Supplementary Material (ESI) for Chemical Communications

The first Synthesis and complete Characterization of N-Acetylneuraminic Acid 1,7-Lactone

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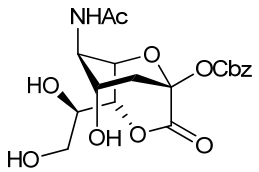
(i) General

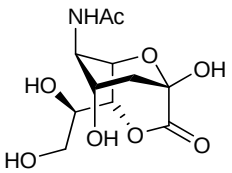
Melting points were measured on a SMP3 mp apparatus (Stuart Scientific, USA) and are not corrected. Nuclear magnetic resonance spectra were recorded at 298 K on Bruker AM-500 spectrometer operating at 500.13 MHz for ^{1}H and 125.76 MHz for ^{13}C. Chemical shifts are reported in parts for million (ppm, δ units) relative to CD_3OD signal fixed at 3.31 ppm for ^{1}H spectra and to CD_3OD signal fixed at 49.05 ppm for ^{13}C spectra. Proton and carbon assignments were established, if necessary, with ^{1}H-^{1}H and ^{1}H-^{13}C correlated NMR experiments. ^{1}H NMR data are tabulated in the following order: number of protons, multiplicity (s, singlet; d, doublet; br s, broad singlet; m, multiplet), coupling constant(s) in Hz, assignment of proton(s). Optical rotations were taken at 23°C on a Perkin-Elmer 241 polarimeter and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Mass spectra were obtained using a Finnigan LCQdeca (ThermoQuest) ion trap mass spectrometer fitted with an electrospray source (ESI). All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60 F_{254}) using UV light, 50% sulphuric acid and heat as developing agent. E. Merck 230-400 mesh silica gel was used for rapid silica gel chromatography.



6

(ii)2-Benzyloxycarbonyl-N-acetylneuraminic acid 1,7-lactone 6.

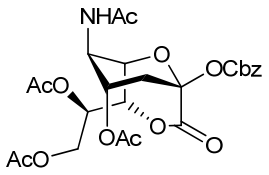
Preparation and physicochemical properties are reported as footnote in the paper.
Found: C, 52.40, H, 5.50, N, 3.60. $C_{18}H_{23}NO_{10}$ requires C, 52.30, H, 5.61, N, 3.39 %.



4a

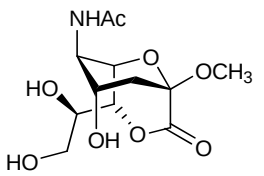
(iii) Preparation of the N-acetylneuraminic acid 1,7-lactone 4a.

The 2-carbobenzyloxy N-acetylneuraminic acid 1,7-lactone **6** (425.5 mg, 1.0 mmol) was dissolved in ethyl acetate (350 mL) and hydrogenated in the presence of 10% Pd/C (200.0 mg) for 4 h. At this time, the catalyst was filtered and the solvent was evaporated under reduced pressure. Then the solid residue was dried to afford the title compound **4a** (270,6 mg, Yeld 93%): mp 110-113 °C (dec., in sealed tube); $[\alpha]_D$ = + 23 (THF, *c* = 1). Other characteristic are in the paper as selected data.
Found: C, 45.20; H, 6.00, N, 5.00 $C_{11}H_{17}NO_8$ require C, 45.36; H, 5.88, N, 4.81 %.



7

(iv) Preparation of the 4,8,9-tri-O-acetylated 2-benzyloxycarbonyl N-acetylneuraminic acid 1,7-lactone 7. The 2-benzyloxycarbonyl N-acetylneuraminic acid 1,7-lactone **6** (213.0 mg, 0.5 mmol) was dissolved in pyridine (1.5 mL) and treated with acetic anhydride (0.70 mL) containing a trace of 4-dimethylamino pyridine, for 24 h at 23 °C. At this time methanol was added to the mixture and the solution was concentrated. The residue was recovered with ice cold water and extracted with ethyl acetate. The organic layers were washed with an aquous $NaHCO_3$ solution and then with water, to afford, after evaporation of the solvent under reduced pressure, a crude compound which was purified by column chromatography on silica, eluting first less polar impurities, with ethyl acetate, then compound **7**, with a mixture of methanol in ethyl acetate (1%, v/v). The obtained compound **7**, a glass, showed: $[\alpha]_D$ +41 ($CHCl_3$, *c* = 1); δ_H (500.13 MHz; CD_3OD, T =298 K) 7.39 (5H, m, Ph), 5.51 (1H, ddd, $J_{9a,8}$ 2.6 Hz, $J_{9b,8}$ 4.7 Hz, $J_{8,7}$ 7.6 Hz, H-8), 5.23 (2H, AB system, C<u>H</u>$_2$Ph), 5.12 (1H, br m, $J_{4,3a}$ 3.77 Hz, $J_{4,3b}$ 1.3 Hz, H-4), 4.84 (1H, d, $J_{8,7}$ 7.6 Hz, H-7), 4.67 (1H, dd, $J_{9a,8}$ 2.6 Hz, $J_{9a,9b}$ 12.5 Hz, H-9a), 4.44 (1H, br s, H-6), 4.28 (1H, dd, $J_{9b,8}$ 4.7 Hz, $J_{9a,9b}$ 12.5, H-9b), 4.12 (1H, br s, H-5), 2.41 (1H, dd, $J_{4,3a}$ 3.8, $J_{3a,3b}$ 14.7 Hz, H-3a), 2.28 (1H, $J_{4,3b}$ 1.3 Hz, $J_{3a,3b}$ 14.7 Hz, H-3b), 2.094 (3H, s, C<u>H</u>$_3$COO at C-9), 2.090 (3H, s, C<u>H</u>$_3$COO at C-8), 2.048 (3H, s, C<u>H</u>$_3$COO at C-4), 2.027 (3H, s, C<u>H</u>$_3$CONH); δ_C (125.76 MHz; CD_3OD, T =298 K) 173.1 (CH_3<u>C</u>ONH), 172.4 (CH_3<u>C</u>OO at C-9), 171.6 (CH_3<u>C</u>OO at C-8), 170.5 (CH_3<u>C</u>OO at C-4), 166.7 (C-1), 153.5 (PhCH$_2$O<u>C</u>OO), 136.2, 129.9, 129.7, 129.5 (Ph), 94.6 (C-2), 78.3 (C-7), 73.1 (C-6), 71.8 (Ph<u>C</u>H$_2$OCOO), 71.7 (C-8), 69.2 (C-4), 62.8 (C-9), 50.1 (C-5), 34.1 (C-3), 22.5 (<u>C</u>H$_3$CONH), 20.8 (<u>C</u>H$_3$COO at C-8), 20.7 (<u>C</u>H$_3$COO at C-4), 20.6 (<u>C</u>H$_3$COO at C-9). MS (ESI positive): *m/z* 574.2 (M+Na$^+$), 606.1 (2M+Na$^+$+MeOH), 1124 (2M+Na$^+$).
Found: C, 53.40, H, 5.30, N, 2.50. $C_{24}H_{29}NO_{13}$ requires C, 53.43, H, 5.42, N, 2.60 %.

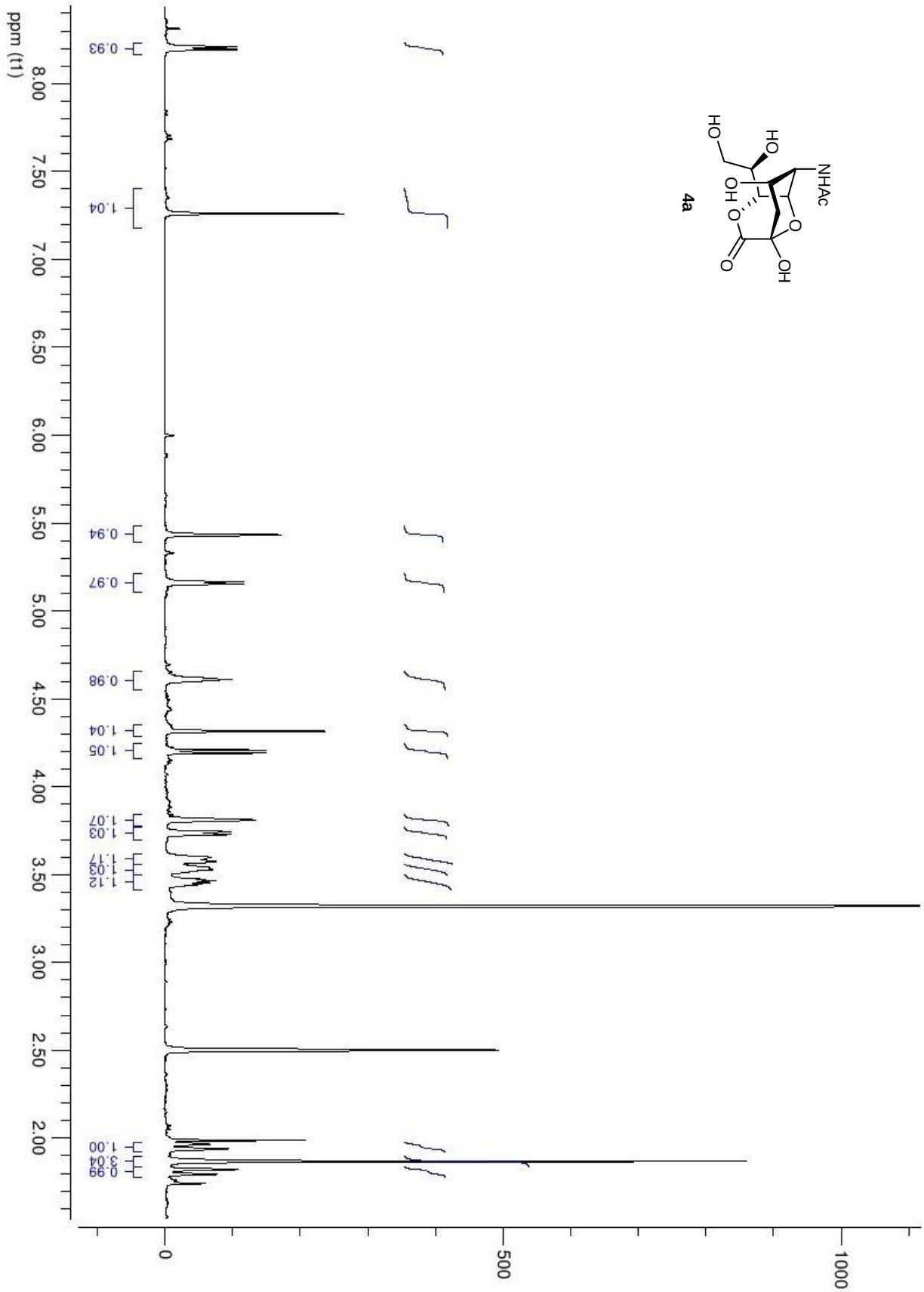


9

(v) Preparation of the 2-methoxy N-acetylneuraminic acid 1,7 lactone 9.
CbzCl (0.4 mL, 2.8 mmol) dissolved in THF (1.5 mL) was added drop wise to a solution of anhydrous THF (2.5 mL) containing triethylamine (0.5 mL; 3.6 mmol) under stirring, at 0°C. At this point the 2-methoxy-N-acetylneuraminic acid **8** (94.0 mg; 2.91 mmol) was added, followed by DMF (3.0 mL). The mixture was then stirred at 23 °C for 24 h. At this time MeOH (4 mL) is added and stirring is continued for 2 h. After evaporation of the MeOH-THF mixture, the residue DMF was removed under high vacuum to afford a crude residue which was chromatography on silica (eluting with 10% MeOH

