ (5 mL) and stirred for 15 min. The mixture was extracted with ethyl acetate. After evaporation of solvent, the product was purified by silica gel chromatography, eluting with hexane/ethyl acetate (v/v=1/1) to give compound **5b** (83 mg, 65% yield). The β/α selectivity is 96:4 based on the ^{1}H NMR spectra of **5b**. β-anomer: ^{1}H NMR ($CDCl_3$/TMS) δ 9.75 (brs, 1H), 7.77 (d, 1H, *J* = 8.2 Hz), 7.50 (brs, 1H), 7.37-7.24 (m, 10H), 6.08 (d, 1H, *J* = 6.6 Hz), 5.41 (d, 1H, *J* = 8.2 Hz), 4.60-4.40 (m, 4H), 4.24 (m, 1H), 4.20 (m, 1H), 3.79 (m, 2H), 3.60-3.38 (m, 2H), 2.70 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 163.1, 157.3 (q), 150.9, 139.5, 136.7, 136.5, 128.4, 128.1, 128.0, 127.5, 116.0 (q), 102.5, 87.8, 82.3, 78.4, 73.4, 71.9, 69.2, 46.5, 36.4; HRMS calcd for $C_{26}H_{26}N_3O_6F_3Na$ [MNa^+] 556.1671, found 556.1655.

***N*^{4}-Acetyl-3′,5′-di-*O*-benzyl-2′-deoxy-2′-*C*-α-phthalimidomethylcytidine (6a)**:

Persilylated *N*^{4}-acetylcytosine was prepared under an argon atmosphere by the reaction of *N*^{4}-acetylcytosine (306 mg, 2.0 mmol) with refluxing TMS_2NH (5 mL) in the presence of $(NH_4)_2SO_4$ (5 mg) for 30 min to get a clear solution. The excess TMS_2NH was evaporated under vacuum, and the residue was dried under vacuum for 1 h. Under argon, the persilylated base was dissolved into acetonitrile (10 mL), and the solution was

transferred into the flask containing compound **3** (244 mg, 0.501 mmol). $SnCl_4$ (0.234 mL, 2.00 mmol) was added in one-portion with vigorous stirring and exclusion of moisture at 0 ºC. The homogeneous pale yellow solution was stirred at room temperature for 2 h. TLC showed that no starting material remained. The reaction mixture was quenched carefully by addition of saturated aqueous $NaHCO_3$ (10 mL) and stirred for 15 min. The mixture was extracted with dichloromethane, and the organic phase was washed with brine and dried over $MgSO_4$. After evaporation of solvent, the product was purified by silica gel chromatography, eluting with 3% methanol in chloroform to give compound **6a** (273 mg, 90% yield). The β/α selectivity is >99:1 based on the ^{1}H NMR spectra of **6a**.

β-anomer:

^{1}H NMR ($CDCl_3$/TMS) δ 10.43 (s, 1H), 8.31 (d, 1H, *J* = 7.6 Hz), 7.81 (dd, 2H, *J* = 5.4, 3.0 Hz), 7.66 (dd, 2H, *J* = 5.4, 3.0 Hz), 7.40-7.23 (m, 10H), 7.00 (d, 1H, *J* = 7.6 Hz), 6.04 (d, 1H, *J* = 2.8 Hz), 4.74 (d, 1H, *J* = 11.4 Hz), 4.56 (d, 1H, *J* = 11.4 Hz), 4.49 (d, 1H, *J* = 11.4 Hz), 4.47 (d, 1H, *J* = 11.4 Hz), 4.27 (m, 2H), 4.00 (m, 2H), 3.93 (m, 1H), 3.64 (m, 1H), 2.97 (m, 1H), 1.93 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.4, 168.5, 162.8, 154.5, 144.4, 137.1, 137.0, 133.7, 132.1, 128.5, 128.4, 128.02, 127.97, 127.9, 127.7, 123.0, 96.1, 88.9, 81.8, 75.0, 73.4, 72.3, 67.7, 46.4, 34.1, 24.4; HRMS calcd for $C_{34}H_{32}N_4O_7Na$ [MNa^+] 631.2169, found 631.2172.

***N*^{4}-Acetyl-3′,5′-di-*O*-benzyl-2′-deoxy-2′-*C*-α-[(α,α,α-trifluoroacetyl)aminomethyl]cytidine (6b)**: Persilylated *N*^{4}-acetylcytosine was prepared under an argon atmosphere by the reaction of *N*^{4}-acetylcytosine (153 mg, 1.00 mmol) with refluxing TMS_2NH (2.5 mL) in the presence of $(NH_4)_2SO_4$ (5 mg) for 30 min.

After the reaction mixture became clear, the excess TMS_2NH was evaporated under vacuum, and the residue was dried under vacuum. Under argon, the persilylated base was dissolved into acetonitrile (10 mL), and the solution was transferred into the flask containing compound **4** (113 mg, 0.25 mmol). $SnCl_4$ (0.12 mL, 1.0 mmol) was added in one-portion with vigorous stirring. The solution was stirred at room temperature for 18 h. TLC showed that no starting material remained. The reaction mixture was quenched carefully by addition of saturated aqueous $NaHCO_3$ (5 mL) and stirred for 15 min. The mixture was extracted with ethyl acetate. After evaporation of solvent, the product was purified by silica gel chromatography, eluting with hexane/ethyl acetate (v/v=4/6) to give compound **6b** (119 mg, 83% yield). The β/α selectivity is 91:9 based on the ^{1}H NMR spectra of **6b**. β-anomer: ^{1}H NMR ($CDCl_3$/TMS) δ 9.90 (brs, 1H), 8.71 (brs, 1H), 8.40 (d, 1H, *J* = 7.2 Hz), 7.45-7.20 (m, 11H), 5.93 (d, 1H, *J* = 2.8 Hz), 4.54 (m, 2H), 4.42 (m, 2H), 4.27 (m, 1H), 4.22 (m, 1H), 3.90 (m, 1H), 3.80 (m, 1H), 3.60 (m, 1H), 3.47 (m, 1H), 2.64 (m, 1H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.9, 163.0, 157.8 (q), 155.7, 144.5, 136.9, 136.7, 128.7, 128.6, 128.4, 128.3, 128.0, 127.9, 115.8 (q), 97.1, 89.7, 82.6, 75.6, 73.6, 72.7, 67.7, 47.1, 37.5, 24.7; HRMS calcd for $C_{28}H_{29}N_4O_6F_3Na$ [MNa^+] 597.1937, found 597.1963.

