Supporting Information

A Very Efficient Synthesis of a Mannosyl Orthoester Rotaxane and Mannosidic Rotaxanes

Frédéric Coutrot*, Eric Busseron, and Jean-Louis Montero

Institut des Biomolécules Max Mousseron (IBMM), UMR 5247CNRS-Universités Montpellier 2 et 1, Bâtiment de Recherche Max Mousseron, Ecole Nationale Supérieure de Chimie de Montpellier, 8 rue de l'Ecole Normale, 34296 Montpellier cedex 5, France

frederic.coutrot@univ-montp2.fr

1. General methods S2

2. Complexation study between compound **2** and DB24C8 ..... S2

3. Synthetic procedures and characterization of compounds 1 and 2 ..... S3

*3.1 Synthetic procedure of compound **1*** *S3*

*3.2 Synthetic procedure and characterization of compound **2*** *S3*

4. General procedure for glycosylation S4

5. General procedure for isomerization of orthoester **6** S4

6. Characterization of rotaxanes **5a-c**, **6** S4

*6.1 Characterization of compound **5a*** *S4*

*6.2 Characterization of compound **5b*** *S5*

*6.3 Characterization of compound **5c*** *S5*

*6.4 Characterization of compound **6*** *S5*

7. Characterization of threads **3a-b**, **4** S6

7.1 Note about threads. *S6*

*7.2 Characterization of deprotonated compound **3a*** *S6*

*7.3 Characterization of deprotonated compound **3b*** *S6*

*7.4 Characterization of deprotonated compound **4*** *S7*

8. NMR spectra S8

*8.1 NMR spectra of compound **2*** *S8*

*8.2 NMR spectra of compound **5a*** *S12*

*8.3 NMR spectra of compound **5b*** *S14*

*8.4 NMR spectra of compound **5c*** *S16*

*8.5 NMR spectra of compound **6*** *S18*

*8.6 NMR spectra of deprotonated compound **3a*** *S20*

*8.7 NMR spectra of deprotonated compound **3b*** *S22*

*8.8 NMR spectra of deprotonated orthoester compound **4*** *S24*

9. References S26

1. General methods

All reactions were achieved under an atmosphere of argon unless otherwise indicated and all reactions of glycosylation were carried out on a 100 mg scale. Flasks were oven dried and allowed to cool under argon prior to use. All reagents were purchased from Aldrich or Senn Chemical and were used as received without further purification. Dichloromethane was distilled over P_2O_5. Analytical thin-layer chromatography (TLC) was performed on Merck silicagel 60 F254 plates. Compounds were visualized by dipping the plates in an ethanolic solution of 10% sulphuric acid or in an ethanolic solution of 10% ninhydrine, followed by heating. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker DRX-400 spectrometer (respectively at 400.13 MHz and 100.62 MHz). Chemical shifts of ^{1}H NMR and ^{13}C NMR are given by using $CHCl_3$ as the reference (7.27 ppm for ^{1}H spectrum and 77 ppm for ^{13}C spectrum). Coupling constants (J) are reported in hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: s (singlet), br (broad), d (doublet), t (triplet), q (quartet), m (multiplet). Lettering and numbering of hydrogens and carbons correspond to the assignments indicated in Scheme 1 of the article. The electrospray ionisation spectra were obtained on a Waters 2614 Micromass ZQ mass spectrometer in positive (ESI+) or negative (ESI-) mode. High-resolution mass spectra (HRMS) were recorded on a Q-TOF Micro (water) apparatus.

2. Complexation study between compound 2 and DB24C8

In order to study, by ^{1}H NMR spectroscopy, the binding of *N*-alkyl anilinium cation **2** with DB24C8, stock solutions of **2** and DB24C8 were made. The 20 mM solution of alcohol **2** was prepared by dissolving 18.5 mg (0.047 mmol) in $CDCl_3$ (2.340 mL) and the 100 mM solution of DB24C8 by dissolving 44.2 mg (0.099 mmol) in $CDCl_3$ (0.985 mL). Six samples of thread **2** were made according to table 1. Overlay of ^{1}H NMR spectra is reported in figure 1 of the article.