in AcOEt), to give the pure lactone **9** (67.0 mg; 73% Y). The compound, a glass, showed: $[\alpha]_D$ = + 15 (CH_3OH, *c* = 1); IR, (nujol) 3 332, 1 760 cm^{-1}; δ_H (500.13 MHz; CD_3OD, T =298 K) 4.57 (1H, br s, H-6), 4.45 (1H, d, $J_{8,7}$ 7.8Hz, H-7), 4.03 (1H, m, $J_{4,3b}$ 2.1 Hz, $J_{4,3a}$ 3.3 Hz, H-4), 3.95 (1H, br s, H-5), 3.79 (1H, dd, $J_{9a,8}$ 3.1 Hz, $J_{9a,9b}$ 10.8 Hz, H-9a), 3.75 (1H, ddd, $J_{9a,8}$ 3.1 Hz, $J_{8,7}$ 7.8 Hz, $J_{9b,8}$ 4.6 Hz, H-8), 3.70 (1H, dd, $J_{9b,8}$ 4.6 Hz, $J_{9a,9b}$ 10.8 Hz, H-9b), 3.33 (3H, s, C<u>H</u>$_3$O), 2.76 (1H, dd, $J_{4,3a}$ 3.3 Hz, $J_{3a,3b}$ 14.1 Hz, H-3a), 2.02 (1H, dd, $J_{4,3b}$ 2.1 Hz, $J_{3a,3b}$ 14.1 Hz, H-3b), 2.00 (3H, s, C<u>H</u>$_3$CONH); δ_C (125.76 MHz; CD_3OD, T =298 K) 173.0 (CH_3<u>C</u>ONH), 170.0 (C-1), 96.3 (C-2), 79.7 (C-7), 73.2 (C-8), 72.1 (C-6), 67.6 (C-4), 63.6 (C-9), 52.8 (C-5), 51.6 (<u>C</u>H_3O), 37.8 (C-3), 22.5 (<u>C</u>H_3CONH). MS (ESI negative): *m/z* 304.4 (M-H), 609.1 (2M-H).
Found: C, 47.00; H, 6.30, N, 4.70 $C_{12}H_{19}NO_8$ requires C, 47.21; H, 6.27, N, 4.59 %.