***N*^{6}-Octanoyl-3′,5′-di-*O*-benzyl-2′-deoxy-2′-*C*-α-phthalimidomethyladenosine (8)**: Persilylated *N*^{6}-octanoyladenine (**7**) was prepared *in situ* under an argon atmosphere by the reaction of *N*^{6}-octanoyladenine (261 mg, 1.00 mmol) and *N,O*-bis(trimethylsilyl)acetamide (0.49 mL, 2.0 mmol) in 1,2-dichloroethane (15 mL) in a 50 ºC bath for 30 min. To the resulting solution at room temperature, **3** (244 mg, 0.501

mmol) was added, followed by the addition of TMSOTf (0.18 mL, 1.0 mmol). The reaction mixture was heated to 50 ºC for 3.5 h. TLC showed only small amount of product formed. The reaction mixture was then heated to reflux for 2 h. After it was cooled to room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$. The product was extracted with dichloromethane. The solvent was removed, the residue was isolated by silica gel chromatography, eluting with 1% methanol in chloroform to give **8** (0.244 g, 68% yield). The β/α selectivity is 96:4 based on the ^{1}H NMR spectra of **8**. β-anomer: ^{1}H NMR ($CDCl_3$/TMS) δ 8.83 (brs, 1H), 8.21 (s, 1H), 8.19 (s, 1H), 7.63-7.55 (m, 4H), 7.36-7.25 (m, 10H), 6.34 (d, 1H, *J* = 7.3 Hz), 4.65-4.58 (m, 3H), 4.52 (d, 1H, *J* = 12.0 Hz), 4.40 (m, 1H), 4.35 (dd, 1H, *J* = 5.8, 2.8 Hz), 4.16 (dd, 1H, *J* = 14.4, 10.0 Hz), 4.00 (dd, 1H, *J* = 14.4, 4.4 Hz), 3.84 (m, 1H), 3.77 (dd, 1H, *J* = 10.4, 4.9 Hz), 3.62 (dd, 1H, *J* = 10.4, 3.7 Hz), 2.75 (t, 2H, *J* = 7.5 Hz), 1.72 (m, 2H), 1.40-1.25 (m, 8H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 172.8, 167.8, 151.9, 150.5, 148.7, 142.0, 137.4, 137.0, 133.7, 131.3, 128.41, 128.37, 128.0, 127.9, 127.8, 127.6, 122.8, 121.7, 87.9, 82.4, 78.7, 73.4, 71.7, 69.3, 44.8, 37.7, 34.2, 31.6, 29.1, 28.9, 24.8, 22.5, 14.0; HRMS calcd for $C_{41}H_{44}N_6O_6Na$ [MNa^+] 739.3215, found 739.3235.

***N*^{2}-Acetyl-3′,5′-di-*O*-benzyl-2′-deoxy-*O*^{6}-(diphenylcarbamoyl)-2′-*C*-α-phthalimidomethylguanosine (10):** Persilylated *N*^{2}-acetyl-*O*^{6}-(diphenylcarbamoyl)-guanine (**9**) was prepared under an argon atmosphere by the reaction of *N*^{2}-acetyl-*O*^{6}-(diphenylcarbamoyl)-guanine (582 mg, 1.50 mmol) and *N,O*-bis(trimethylsilyl)acetamide (0.73 mL, 3.0 mmol) in 1,2-dichloroethane (20 mL) in a 80 ºC bath for 15 min. To the resulting solution at room temperature, **4** (339 mg, 0.695 mmol) was added, followed by

the addition of TMSOTf (0.27 mL, 1.5 mmol). The reaction mixture was heated to reflux for 1.5 h. After it was cooled to room temperature, the reaction was neutralized with saturated aqueous $NaHCO_3$. The solid was filtered off. The filtrate was washed with brine. The organic layer was evaporated, the residue was isolated by silica gel chromatography, eluting with 2% methanol in chloroform to give **8** (0.338 g, 58% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 8.12 (s, 1H), 7.55-7.27 (m, 24H), 6.20 (d, 1H, *J* = 8.0 Hz), 4.64 (d, 1H, *J* = 11.8 Hz), 4.61 (d, 1H, *J* = 12.1 Hz), 4.54 (d, 1H, *J* = 11.8 Hz), 4.51 (d, 1H, *J* = 12.1 Hz), 4.35 (m, 1H), 4.31 (dd, 1H, *J* = 5.6, 1.7 Hz), 4.23 (dd, 1H, *J* = 14.3, 10.5 Hz), 3.90 (dd, 1H, *J* = 14.3, 4.5 Hz), 3.81 (m, 1H), 3.67 (dd, 1H, *J* = 10.3, 4.6 Hz), 3.55 (dd, 1H, *J* = 10.3, 3.5 Hz), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.1, 167.6, 155.5, 153.9, 151.6, 149.8, 143.2, 141.6, 137.2, 136.9, 134.1, 130.7, 129.0, 128.43, 128.39, 128.0, 127.9, 127.8, 127.6, 122.7, 120.5, 87.6, 82.6, 79.1, 73.4, 71.6, 69.6, 44.6, 34.2, 25.0; HRMS calcd for $C_{48}H_{41}N_7O_8Na$ [MNa^+] 866.2909, found 866.2872.

2′-Deoxy-2′-*C*-α-phthalimidomethyluridine (11a):

Method A: To the solution of **5a** (243 mg, 0.43 mmol) in ethyl acetate (15 mL), $Pd(OH)_2$ on active carbon (20% wt., 30 mg, 0.043 mmol) was added. The mixture was stirred under a hydrogen atmosphere for 17 h. TLC showed the reaction was not complete. Additional $Pd(OH)_2$ on active carbon (20% wt., 30 mg, 0.043 mmol) was added and the mixture was stirred under hydrogen for additional 5 h. TLC showed the reaction was complete. The catalyst was filtered off, rinsed with methanol. The solvent was removed, the residue was isolated by silica gel chromatography, eluting with ethyl acetate to give **11a** (103 mg, 62% yield).

Method B: Under argon atmosphere, to a solution of **5a** (227 mg, 0.40 mmol) in dry dichloromethane (15 mL) at −78 ºC, boron trichloride (1.0 M in CH_2Cl_2, 8.0 mL, 8.0 mmol) was slowly added. After the reaction mixture was stirred at −78 ºC for 4 h, a mixed solvent of CH_3OH/CH_2Cl_2 (v/v 1:1) (15 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 30 min. The solvent was removed, and the residue was isolated by silica gel chromatography, eluting with 5% methanol in chloroform to give **11a** (139 mg, 90% yield).

^{1}H NMR (DMF-d_6/TMS) δ 7.99 (d, 1H, J = 8.1 Hz), 7.84 (m, 4H), 6.13 (d, 1H, J = 8.1 Hz), 5.56 (d, 1H, J = 8.1 Hz), 4.47 (dd, 1H, J = 5.5, 2.3 Hz), 4.04 (m, 1H), 3.98 (m, 2H), 3.74 (m, 2H), 3.02 (m, 1H); ^{13}C NMR (DMF-d_6) δ 168.7, 163.4, 151.5, 141.0, 134.9, 132.7, 123.5, 102.6, 88.0, 87.3, 72.0, 62.4, 47.1, 34.3; HRMS calcd for $C_{18}H_{18}N_3O_7$ [MH^+] 388.1145, found 388.1142.