Table 1: Dilutions used to study complexation by ^{1}H NMR.

sample ID	thread **2** mmol	DB24C8 mmol	vol. thread **2** stock solution µL	vol. DB24C8 stock solution µL	vol. blank $CDCl_3$ µL
1	10	0	250	0	250
2	10	5	250	25	225
3	10	10	250	50	200
4	10	15	250	75	175
5	10	20	250	100	150
6	10	25	250	125	125

3. Synthetic procedures and characterization of compounds 1 and 2

*3.1 Synthetic procedure of compound **1***

This compound was synthesised in a two-step sequence according to the procedure described by Vishwakarma et al. from 1,2,3,4,6-penta-*O*-acetyl-α-*D*-mannopyranose. [1]

*3.2 Synthetic procedure and characterization of compound **2***

- First step

To a solution of 4-*tert*-butylaniline (7.4 g, 50 mmol, 3.1 equiv) in toluene (60 mL) under reflux was added dropwise 6-aminohexan-1-ol (3.03 g, 16 mmol, 1 equiv) *via* a syringe pump over a period of 5 hours. The mixture was stirred under reflux overnight. The solvent was then removed and the residue was diluted with AcOEt (75mL). The organic layer was washed with an aqueous solution of NaOH (2M) until pH 10. Then the aqueous layer was extracted with AcOEt (4 x 75 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated. The oily residue was distilled under reduced pressure to give pure aminoalcohol (2.24 g, 54%, bp = 170 °C, 1.4 mbar) as a pale yellow oil.

R_f 0.52 (20/80 AcOEt/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ ppm 1.29 (s, 9H, H_{16}), 1.42 – 1.45 (m, 4H, H_9 H_{10}), 1.56 – 1.68 (m, 4H, H_8 H_{11}), 3.12 (t, 2H, J = 7.1 Hz, H_{12}), 3.66 (t, 2H, J = 6.7 Hz, H_7), 6.60 (m, 2H, H_{14}), 7.22 (m, 2H, H_{15}).

^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ ppm 25.5 & 26.9 (C_9 C_{10}), 29.5 (C_{11}), 31.5 (C_{16}), 32.6 (C_8), 33.8 ($C_{q\ tBu}$), 44.3 (C_{12}), 62.8 (C_7), 112.7 (C_{14}), 126.0 (C_{15}), 140.2 & 145.7 ($C_{q\ arom}$).

MS (ESI+): 250 $[M+H]^+$

- Second step

To a solution of the previous oily compound (2.24 g, 9 mmol, 1 equiv) in Et_2O (10 mL), was introduced dropwise at RT a solution of HCl 2M in Et_2O (22.5 mL, 45 mmol, 5 equiv). The mixture was stirred for 30 min to give a biphasic mixture, which was evaporated under reduced pressure to remove the excess of HCl. Then, Et_2O was added to the residue, the biphasic mixture being stirred afterwards for 5 min. Eventually, the ether organic layer was removed. After having evaporated the residual traces of solvent, the hydrochloride ammonium salt was dissolved in H_2O (10 mL) and NH_4PF_6 (3.7 g, 22 mmol, 2.5 equiv) was introduced. CH_2Cl_2 (15 mL) was added and the resulted bilayer solution was vigorously stirred for 2h. After separation, the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and concentrated to obtain the pure compound **2** (3.3 g, 92%) as a pale brown oil.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ ppm 1.29 (s, 9H, H_{16}), 1.32-1.39(m, 4H, H_9 H_{10}), 1.52 (m, 2H, H_8), 1.73 – 1.80 (m, 2H, H_{11}), 3.37 (t, 2H, J = 7.8 Hz, H_{12}), 3.62 (t, 2H, J = 6.4 Hz, H_7), 7.37 (d, 2H, J = 8.7 Hz, H_{15}), 7.49 (d, 2H, J = 8.7 Hz, H_{14}).

^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ ppm 24.5 (C_{10}), 25.1 (C_9), 25.2 (C_{11}), 31.1 (C_{16}), 31.4 (C_8), 34.8 ($C_{q\ tBu}$), 54.0 (C_{12}), 62.7 (C_7), 121.9 (C_{15}), 127.5 (C_{14}), 131.6 & 153.6 ($C_{q\ arom}$).