(vii) $^1H/^{13}C$-NMR spectra; COSY, HSQC, HMBC for compounds **4a**, **6**, **7** and **9**.
(Copies are reported).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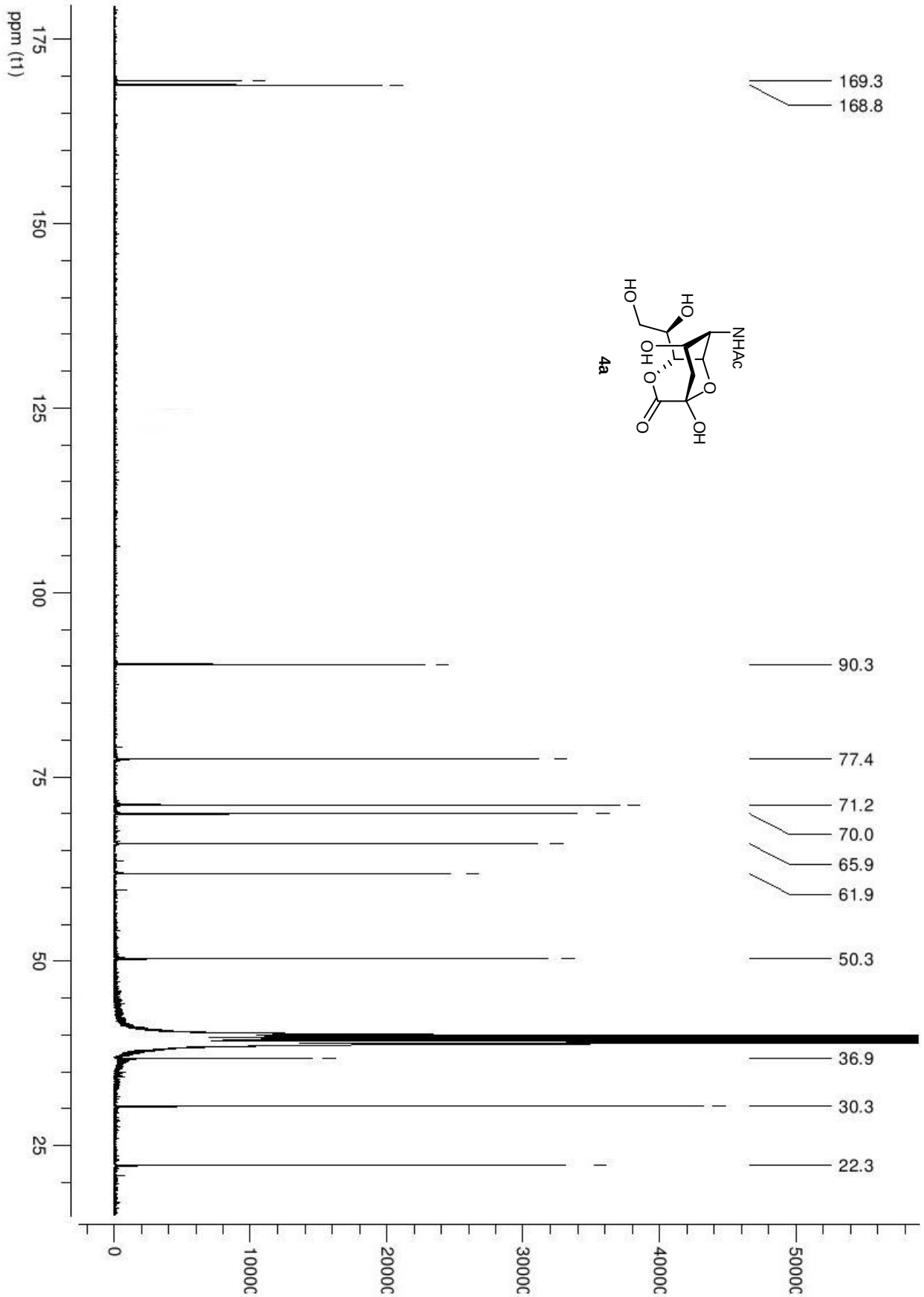
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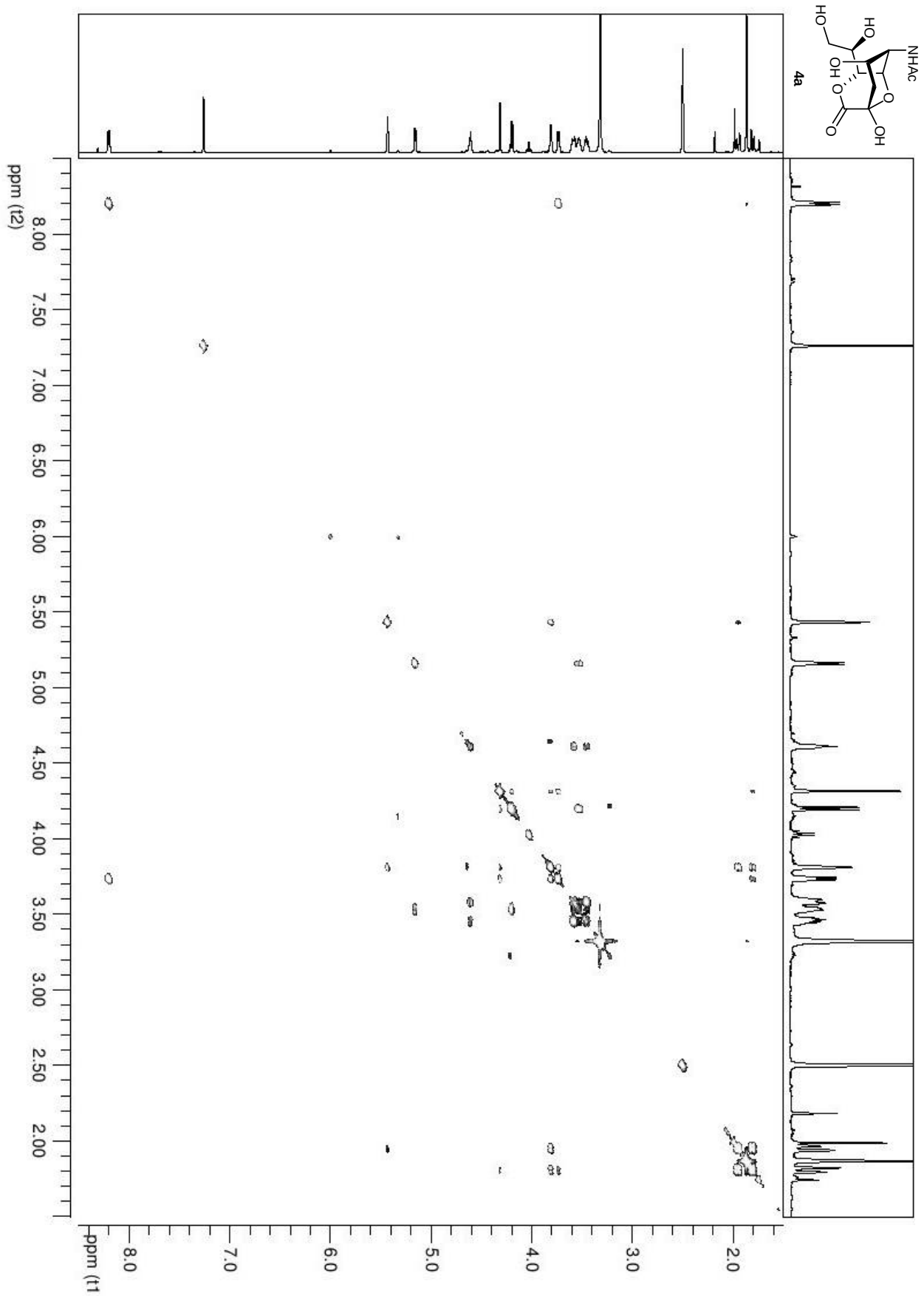
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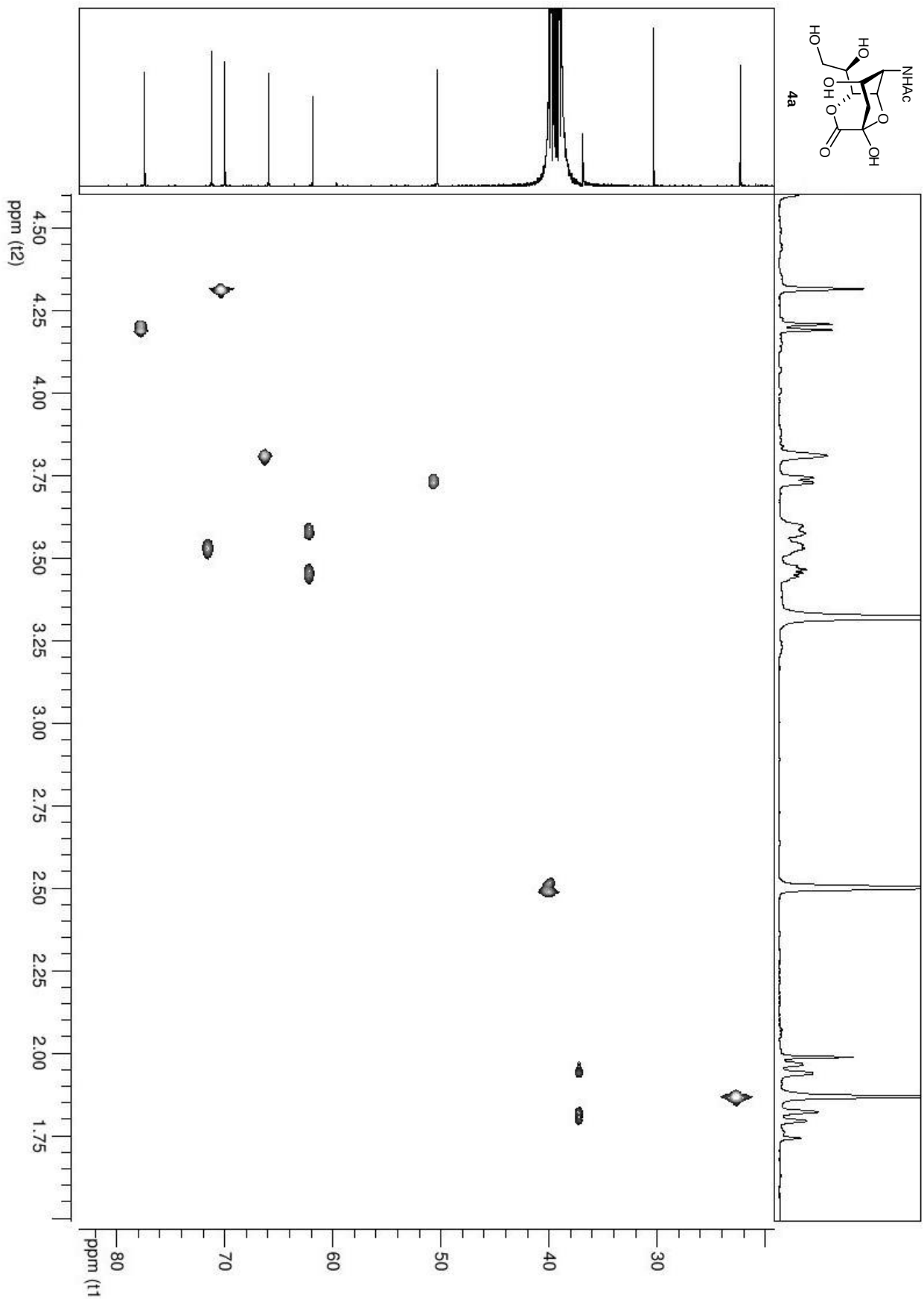