2′-Deoxy-2′-*C*-α-[(α,α,α-trifluoroacetyl)aminomethyl]uridine (11b): To the solution of **5b** (79 mg, 0.15 mmol) in ethyl acetate (5 mL), $Pd(OH)_2$ on active carbon (20% wt., 11 mg, 0.015 mmol) was added. The mixture was stirred under a hydrogen atmosphere for 17 h. TLC showed the reaction was complete. The catalyst was filtered off, rinsed with methanol. The solvent was removed, the residue was isolated by silica gel chromatography, eluting with ethyl acetate to give **11b** (43 mg, 81% yield). ^{1}H NMR (CD_3OD/TMS) δ 7.97 (d, 1H, J = 6.5 Hz), 6.09 (d, 1H, J = 6.8 Hz), 5.72 (d, 1H, J = 6.5 Hz), 4.34 (dd, 1H, J = 4.5, 1.5 Hz), 4.01 (m, 1H), 3.75 (m, 2H), 3.64 (dd, 1H, J = 11.2, 5.7 Hz), 3.46 (m, 1H), 2.70 (m, 1H); ^{13}C NMR (CD_3OD) δ 165.9, 159.2 (q), 152.4, 142.3,

117.2 (q), 103.2, 88.6, 88.4, 73.1, 63.0, 48.7, 36.9; HRMS calcd for $C_{12}H_{15}N_3O_6F_3$ [MH^+] 354.0913, found 354.0916.

2′-Deoxy 2′-*C*-α-phthalimidomethylcytidine (12): Under argon atmosphere, to a solution of **6a** (231 mg, 0.38 mmol) in dry dichloromethane (15 mL) at −78 ºC, boron trichloride (1.0 M in CH_2Cl_2, 7.6 mL, 7.6 mmol) was slowly added. After the reaction mixture was stirred at −78 ºC for 2.5 h, then warmed to 0 ºC for 30 min, the reaction was quenched with CH_3OH (10 mL) at 0 ºC and stirred at room temperature for 12 h. The solvent was removed, and the residue was dissolved into water. The aqueous solution was washed with chloroform. The aqueous layers were combined and evaporated to dryness. The product was isolated by silica gel chromatography, eluting with 20% methanol in ethyl acetate containing 0.4% triethylamine to give **12** (146 mg, 99% yield). ^{1}H NMR (D_2O) δ 7.65-7.50 (m, 4H), 7.42 (d, 1H, *J* = 7.6 Hz), 5.91 (d, 1H, *J* = 9.5 Hz), 5.57 (d, 1H, *J* = 7.6 Hz), 4.35 (m, 1H), 3.97 (m, 1H), 3.88 (dd, 1H, *J* = 14.5, 10.6 Hz), 3.69 (dd, 1H, *J* = 14.5, 5.0 Hz), 3.63 (m, 2H), 2.86 (m, 1H); ^{13}C NMR (D_2O) δ 169.9, 165.5, 157.1, 141.8, 135.5, 131.2, 123.8, 97.1, 88.2, 86.8, 72.3, 62.2, 44.4, 34.4; HRMS calcd for $C_{18}H_{19}N_4O_6$ [MH^+] 387.1305, found 387.1290.

2′-Deoxy-*N*^{6}-octanoyl-2′-*C*-α-phthalimidomethyladenosine (13): Under argon atmosphere, to a solution of **8** (69 mg, 0.069 mmol) in dry dichloromethane (5 mL) at −78 ºC, boron trichloride (1.0 M in CH_2Cl_2, 7.6 mL, 7.6 mmol) was slowly added. After the reaction mixture was stirred at −78 ºC for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (1.0 mL) at −78 ºC. The mixture was allowed to warm to

room temperature and stirred for 30 min. The organic layer was separated, and the aqueous solution was extracted with dichloromethane. The aqueous layers were combined and evaporated to dryness. The product was isolated by silica gel chromatography, eluting with 4% methanol in chloroform to give **13** (27 mg, 52% yield). ^{1}H NMR ($CDCl_3$/TMS) δ 8.70 (brs, 1H), 8.63 (s, 1H), 8.06 (s, 1H), 7.82-7.73 (m, 4H), 5.99 (d, 1H, *J* = 9.8 Hz), 5.94 (brs, 1H), 4.51 (m, 1H), 4.36 (brs, 1H), 4.27 (m, 1H), 4.00-3.94 (m, 2H), 3.76 (m, 1H), 3.69 (dd, 1H, *J* = 14.2, 3.8 Hz), 3.47 (m, 1H), 2.92 (t, 2H, *J* = 7.5 Hz), 1.79 (m, 2H), 1.50-1.20 (m, 8H), 0.89 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 173.6, 168.4, 151.8, 150.1, 149.8, 142.9, 134.3, 131.3, 123.4, 122.9, 88.8, 88.4, 72.6, 63.3, 48.4, 37.9, 31.6, 29.1, 29.0, 24.7, 22.5, 14.0; HRMS calcd for $C_{27}H_{32}N_6O_6Na$ [MNa^+] 559.2281, found 559.2254.

N^2-Acetyl-2′-deoxy-O^6-(diphenylcarbamoyl)-2′-*C*-α-phthalimidomethylguanosine (14):

Method A: To the solution of **10** (160 mg, 0.190 mmol) in ethyl acetate (15 mL), $Pd(OH)_2$ on active carbon (20% wt., 82 mg, 0.117 mmol) was added. The mixture was stirred under a hydrogen atmosphere for 16 h. TLC showed the reaction was not complete. Additional $Pd(OH)_2$ on active carbon (20% wt., 82 mg, 0.117 mmol) was added and the mixture was stirred under hydrogen for additional 96 h. TLC showed the reaction was almost complete. The catalyst was filtered off, rinsed with chloroform. The solvent was removed, the residue was isolated by silica gel chromatography, eluting with 3% methanol in chloroform to give **14** (62 mg, 49% yield).

Method B: To the solution of **10** (260 mg, 0.308 mmol) in ethyl acetate (20 mL), Pd on active carbon (10% wt., 163 mg, 0.154 mmol) was added. The mixture was stirred under a hydrogen atmosphere for 14 h. TLC showed the reaction was not complete. Additional Pd on active carbon (10% wt., 163 mg, 0.154 mmol) was added and the mixture was stirred under hydrogen for additional 96 h. TLC showed the reaction was still not complete. Additional Pd on active carbon (10% wt., 326 mg, 0.308 mmol) was added and the mixture was stirred under hydrogen for additional 48 h. TLC showed the reaction was almost complete. The catalyst was filtered off, rinsed with chloroform. The solvent was removed, the residue was isolated by silica gel chromatography, eluting with 3% methanol in chloroform to give **14** (100 mg, 49% yield).

^{1}H NMR ($CDCl_3$/TMS) δ 8.36 (brs, 1H), 8.19 (s, 1H), 7.67-7.63 (m, 2H), 7.60-7.55 (m, 2H), 7.45-7.22 (m, 10H), 6.04 (d, 1H, *J* = 9.2 Hz), 4.49 (m, 1H), 4.21 (m, 1H), 3.96-3.80 (m, 3H), 3.71 (dd, 1H, *J* = 12.2, 2.0 Hz), 3.45 (m, 1H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.4, 168.4, 156.0, 154.2, 151.7, 150.1, 143.8, 141.6, 134.4, 131.2, 129.2, 127.5, 125.8, 123.3, 121.6, 87.62, 87.55, 72.4, 62.9, 47.8, 33.0, 25.0; HRMS calcd for $C_{34}H_{29}N_7O_8Na$ [MNa^+] 686.1970, found 686.1941.