MS (ESI+): 250 $[M+H]^+$

MS (ESI-): 145 $[PF_6]^-$

4. General procedure for glycosylation

A solution of trichloroacetimidate **1** (102 mg, 0.21 mmol, 1 equiv) in dry CH_2Cl_2 (4 mL), in the presence of 4Å molecular sieves, under argon atmosphere, was cooled until -30 °C. Meanwhile in another flask, DB24C8 (204 mg, 0.45 mmol, 2.2 equiv) was added to a solution of compound **2** (90 mg, 0.23 mmol, 1.1 equiv) in dry CH_2Cl_2 (3 mL) under argon atmosphere. This mixture was stirred for 10 min at RT and was transferred to the first solution. When the temperature was stabilized, TMSOTf (8 µL, 44 µmol, 0.2 equiv) was added and the mixture was stirred for 1 min at the same temperature. The reaction was quenched by addition of triethylamine (6 µL, 44 µmol, 0.2 equiv) and stirred for 5 min. Then the mixture was allowed to reach RT; it was evaporated to dryness and the crude was analysed by ^{1}H NMR (Table 1 of the article). The residue was purified by chromatography on a silicagel column (solvent gradient elution: 5/95 Acetone/CH_2Cl_2, 10/90, 20/80) to give successively compound **5a** (31 mg ,13%) and compound **6** (145 mg, 60%) as solids.

5. General procedure for isomerization of orthoester 6

A solution of rotaxane orthoester **6** (40 mg, 34 µmol, 1 equiv) in dry CH_2Cl_2 (8 mL) in the presence of 4Å molecular sieves under argon atmosphere was cooled to -15 °C. A solution of TMSOTf (25 µL, 7 µmol, 0.2 equiv, C = 0.28 mol.L^{-1}) in CH_2Cl_2 was then added and the reaction mixture was stirred at this temperature for 5 min. The reaction was quenched by addition of a solution of triethylamine (19 µL, 7 µmol, 0.2 equiv, C = 0.36 mol.L^{-1}) in CH_2Cl_2 and stirred for another 5 min. Then the mixture was allowed to reach RT and the solvent was removed. The crude residue was analysed by ^{1}H NMR (Table 2 of the article) and purified by chromatography on a silicagel column (solvent gradient elution: 2/98 Acetone/CH_2Cl_2, 5/95, 10/90) to give **5a** (9 mg; 22%) as a solid.

6. Characterization of rotaxanes 5a-c, 6

*6.1 Characterization of compound **5a***

R_f 0.76 (15/85 Acetone/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ ppm 0.94-1.03 (m, 4H, H_9 H_{10}), 1.17-1.23 (m, 2H, H_8), 1.26 (s, 9H, H_{16}), 1.40-1.48 (m, 2H, H_{11}), 2.01 & 2.06 & 2.11 & 2.17 (4s, 12H, OAc), 3.16-3.23 (m, 1H, H_{7a}), 3.28-3.34 (m, 4H, H_E), 3.47-3.53 (m, 1H, H_{7b}), 3.56-3.62 (m, 4H, $H_{E'}$), 3.78-3.87 (m, 8H, H_D), 3.90-3.99 (m, 3H, H_5 H_{12}), 4.08-4.13 (m, 5H, H_{6b} H_C), 4.20-4.26 (m, 4H, $H_{C'}$), 4.29 (dd, 1H, J = 12.3 Hz, J = 5.2 Hz, H_{6a}), 4.73 (d, 1H, J = 1.3 Hz, H_1), 5.20-5.22 (m, 1H, H_2), 5.26-5.33 (m, 2H, H_3 H_4), 6.85-6.92 (m, 8H, H_A H_B), 7.35 (d, 2H, J = 8.5 Hz, H_{15}), 7.54 (d, 2H, J = 8.5 Hz, H_{14}), 8.52-8.61 (br s, 2H, H_{13}).

^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ ppm 20.7 & 20.7 & 20.8 & 20.9 ($\underline{C}H_3CO$), 25.5 & 25.9 (C_9 C_{10}), 27.1 (C_{11}), 28.8 (C_8), 31.2 (C_{16}), 34.7 ($C_{q\ tBu}$), 50.5 (C_{12}), 62.4 (C_6), 66.1 (C_3), 68.0 (C_7), 68.1 (C_C), 68.3 (C_5), 69.1 (C_4), 69.6 (C_2), 70.1 (C_D), 70.6 (C_E), 97.4 (C_1), 112.3 & 121.6 (C_A C_B), 122.5 (C_{14}), 126.1 (C_{15}), 132.9 & 152.8 ($C_{q\ arom\ thread}$), 147.3 ($C_{q\ DB24C8}$), 169.7 & 170.0 & 170.2 & 170.7 ($\underline{C}OCH_3$).