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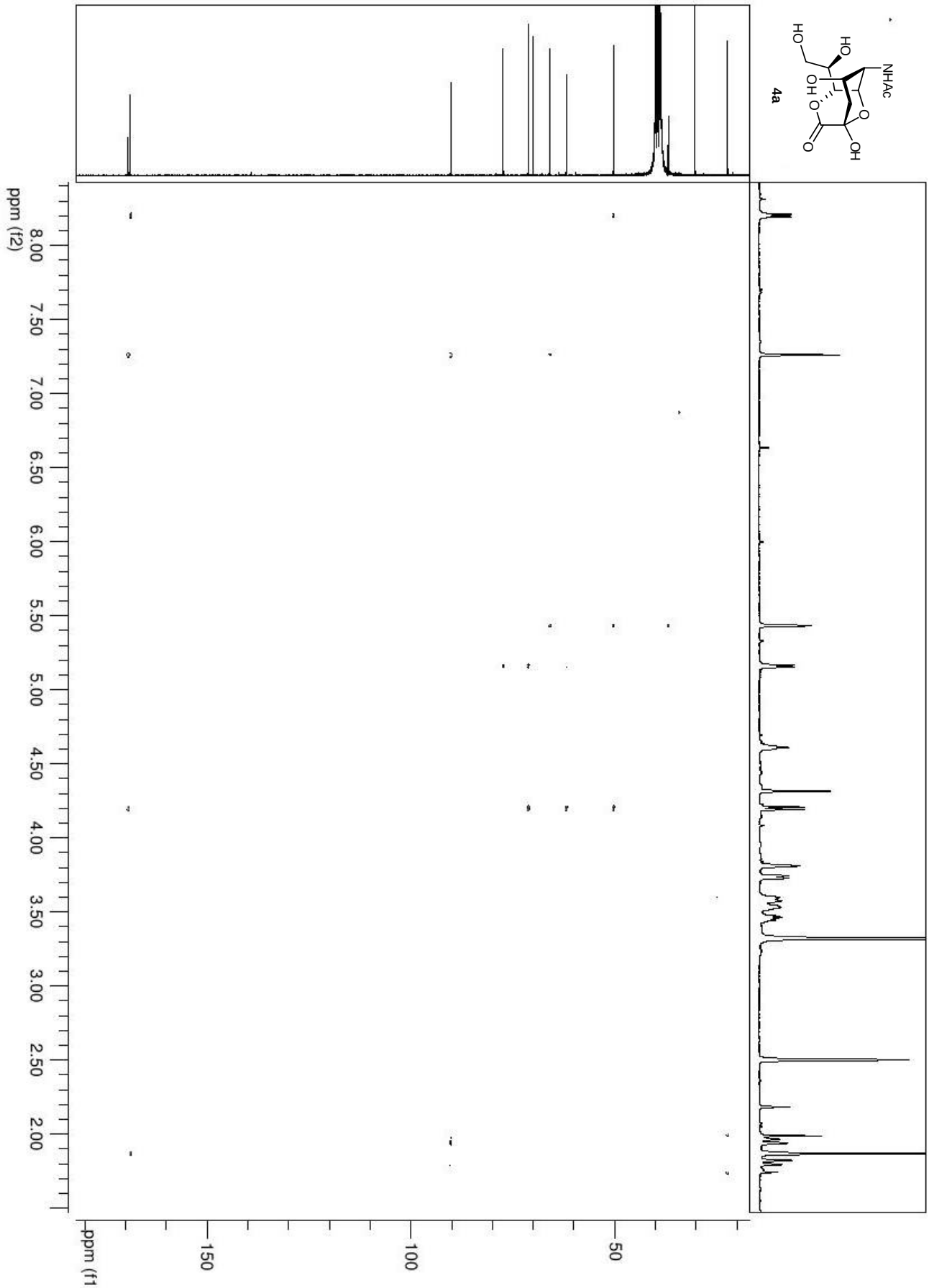
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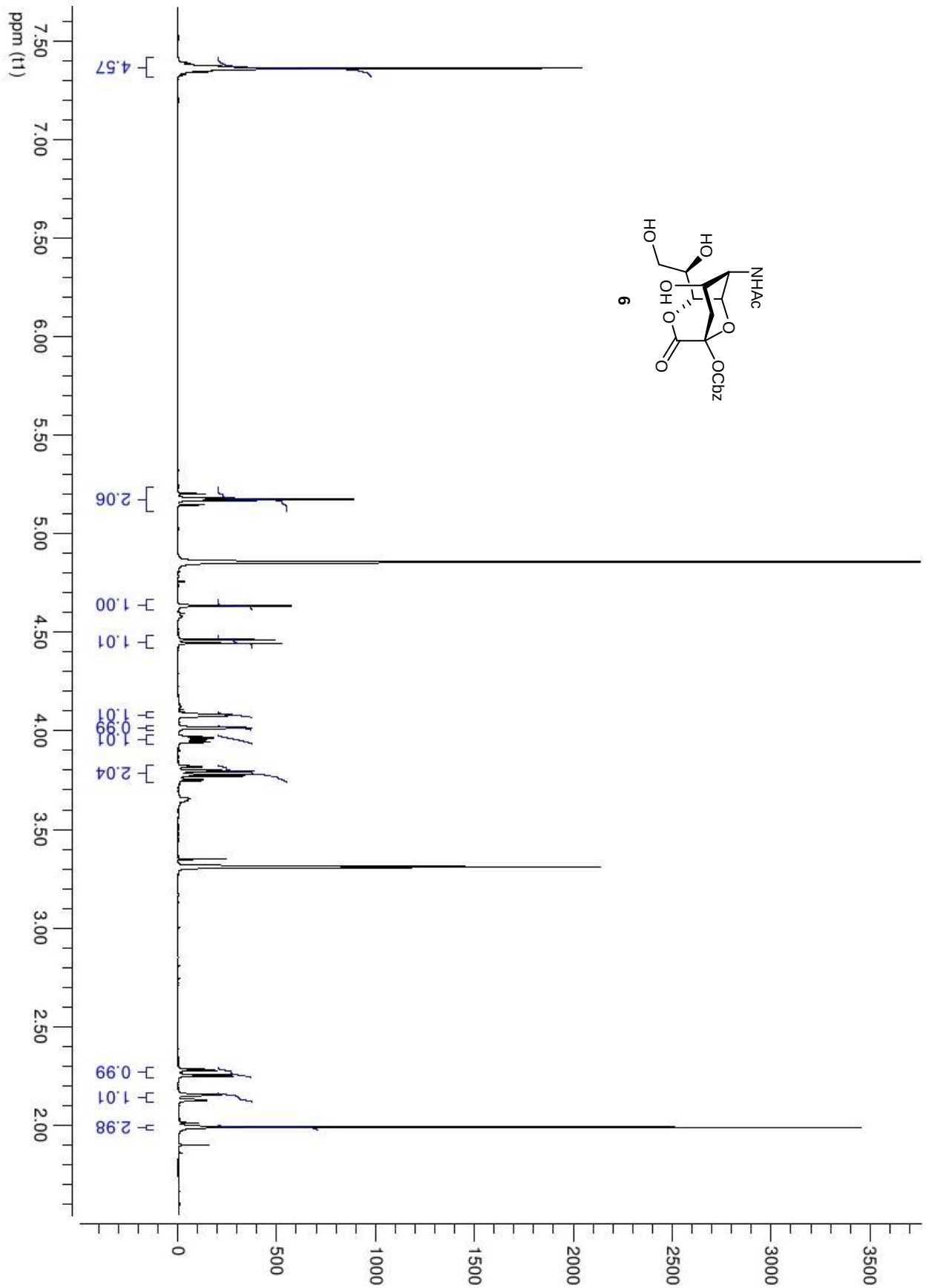
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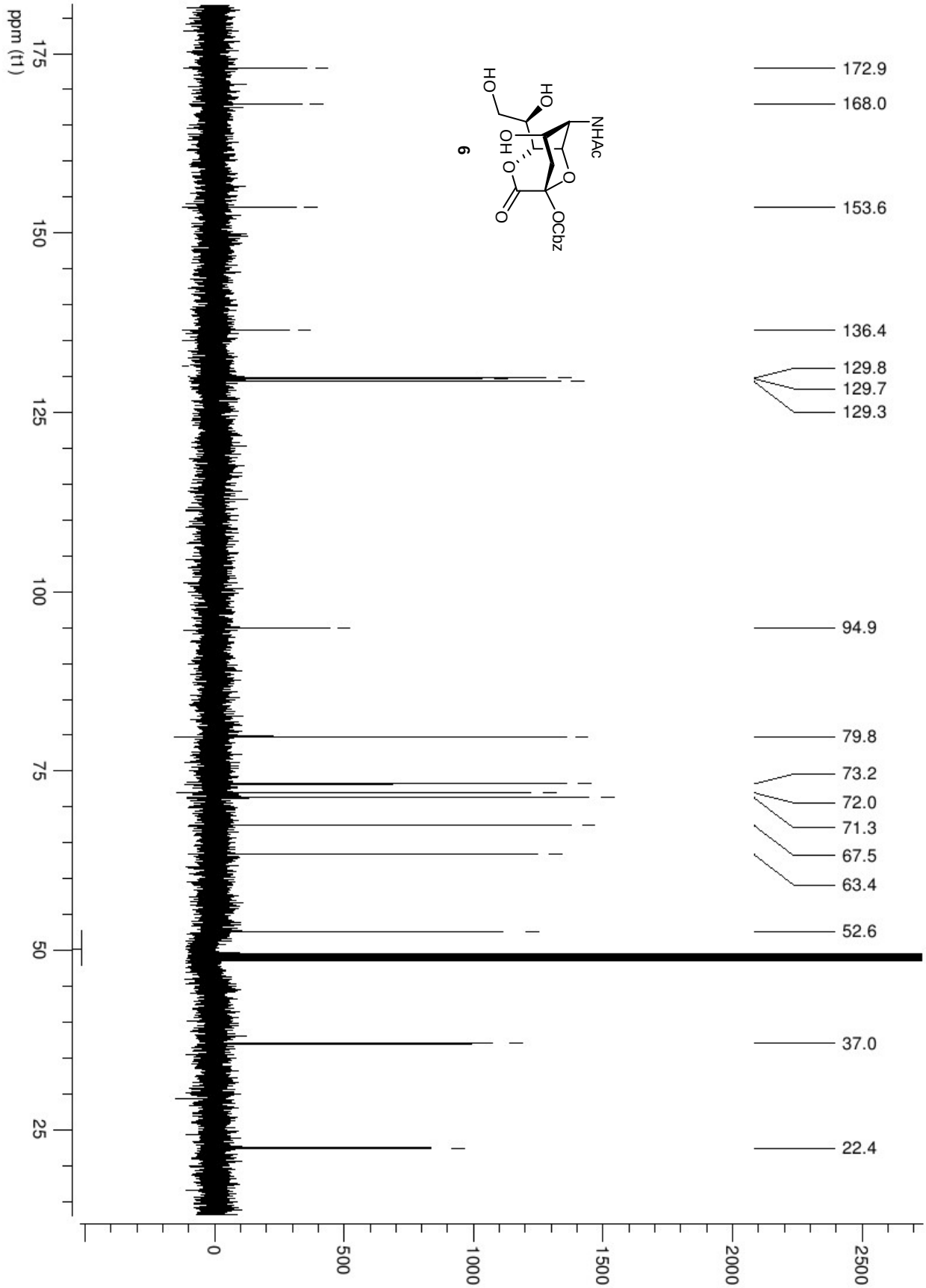