2′-*C*-α-Aminomethyl-2′-deoxyuridine (15a):

*From **11a**:* To a solution of **11a** (31 mg, 0.080 mmol) in EtOH (10 mL), *n*-butylamine (1.0 mL) was added and the mixture was stirred at 55 ºC for 60 h. The solvent was removed, the residue was dissolved into water (25 mL), washed with dichloromethane (3x10 mL). The aqueous layer was evaporated, the residue was purified by silica gel

chromatography, eluting with 10% methanol in chloroform, followed by methanol containing 0.5% Et_3N to give **15a** (20 mg, 97% yield).

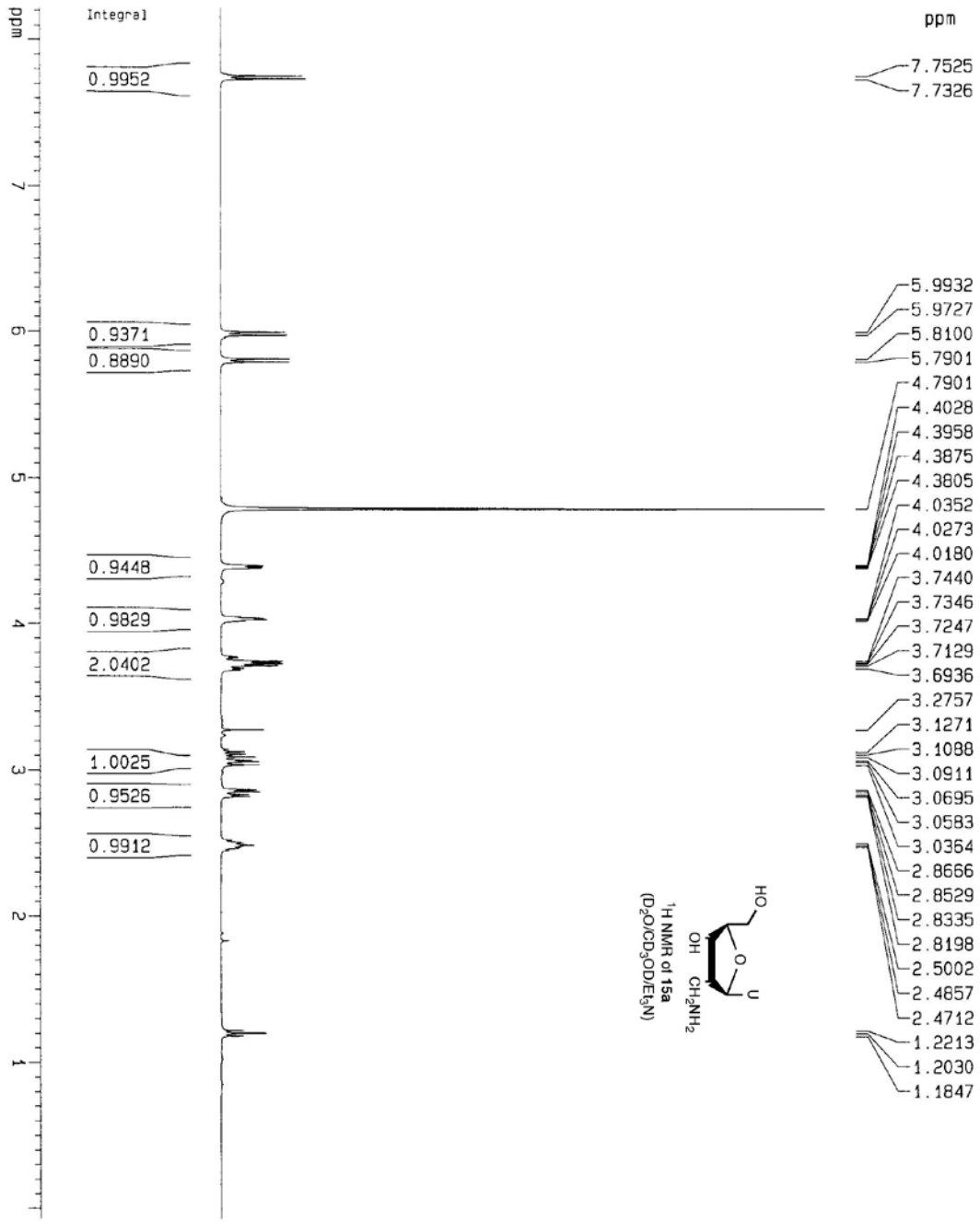
*From **11b**:* To a solution of **11b** (25 mg, 0.072 mmol) in EtOH (10 mL), *n*-butylamine (1.0 mL) was added and the mixture was stirred at 55 ºC for 60 h. The solvent was removed, the residue was dissolved into water (25 mL), washed with dichloromethane (3x10 mL). The aqueous layer was evaporated, the residue was purified by silica gel chromatography, eluting with 10% methanol in chloroform, followed by methanol containing 0.5% Et_3N to give **15a** (15 mg, 81% yield).

^{1}H NMR (D_2O) δ 7.74 (d, 1H, *J* = 8.0 Hz), 5.98 (d, 1H, *J* = 8.2 Hz), 5.80 (d, 1H, *J* = 8.0 Hz), 4.39 (m, 1H), 4.03 (m, 1H), 3.72 (m, 2H), 3.07 (m, 1H), 2.84 (dd, 1H, *J* = 13.2, 5.5 Hz), 2.49 (m, 1H); ^{13}C NMR (D_2O) δ 170.0, 154.5, 140.6, 102.7, 87.0, 86.5, 71.0, 61.2, 48.4, 35.7; HRMS calcd for $C_{10}H_{16}N_3O_5$ [MH^+] 258.1090, found 258.1082.

2′-*C*-α-Aminomethyl-2′-deoxycytidine (15b): To a solution of **12** (38.6 mg, 0.10 mmol) in EtOH (10 mL), *n*-butylamine (1.0 mL) was added and the mixture was stirred at 55 ºC for 60 h. The solvent was removed, the residue was dissolved into water (30 mL), washed with dichloromethane (3x10 mL). The aqueous layer was evaporated to give **15b** (25 mg, 98% yield). ^{1}H NMR (D_2O) δ 7.72 (d, 1H, *J* = 7.6 Hz), 5.95-5.92 (m, 2H), 4.35 (dd, 1H, J = 6.5, 3.8 Hz), 4.02 (m, 1H), 3.74 (dd, 1H, *J* = 12.6, 3.4 Hz), 3.67 (dd, 1H, J = 12.6, 4.8 Hz), 3.25 (dd, 1H, *J* = 13.3, 8.5 Hz), 3.07 (dd, 1H, *J* = 13.3, 5.7 Hz), 2.56 (m, 1H); ^{13}C NMR (D_2O) δ 166.0, 157.5, 140.8, 96.6, 87.4, 86.2, 70.5, 60.9, 46.6, 35.6; HRMS calcd for $C_{10}H_{17}N_4O_4$ [MH^+] 257.1250, found 257.1251.