HRMS (ESI): $[M\text{-}PF_6]^+$ calcd for $C_{54}H_{78}NO_{18}$: 1028.5219, found 1028.5200

*6.2 Characterization of compound **5b***

R_f 0.30 (15/85 Acetone/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ ppm 0.94-1.03 (m, 4H, H_9 H_{10}), 1.17-1.23 (m, 2H, H_8), 1.25 (s, 9H, H_{16}), 1.40-1.48 (m, 2H, H_{11}), 2.02 & 2.07 & 2.08 (3s, 9H, OAc), 3.17-3.23 (m, 1H, H_{7a}), 3.27-3.33 (m, 4H, H_E), 3.45-3.50 (m, 1H, H_{7b}), 3.56-3.62 (m, 4H, $H_{E'}$), 3.77-3.88 (m, 9H, H_5 H_D), 3.89-4.00 (m, 2H, H_{12}), 4.03-4.05 (m, 1H, H_2), 4.07-4.14 (m, 5H, H_{6a} H_C), 4.19-4.25 (m, 5H, H_{6b} $H_{C'}$), 4.79 (d, 1H, J = 1.4 Hz, H_1), 5.22 (dd, 1H, J = 10 Hz, J = 3.2 Hz, H_3), 5.33 (t, 1H, J = 10 Hz, H_4), 6.84-6.92 (m, 8H, H_A H_B), 7.32 (d, 2H, J = 8.6 Hz, H_{15}), 7.52 (d, 2H, J = 8.6 Hz, H_{14}), 8.48-8.61(br s, 2H, H_{13}).

^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ ppm 20.7 & 20.7 & 20.9 ($\underline{C}H_3CO$), 25.4 & 25.8 (C_9 C_{10}), 27.1 (C_{11}), 28.7 (C_8), 31.1 (C_{16}), 34.7 ($C_{q\ tBu}$), 50.4 (C_{12}), 62.6 (C_6), 66.6 (C_4), 67.5 (C_7), 68.0 (C_C), 68.2 & 68.9 (C_2 C_5), 70.0 (C_D), 70.6 (C_E), 71.5 (C_3), 99.6 (C_1), 112.3 & 121.6 (C_A C_B), 122.5 (C_{14}), 126.0 (C_{15}), 132.8 & 152.8 ($C_{q\ arom\ thread}$), 147.2 ($C_{q\ DB24C8}$), 169.7 & 170.3 & 170.8 ($\underline{C}OCH_3$).

HRMS (ESI): $[M\text{-}PF_6]^+$ calcd for $C_{52}H_{76}NO_{17}$: 986.5113, found: 986.5109

*6.3 Characterization of compound **5c***

R_f 0.31 (5/95 MeOH/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ ppm 0.14 (s, 9H, $(CH_3)_3Si$), 0.94-1.03 (m, 4H, H_9 H_{10}), 1.17-1.23 (m, 2H, H_8), 1.27 (s, 9H, H_{16}), 1.40-1.47 (m, 2H, H_{11}), 2.04 & 2.07 & 2.09 (3s, 9H, OAc), 3.17-3.23 (m, 1H, H_{7a}), 3.28-3.34 (m, 4H, H_E), 3.43-3.51 (m, 1H, H_{7b}), 3.57-3.63 (m, 4H, $H_{E'}$), 3.80-3.89 (m, 9H, H_5 H_D), 3.89-3.95 (m, 2H, H_{12}), 3.99 (dd, 1H, J = 3 Hz, J = 1.8 Hz, H_2), 4.09-4.15 (m, 5H, H_{6a} H_C), 4.21-4.28 (m, 5H, H_{6b} $H_{C'}$), 4.59 (d, 1H, J = 1.8 Hz, H_1), 5.17 (dd, 1H, J = 10 Hz, J = 3 Hz, H_3), 5.35 (t, 1H, J = 10 Hz, H_4), 6.85-6.98 (m, 8H, H_A H_B), 7.35 (d, 2H, J = 8.5 Hz, H_{15}), 7.54 (d, 2H, J = 8.5 Hz, H_{14}), 8.50-8.69 (br s, 2H, H_{13}).