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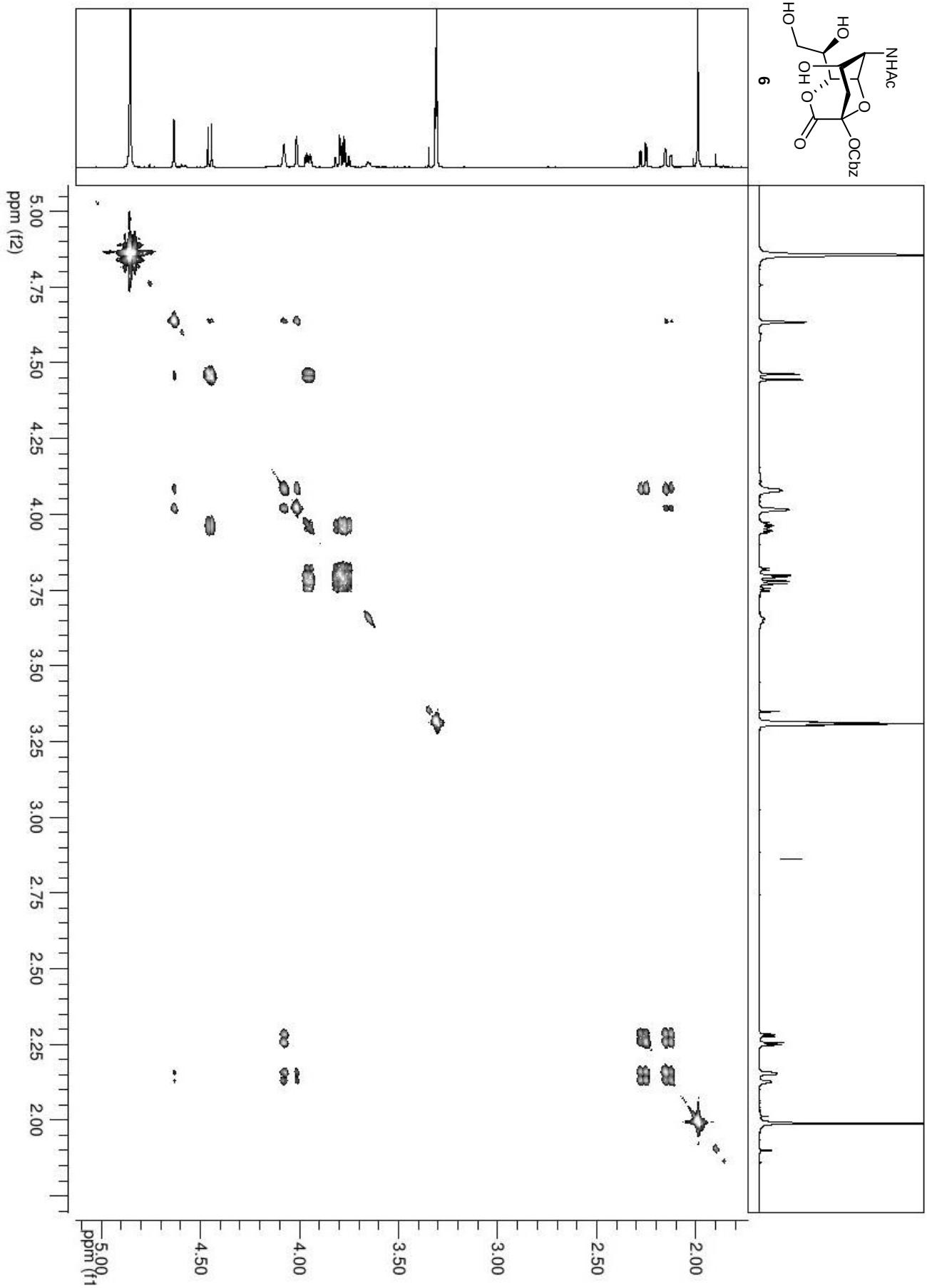
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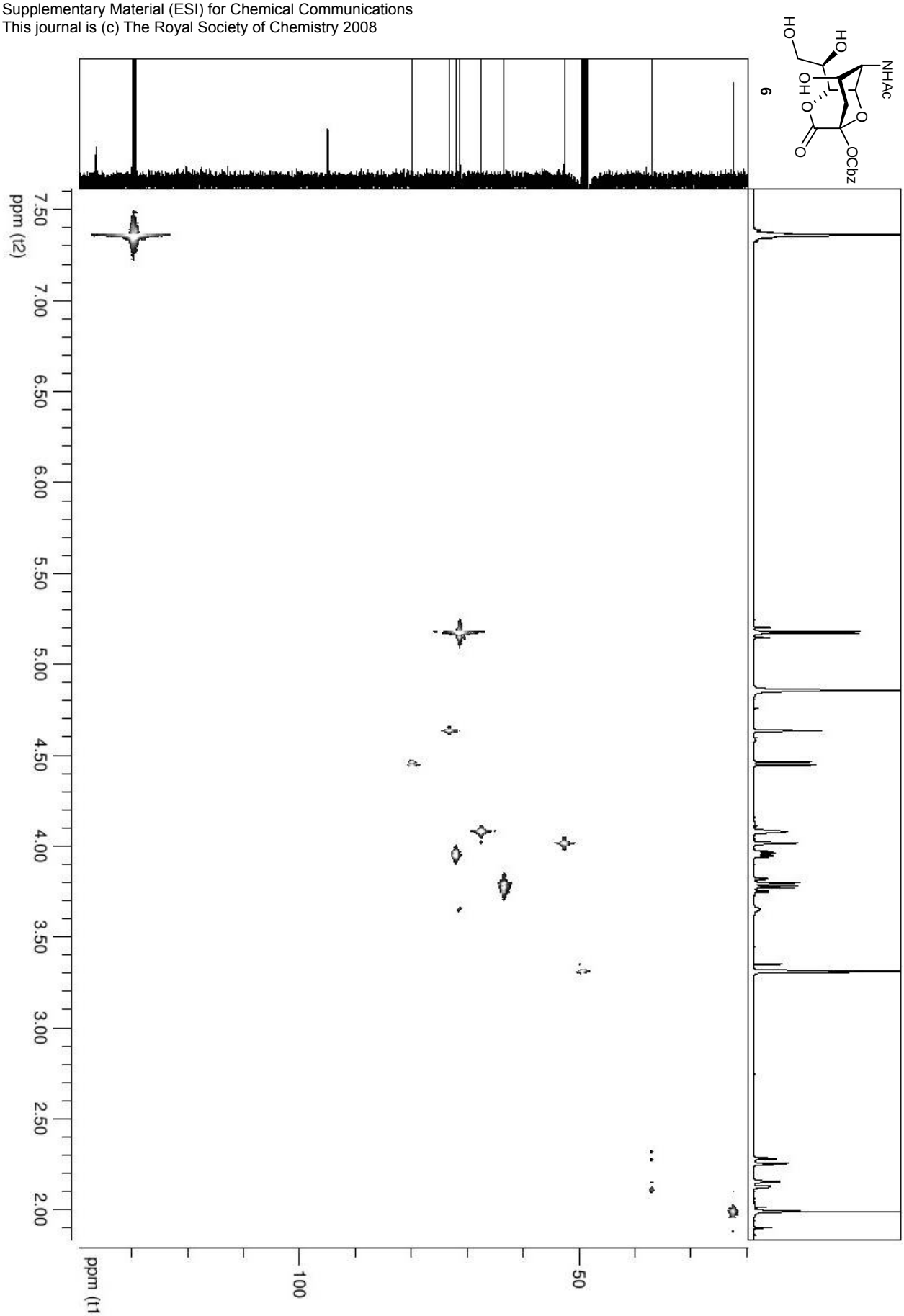
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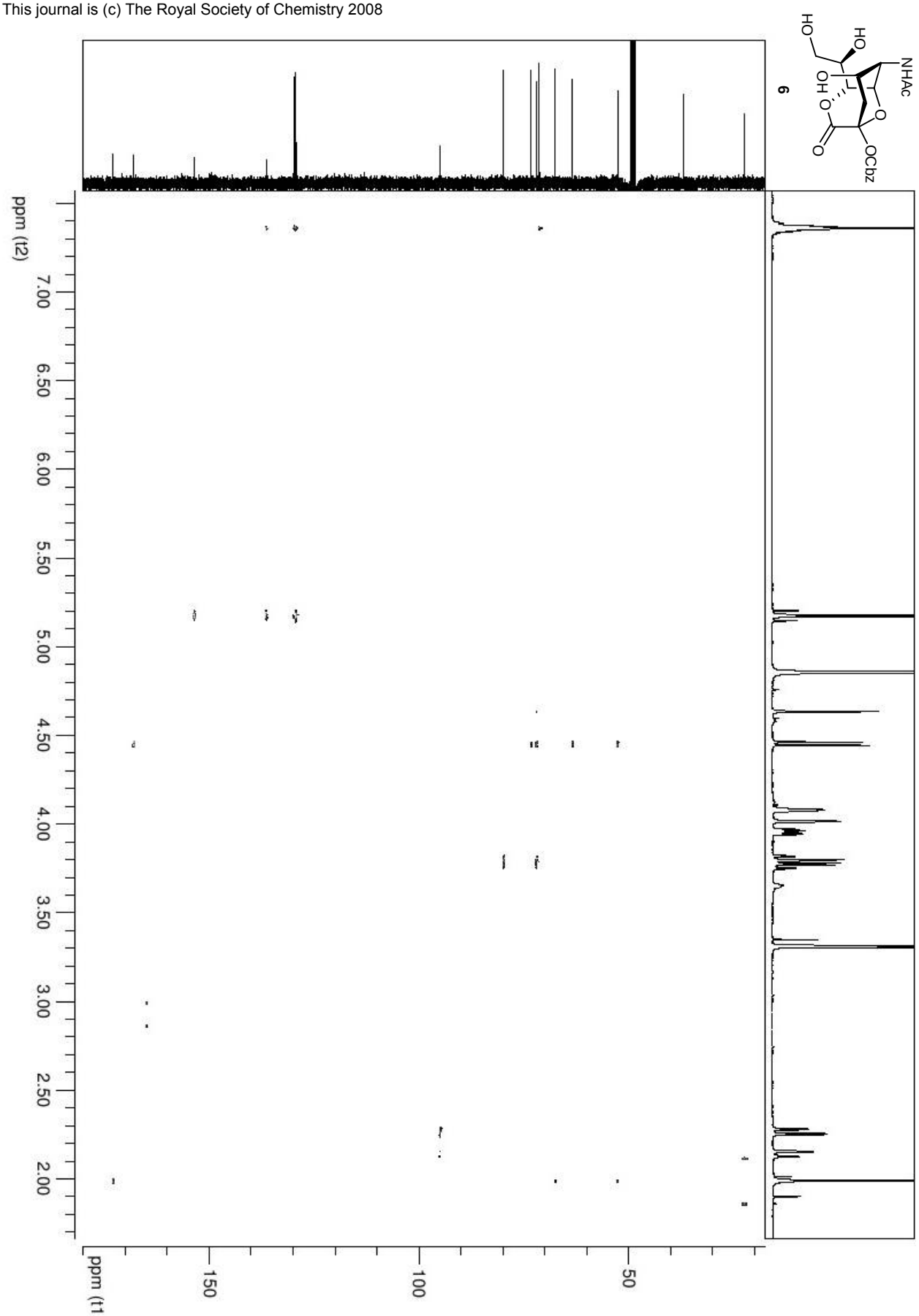
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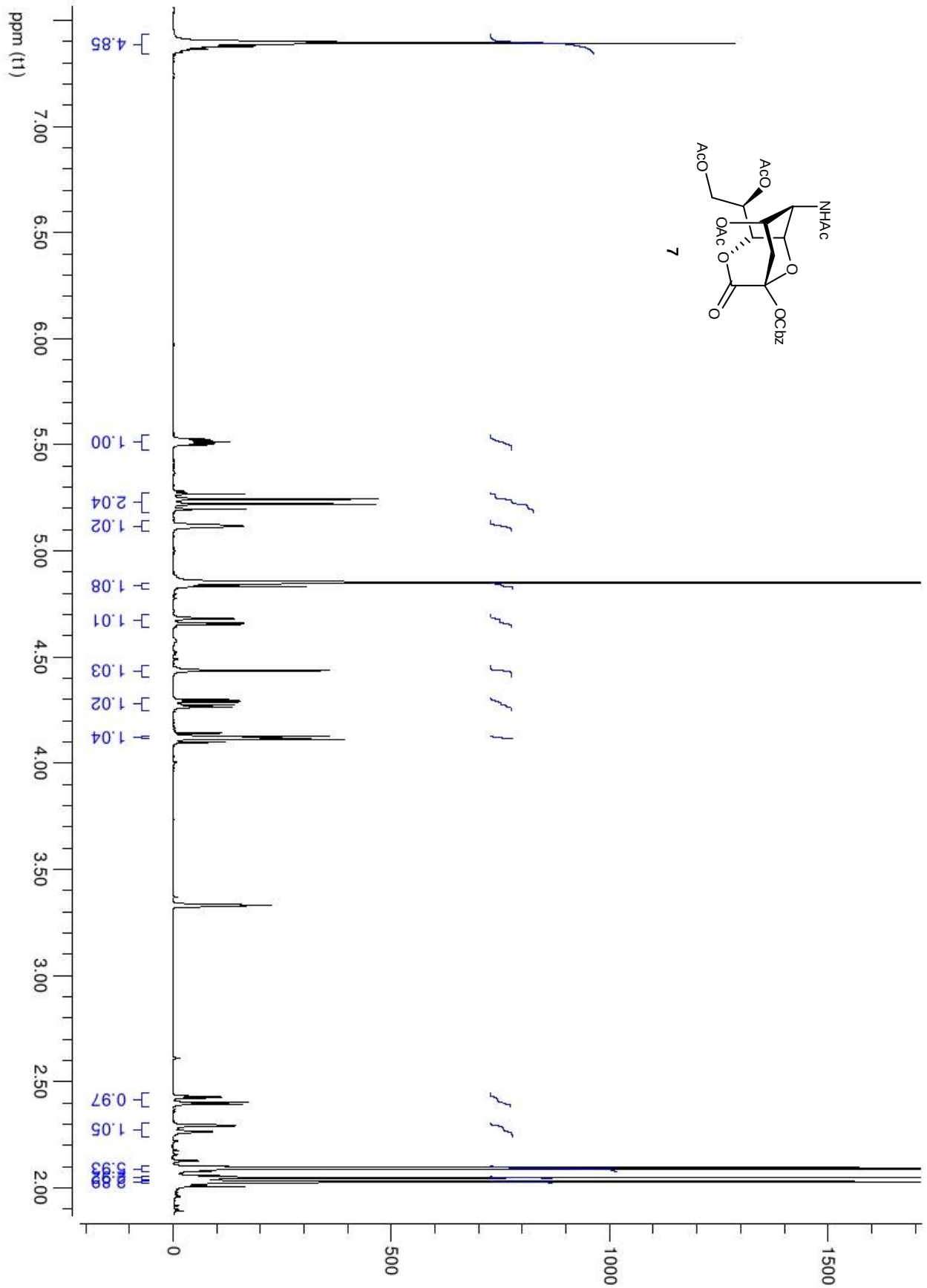