2′-*C*-α-Aminomethyl-2′-deoxyadenosine (15c): To a solution of **13** (49 mg, 0.091 mmol) in EtOH (10 mL), *n*-butylamine (1.0 mL) was added and the mixture was stirred at 55 ºC for 24 h. The solvent was removed, the residue was dissolved into water (30 mL), washed with dichloromethane (3x10 mL). The aqueous layer was evaporated, the residue was purified by silica gel chromatography, eluting with ethanol/water/Et_3N (v/v/v 7.5:2.5:0.05) to give **15b** (218 mg, 71% yield). ^{1}H NMR (D_2O) δ 8.28 (s, 1H), 8.15 (s, 1H), 6.08 (d, 1H, *J* = 8.6 Hz), 4.62 (dd, 1H, J = 5.6, 1.7 Hz), 4.25 (m, 1H), 3.82 (m, 2H), 3.30 (dd, 1H, *J* = 12.8, 9.6 Hz), 3.20 (m, 1H), 2.93 (dd, 1H, *J* = 12.8, 4.3 Hz); ^{13}C NMR (D_2O) δ 155.7, 152.6, 148.5, 140.5, 119.1, 88.1, 86.9, 71.4, 61.9, 47.4, 35.3; HRMS calcd for $C_{11}H_{17}N_6O_3$ [MH^+] 281.1362, found 281.1353.

2′-*C*-α-Aminomethyl-2′-deoxyguanosine (15d): To a solution of **13** (61 mg, 0.092 mmol) in EtOH (10 mL), *n*-butylamine (1.0 mL) was added and the mixture was stirred at 55 ºC for 15 h. The solvent was removed, the residue was dissolved into water (20 mL), washed with dichloromethane (3x20 mL). The aqueous layer was evaporated, the residue was purified by silica gel chromatography, eluting with ethanol/water/Et_3N (v/v/v 7.5:2.5:0.05) to give **15b** (24 mg, 88% yield). ^{1}H NMR (D_2O) δ 7.78 (s, 1H), 5.81 (d, 1H, *J* = 8.4 Hz), 4.48 (dd, 1H, J = 5.8, 2.2 Hz), 4.08 (m, 1H), 3.67 (m, 2H), 3.30 (dd, 1H, *J* = 13.0, 9.6 Hz), 3.12 (m, 1H), 3.00 (m, 1H); ^{13}C NMR (D_2O) δ 159.6, 154.6, 152.0, 138.5, 117.4, 88.6, 87.1, 71.8, 62.4, 46.4, 35.8; HRMS calcd for $C_{11}H_{15}N_6O_4$ [$M\text{-}H^+$] 295.1154, found 295.1140.

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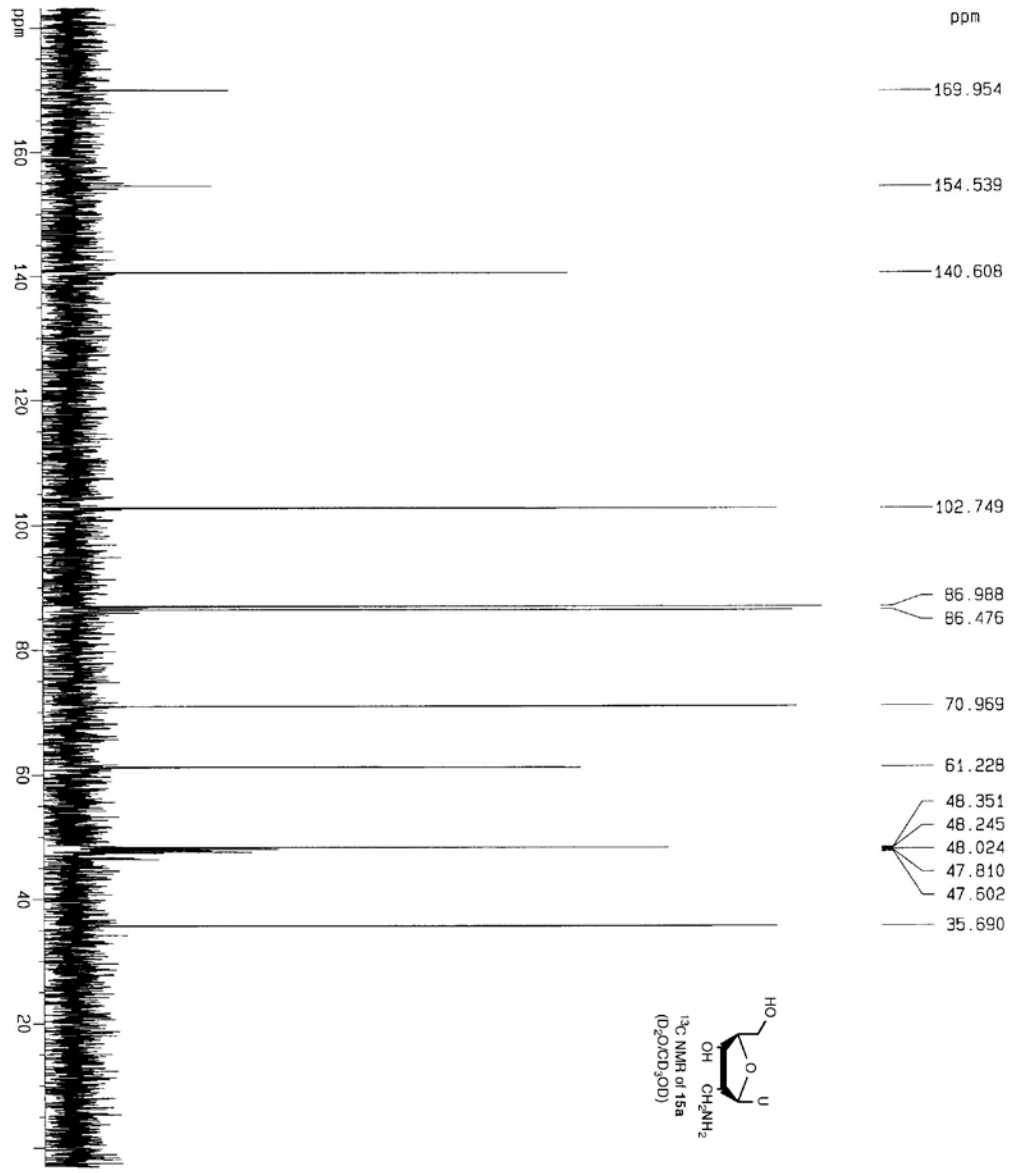