^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ ppm 0.0 (($\underline{C}H_3)_3Si$), 20.8 & 20.8 & 21.0 ($\underline{C}H_3CO$), 25.6 & 26.1 (C_9 C_{10}), 27.2 (C_{11}), 29.0 (C_8), 31.2 (C_{16}), 34.7 ($C_{q\ tBu}$), 50.5 (C_{12}), 62.7 (C_6), 66.5 (C_4), 67.8 (C_7), 68.1 (C_C), 68.7 & 69.8 (C_2 C_5), 71.4 (C_3), 70.1 (C_D), 70.6 (C_E), 100.4 (C_1), 112.3 & 121.6 (C_A C_B), 122.5 (C_{14}), 126.1 (C_{15}), 132.9 & 152.8 ($C_{q\ arom\ thread}$), 147.3 ($C_{q\ DB24C8}$), 169.6 ($\underline{C}OCH_3$).

HRMS (ESI): $[M\text{-}PF_6]^+$ calcd for $C_{55}H_{84}NO_{17}Si$: 1058.5509, found: 1058.5498

*6.4 Characterization of compound **6***

R_f 0.60 (20/80 Acetone/CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ ppm 0.94-1.03 (m, 4H, H_9 H_{10}), 1.17 -1.21 (m, 2H, H_8), 1.23 (s, 9H, H_{16}), 1.38-1.47 (m, 2H, H_{11}), 1.70 (s, 3H, CH_3 orthoester), 2.03 & 2.06 & 2.09 (3s, 9H, OAc), 3.26-3.35 (m, 6H, H_{7a} H_{7b} H_E), 3.54-5.60 (m, 4H, $H_{E'}$), 3.70 (ddd, 1H, J = 9.8 Hz, J = 4.7 Hz, J = 2.7 Hz, H_5), 3.78-3.85 (m, 8H, H_D), 3.91-3.99 (m, 1H, H_{12}), 4.06-4.12 (m, 5H, H_{6b} H_C), 4.16-4.26 (m, 5H, H_{6a} $H_{C'}$), 4.58 (dd, 1H, J = 4 Hz, J = 2.4 Hz, H_2), 5.14 (dd, 1H, J = 9.8 Hz, J = 4 Hz, H_3), 5.27 (t, 1H, J = 9.8 Hz, H_4), 5.48 (d, 1H, J = 2.4 Hz, H_1), 6.81-6.89 (m, 8H, H_A H_B), 7.29 (d, 2H, J = 8.6 Hz, H_{15}), 7.49(d, 2H, J = 8.6 Hz, H_{14}), 8.41-8.61(br, 2H, H_{13}).

^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ ppm 20.6 & 20.7 & 20.7 ($\underline{C}H_3CO$), 24.8 (CH_3 orthoester), 25.5 & 25.9 (C_9 C_{10}), 27.2 (C_{11}), 29.0 (C_8), 31.1 (C_{16}), 34.7 ($C_{q\ tBu}$), 50.4 (C_{12}), 62.0 (C_7), 62.3 (C_6), 65.5 (C_4), 68.0 (C_C), 70.0 (C_D), 70.6 (C_E), 70.7 & 71.0 (C_3 C_5), 76.4 (C_2), 97.3 (C_1), 112.2 & 121.6 (C_A C_B), 122.4 (C_{14}), 124.0 ($C_{q\ orthoester}$), 126.0 (C_{15}), 132.7 & 152.7 ($C_{q\ arom\ thread}$), 147.2 ($C_{q\ DB24C8}$), 169.4 & 170.2 & 170.6 ($\underline{C}OCH_3$).

HRMS (ESI): $[M\text{-}PF_6]^+$ calcd for $C_{54}H_{78}NO_{18}$: 1028.5219, found: 1028.5193

7. Characterization of threads 3a-b, 4

7.1 Note about threads.

Although 0.2 equiv of triethylamine (necessary amount to quench the 0.2 equiv of TMSOTf) was added at the end of reaction, we noticed that every thread was totally deprotonated after purification by chromatography. We could suppose that deprotonation occured during the purification. Equilibrium between anilinium and aniline thread has already been described by S.J. Loeb. [2]