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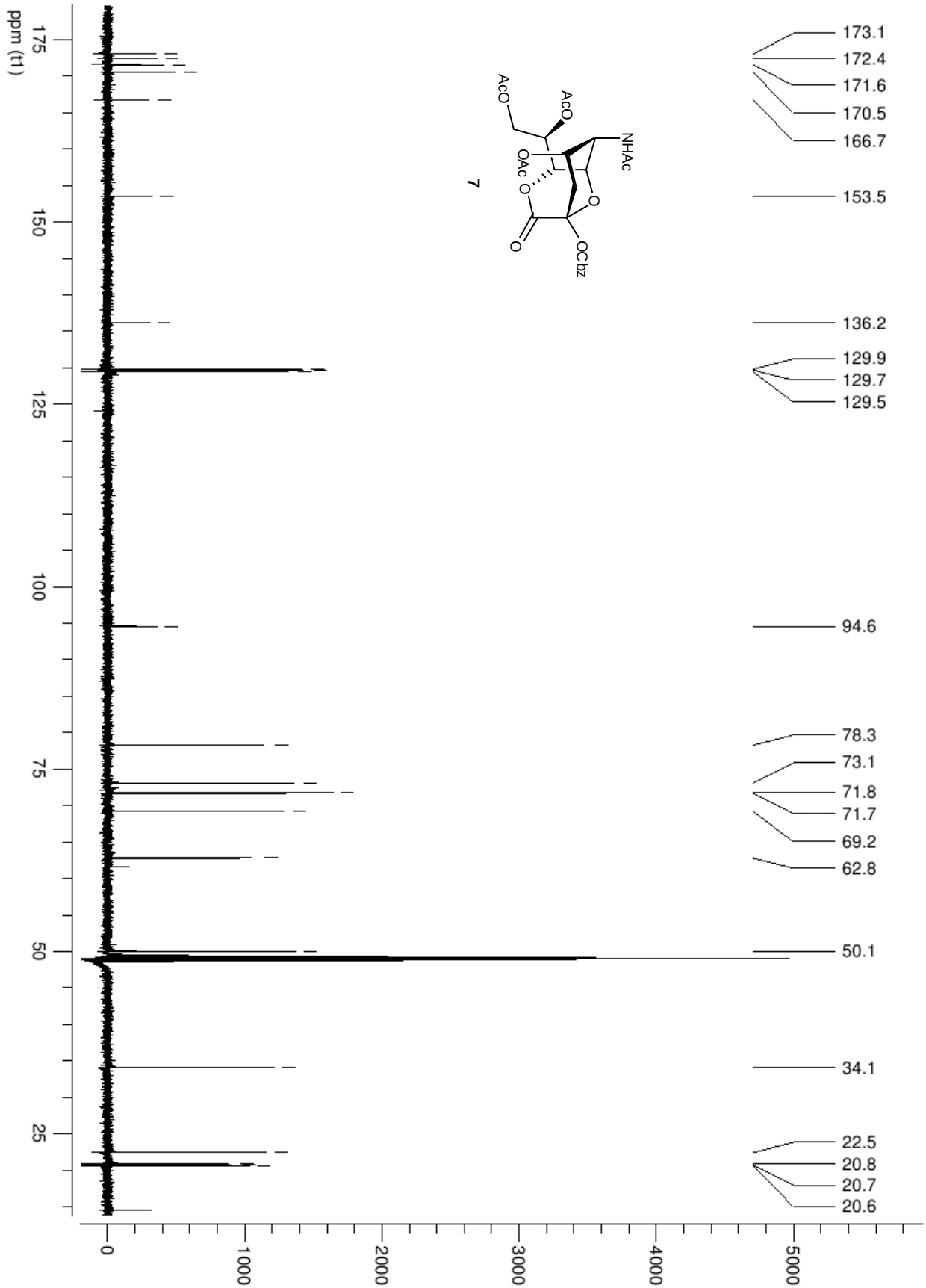
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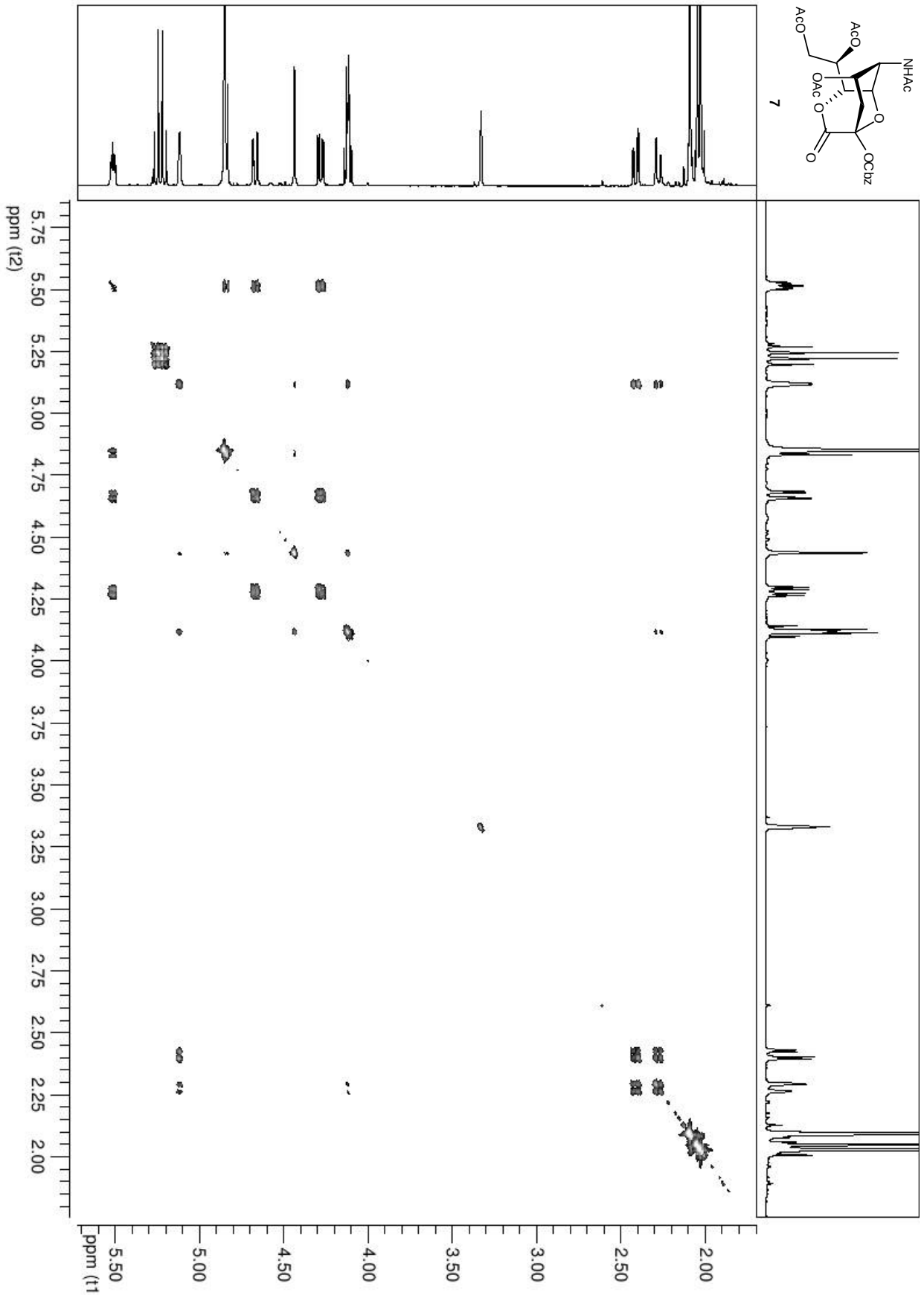
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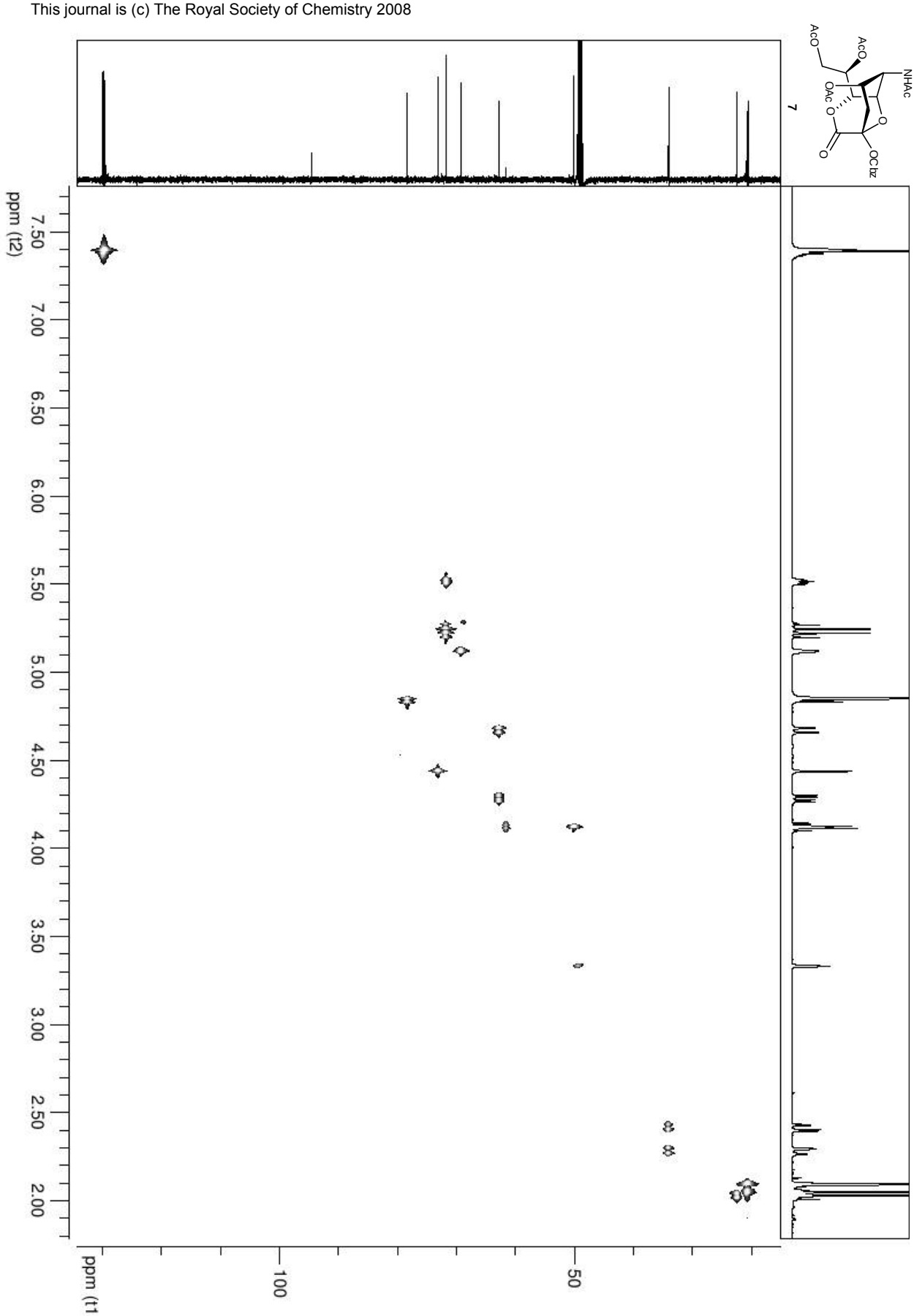
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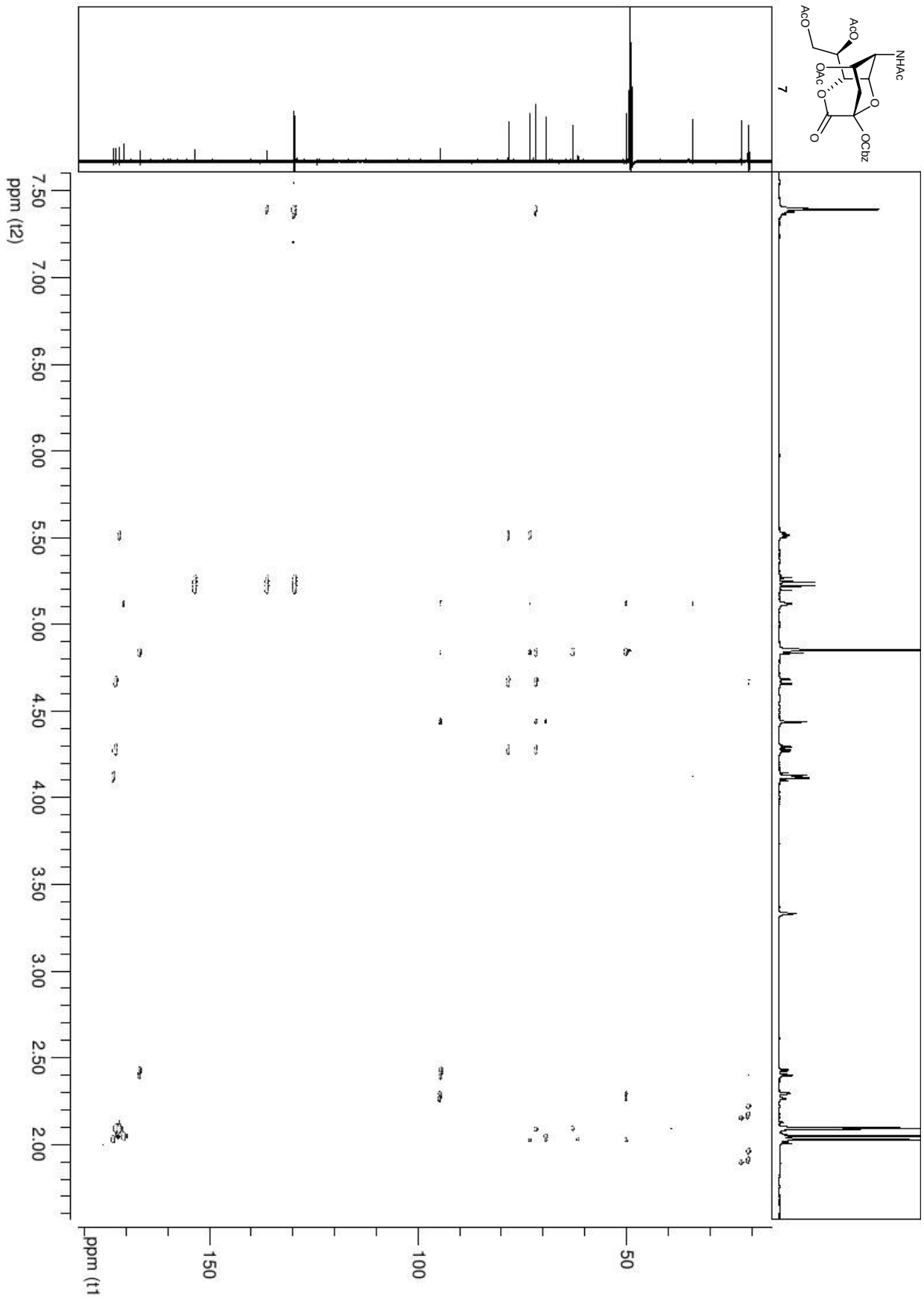