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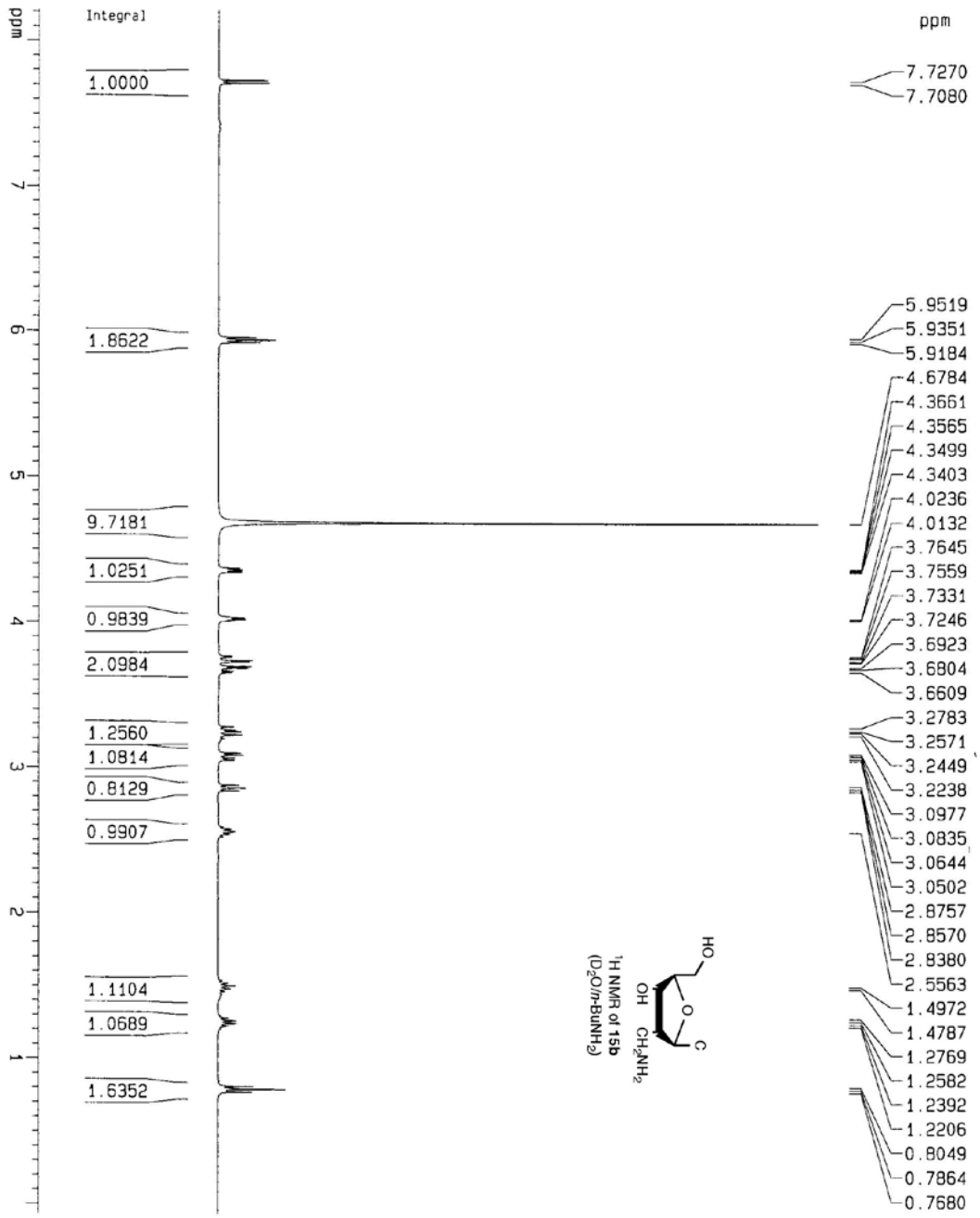


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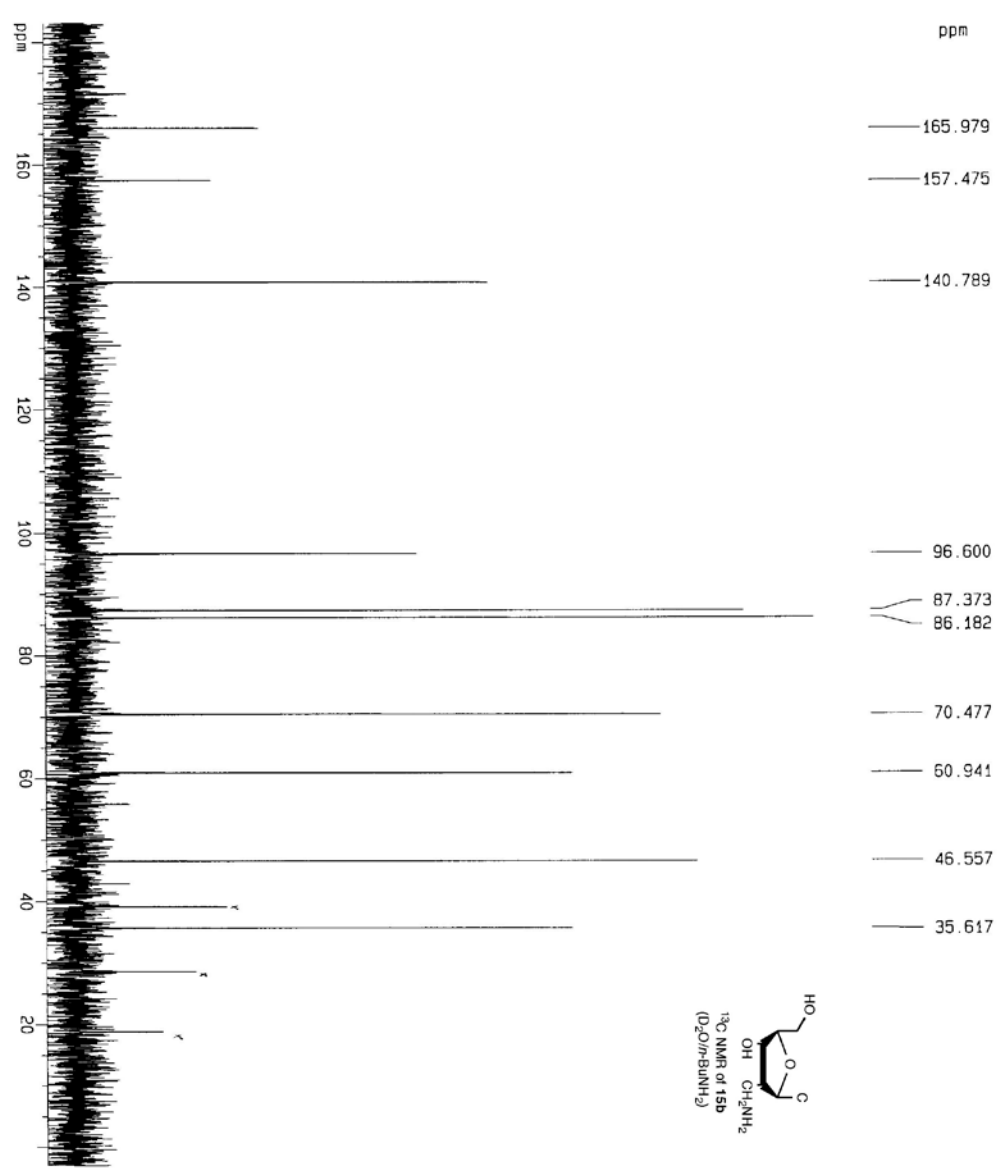


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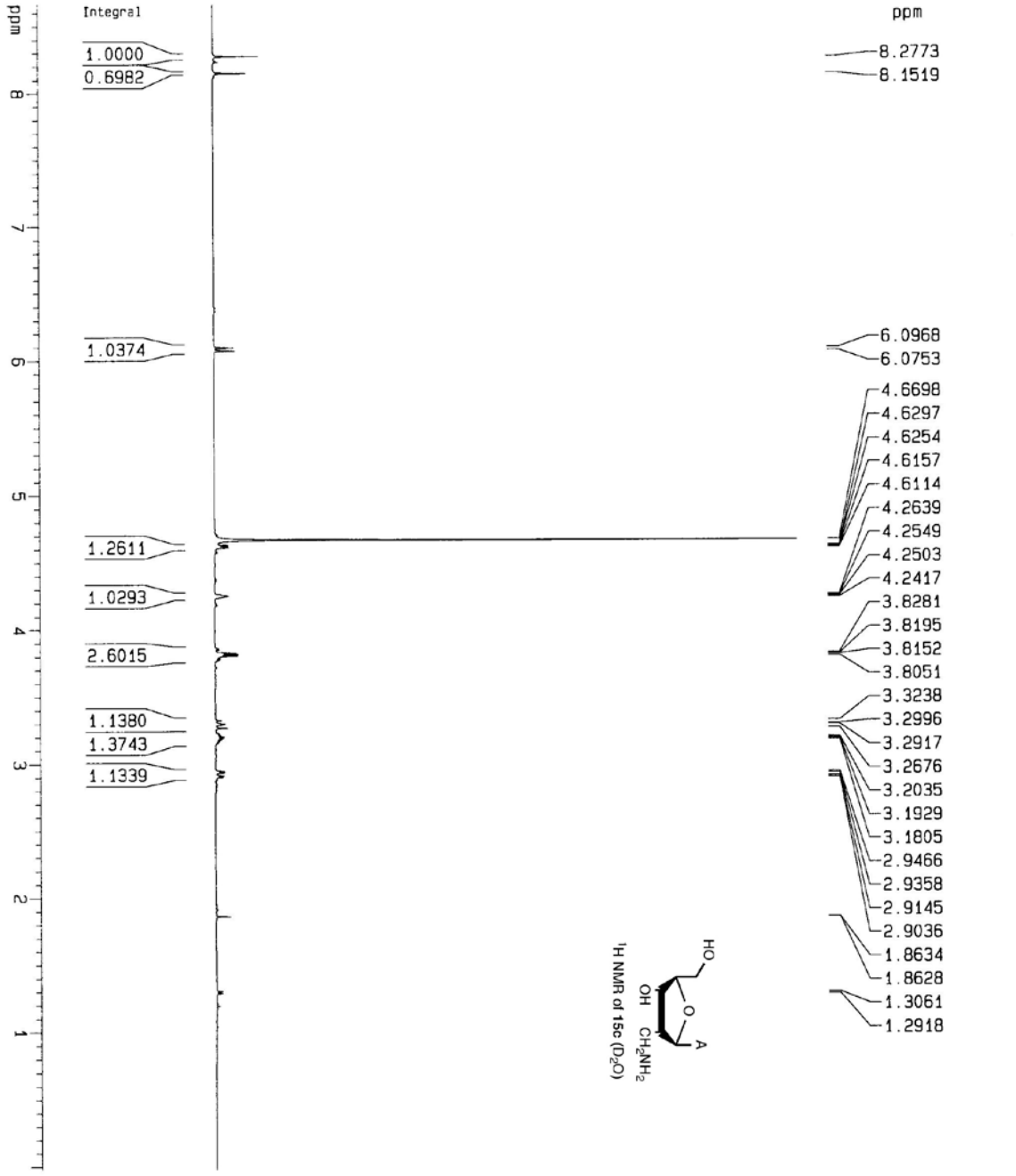


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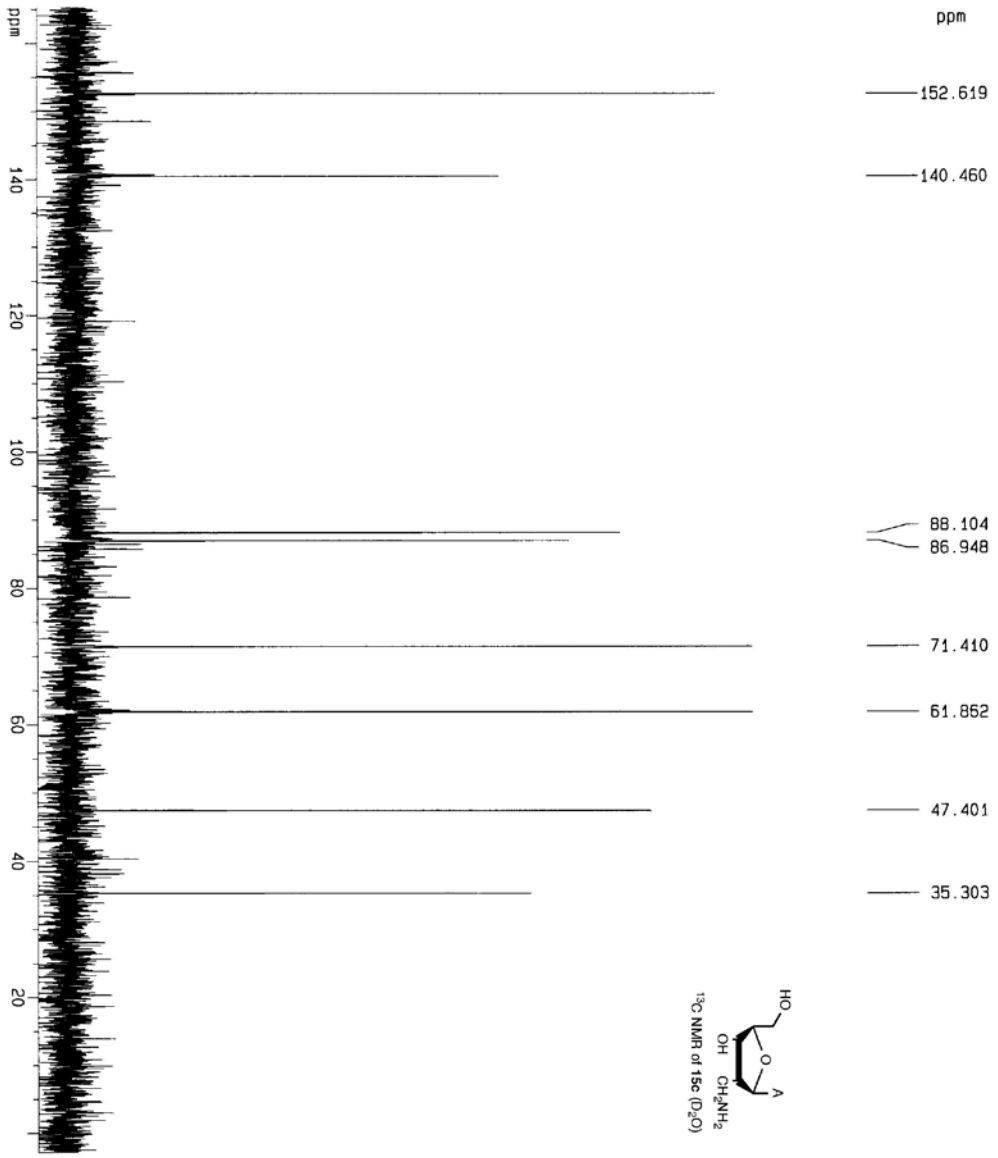