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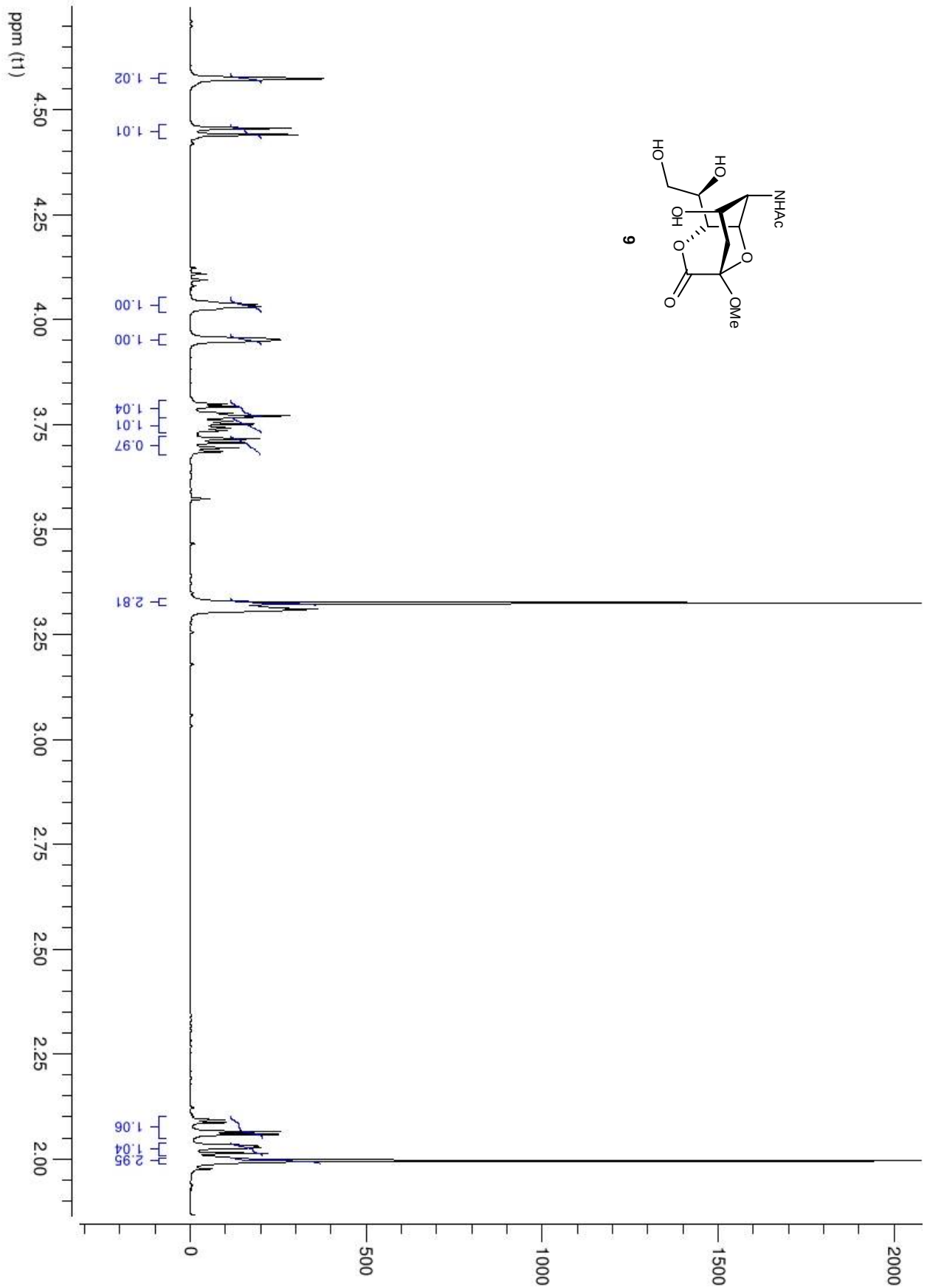
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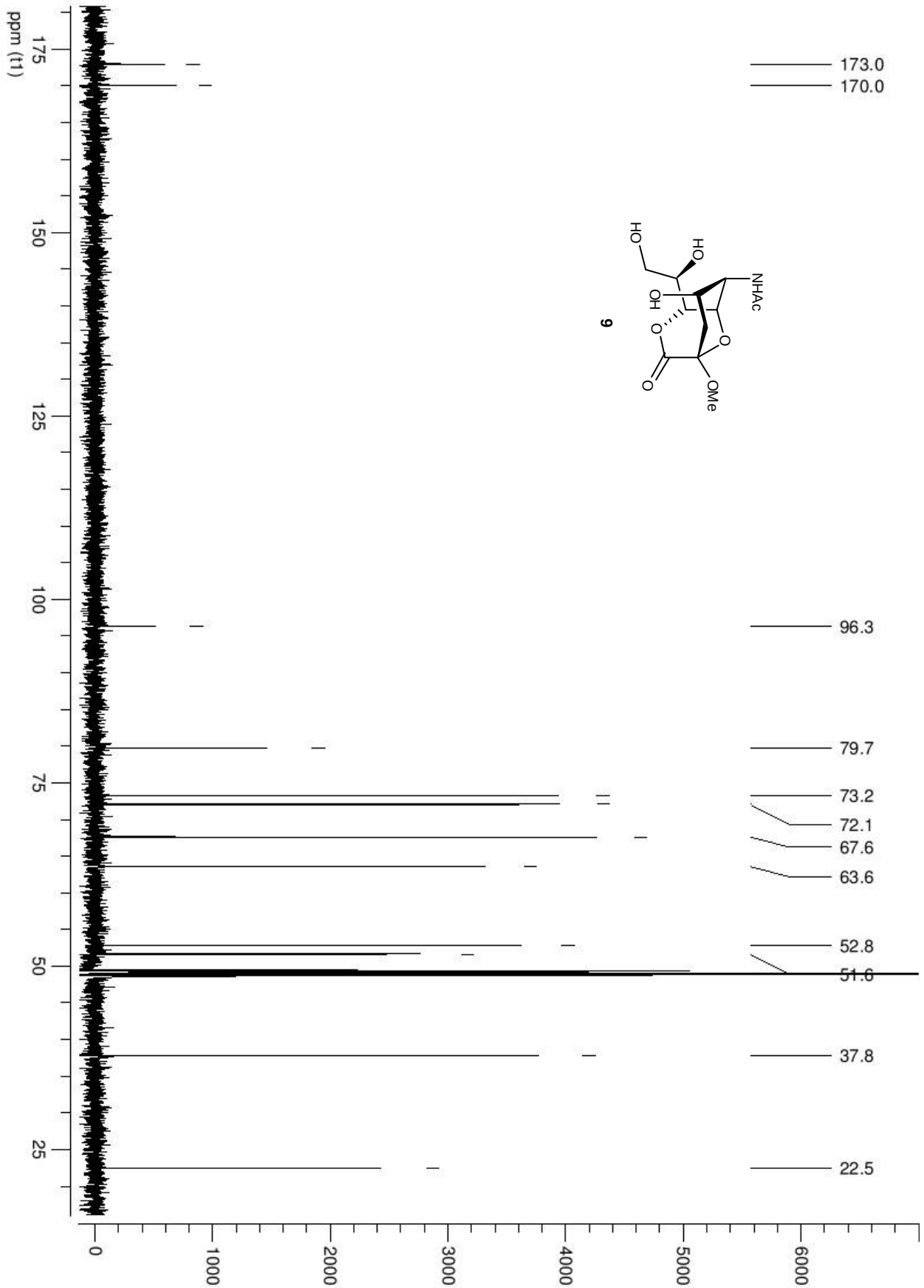
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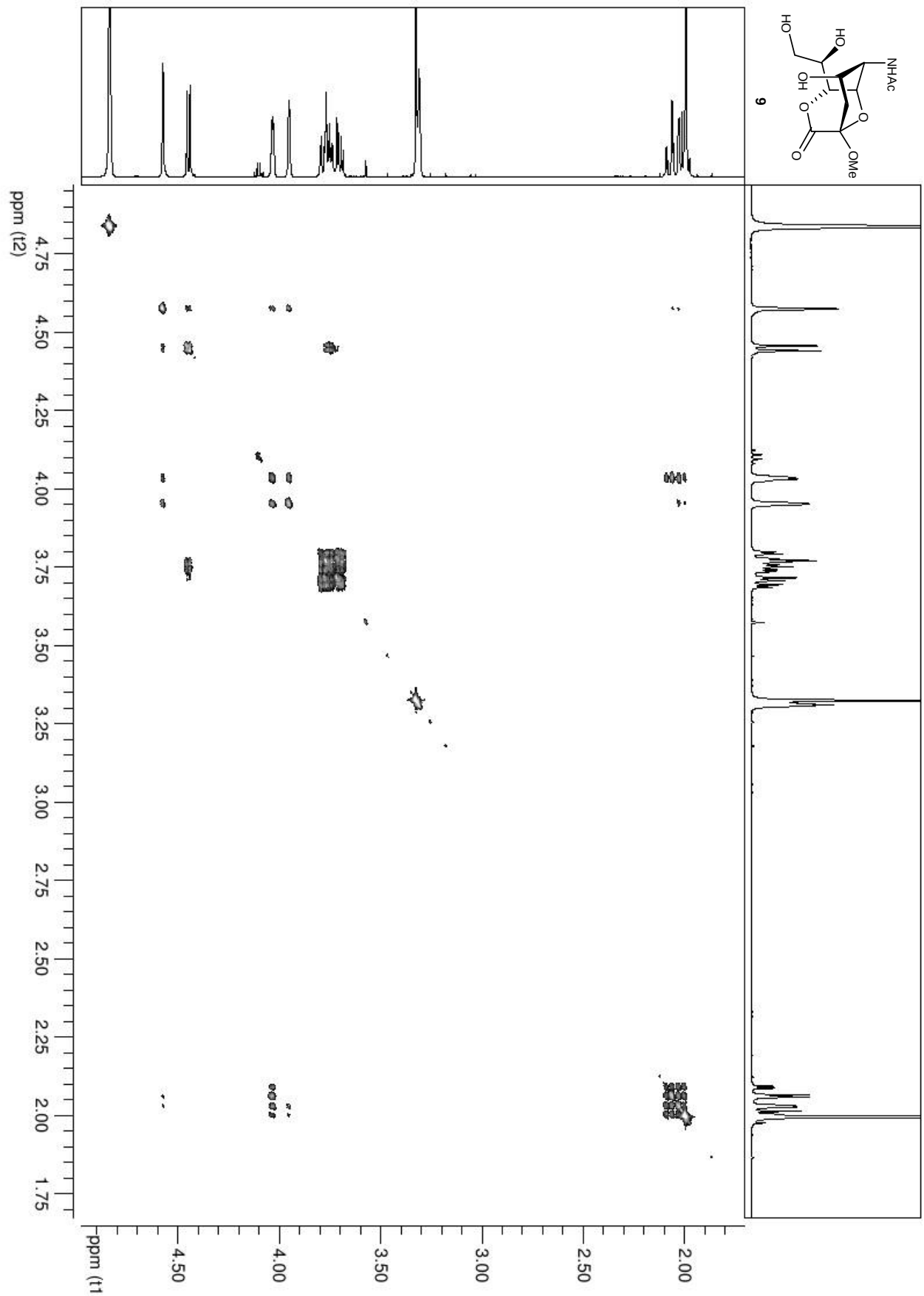
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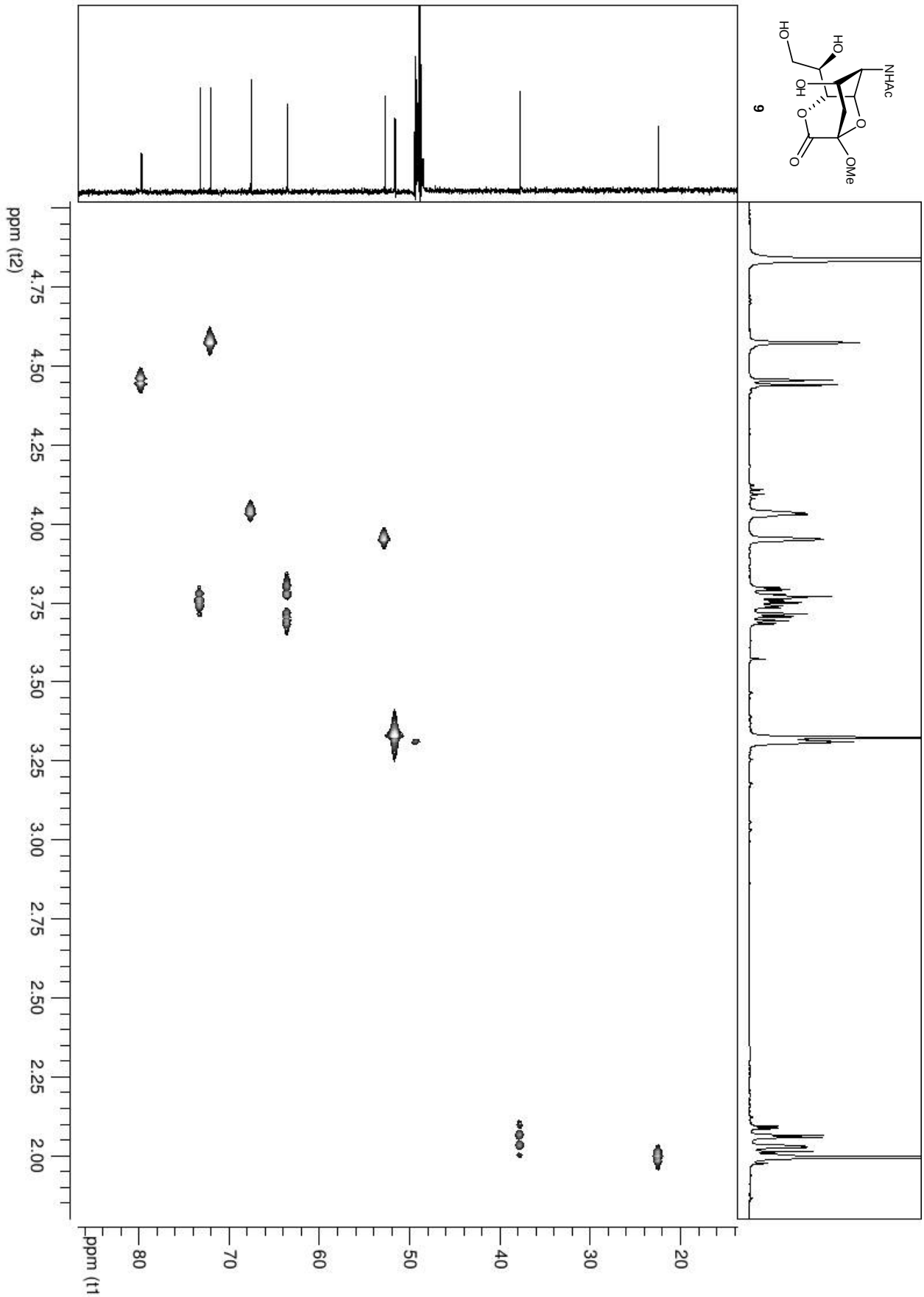