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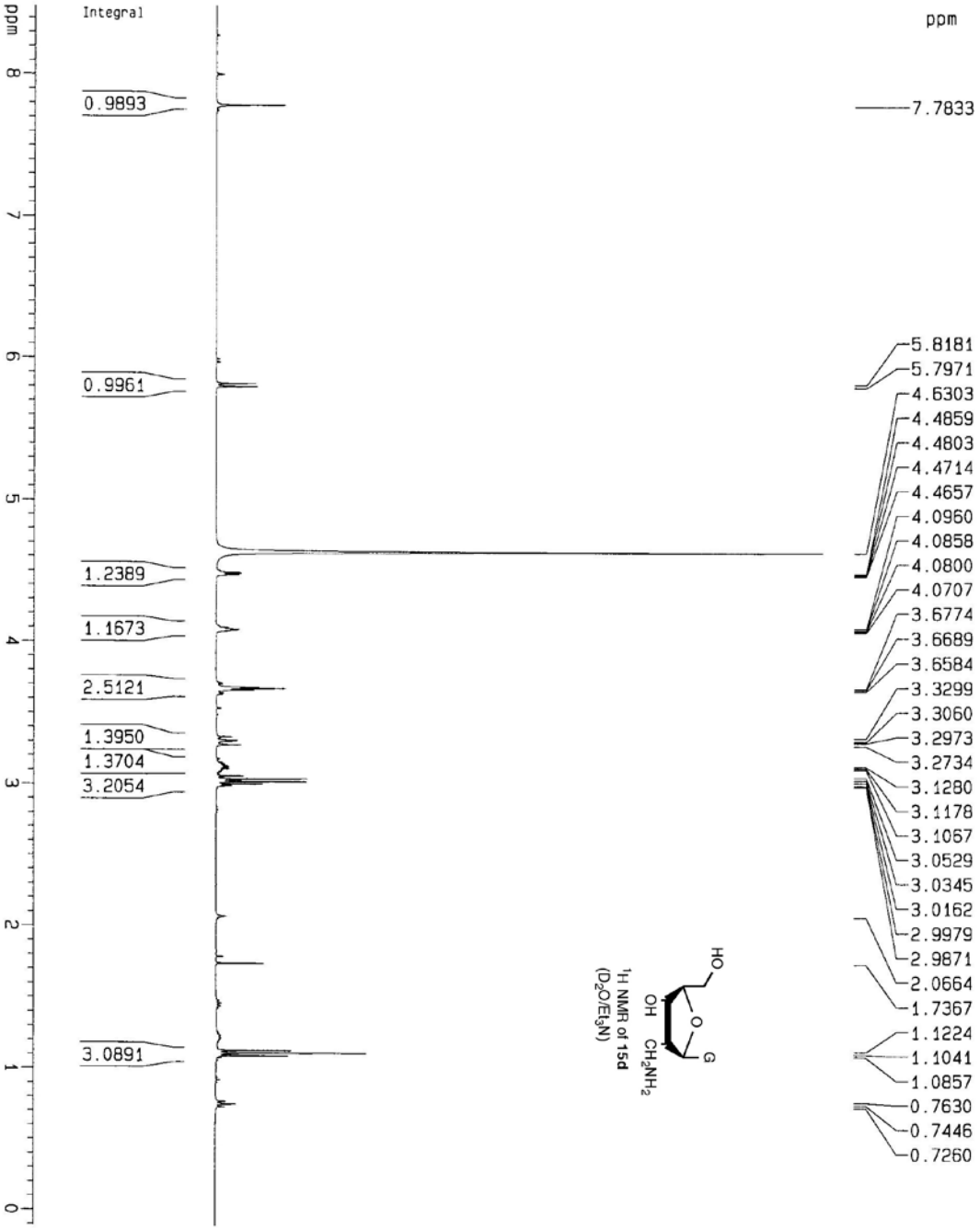


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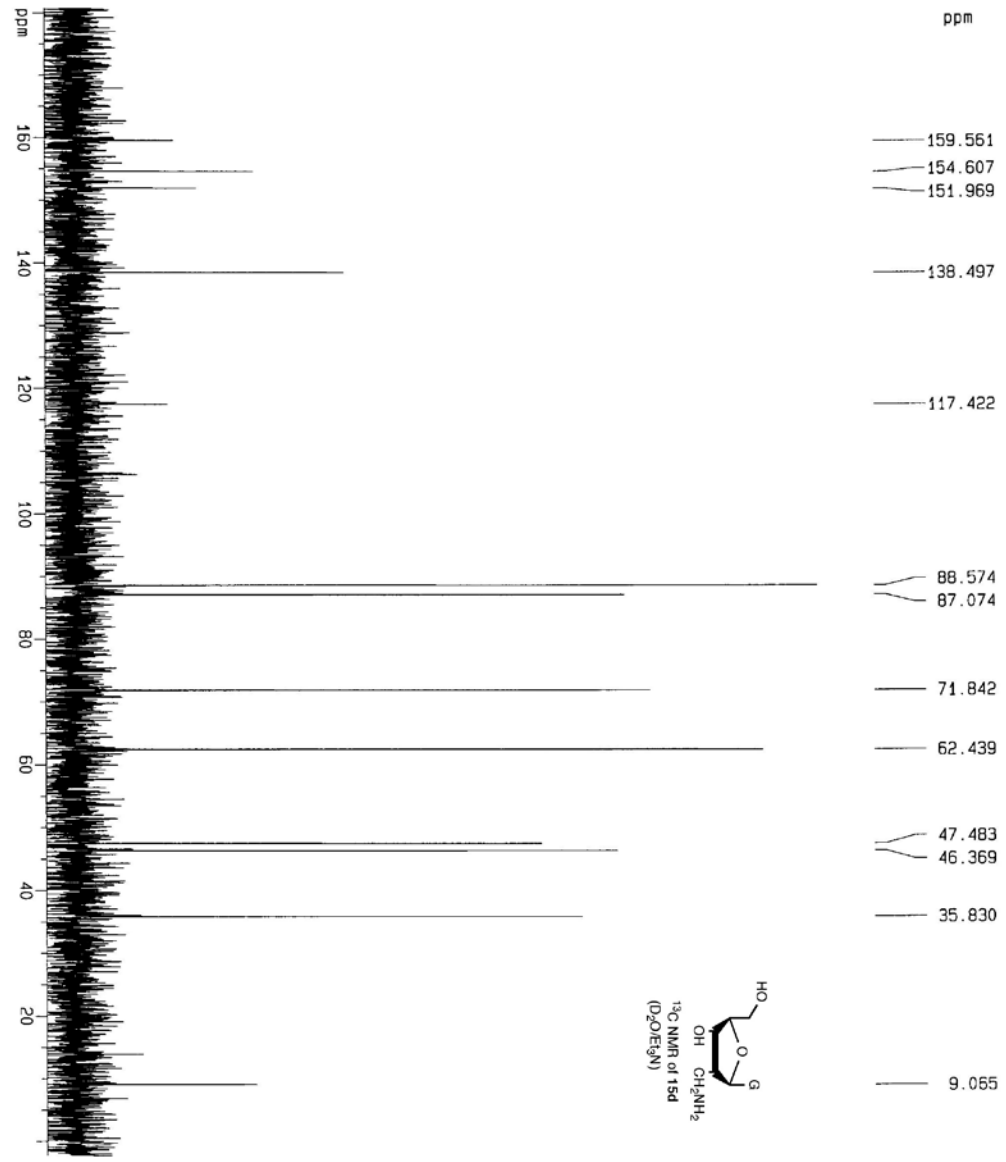


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