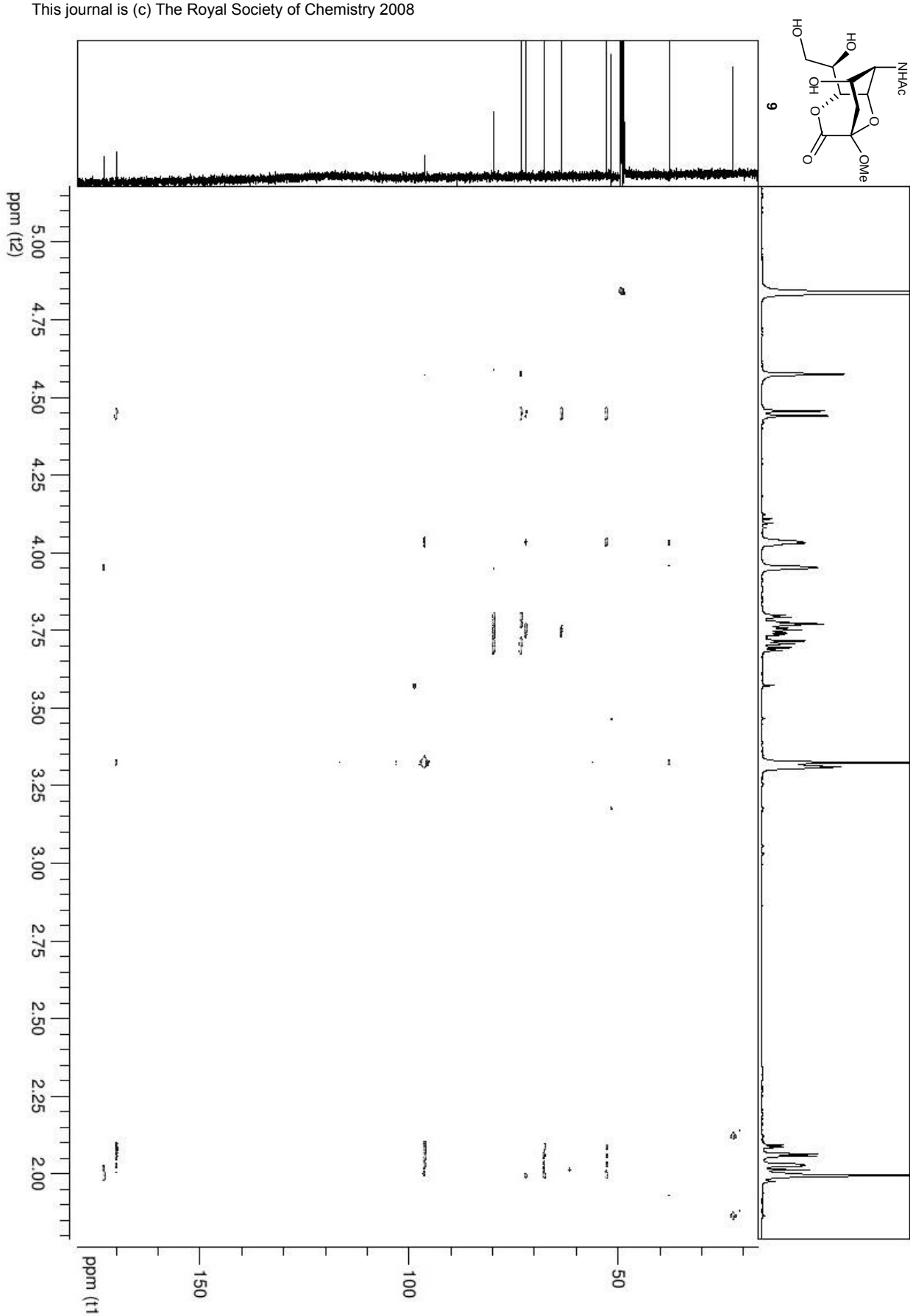
2.75
2.50
2.25
2.00
1.75
ppm (t1
4.50
4.00
3.50
3.00
2.50
2.00


HO
HO
NHAc
OH
O
O
O
OMe
9
ppm (t2)
4.75
4.50
4.25
4.00
3.75
3.50
3.25
3.00
2.75
2.50
2.25
2.00
ppm (t1
80
70
60
50
40
30
20


HO
HO
NHAc
OH
O
O
O
OMe
6
ppm (t2)
5.00
4.75
4.50
4.25
4.00
3.75
3.50
3.25
3.00
2.75
2.50
2.25
2.00
ppm (t1
150
100
50