*7.2 Characterization of deprotonated compound **3a***

R_f 0.72 (50/50 AcOEt/Petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ ppm 1.28 (s, 9H, H_{16}), 1.39-1.47 (m, 4H, H_9 H_{10}), 1.60-1.67 (m, 4H, H_8 H_{11}), 2.04 & 2.05 & 2.11 & 2.17 (4s, 12H, OAc), 3.11 (t, 2H, J = 7.1Hz, H_{12}), 3.43-3.49 (m, 1H, H_{7a}), 3.66-3.72 (m, 1H, H_{7b}), 3.99 (ddd, 1H, J = 9.9 Hz, J = 5.3 Hz, J = 2.4 Hz, H_5), 4.11 (dd, 1H, J = 12.2 Hz, J = 2.4 Hz, H_{6a}), 4.29 (dd, 1H, J = 12.2 Hz, J = 5.3 Hz, H_{6b}), 4.81 (d, 1H, J = 1.4 Hz, H_1), 5.24 (dd, 1H, J = 3.3 Hz, J = 1.4 Hz, H_2), 5.29 (t, 1H, J = 9.9 Hz, H_4), 5.36 (dd, 1H, J = 9.9 Hz, J = 3.3 Hz, H_3), 6.58 (d, 2H, J = 8.6 Hz, H_{14}), 7.21 (d, J = 8.6 Hz, H_{15}).

^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ ppm 20.7 & 20.9 ($\underline{C}H_3CO$), 26.0 & 26.9 (C_9 C_{10}), 29.2 & 29.5 (C_8 C_{11}), 31.5 (C_{16}), 33.7 ($C_{q\ tBu}$), 44.0 (C_{12}), 62.5 (C_6), 66.2 (C_4), 68.3 (C_5), 68.4 (C_7), 69.0 (C_3), 69.7 (C_2), 97.5 (C_1), 112.3 (C_{14}), 125.9 (C_{15}), 139.8 & 146.1 ($C_{q\ arom}$), 169.7 & 169.9 & 170.1 & 170.6 ($\underline{C}OCH_3$).

HRMS (ESI): $[M+H]^+$ calcd for $C_{30}H_{46}NO_{10}$: 580.3122, found: 580.3138

*7.3 Characterization of deprotonated compound **3b***

R_f 0.65 (20/80 Acetone/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ ppm 1.28 (s, 9H, H_{16}), 1.39-1.47 (m, 4H, H_9 H_{10}), 1.60-1.67 (m, 4H, H_8 H_{11}), 2.04 & 2.10 (2s, 9H, OAc), 3.11 (t, 2H, J = 7.1Hz, H_{12}), 3.43-3.50 (m, 1H, H_{7a}), 3.67-3.74 (m, 1H, H_{7b}), 3.97 (ddd, 1H, J = 9.5 Hz, J = 4.8 Hz, J = 2.4 Hz, H_5), 4.04 (dd, 1H, J = 2.8 Hz, J = 1.7 Hz, H_2), 4.11 (dd, 1H, J = 12.2 Hz, J = 2.4 Hz, H_{6a}), 4.29 (dd, 1H, J = 12.2 Hz, J = 4.8 Hz, H_{6b}), 4.87 (d, 1H, J = 1.7 Hz, H_1), 5.27-5.36 (m, 2H, H_3 H_4), 6.58 (d, 2H, J = 8.6 Hz, H_{14}), 7.21 (d, J = 8.6 Hz, H_{15}).

^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ ppm 20.7 & 20.8 & 20.9 ($\underline{C}H_3CO$), 26.0 & 26.9 (C_9 C_{10}), 29.3 & 29.6 (C_8 C_{11}), 31.5 (C_{16}), 33.7 ($C_{q\ tBu}$), 44.2 (C_{12}), 62.5 (C_6), 66.3 (C_3), 68.2 (C_5), 68.3 (C_7), 69.5 (C_2), 71.7 (C_4), 99.4 (C_1), 112.5 (C_{14}), 126.0 (C_{15}), 139.9 & 146.2 ($C_{q\ arom}$), 169.9 & 170.8 ($\underline{C}OCH_3$).

HRMS (ESI): $[M+H]^+$ calcd for $C_{28}H_{44}NO_9$: 538.3016, found: 538.3008

*7.4 Characterization of deprotonated compound **4***

R_f 0.70 (50/50 AcOEt/Petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ ppm 1.27 (s, 9H, H_{16}), 1.36-1.42 (m, 4H, H_9 H_{10}), 1.52-1.65 (m, 4H, H_8 H_{11}), 1.76 (s, 3H, $CH_{3\ orthoester}$), 2.05 & 2.08 & 2.12 (3s, 9H, OAc), 3.11 (t, 2H, J = 7.1Hz, H_{12}), 3.45-3.53 (m, 2H, H_7), 3.67 (ddd, 1H, J = 9.7Hz, J = 4.9 Hz, J = 2.6 Hz, H_5), 4.14 (dd, 1H, J = 12.2 Hz, J = 2.6 Hz, H_{6a}), 4.24 (dd, 1H, J = 12.2Hz, J = 4.9 Hz, H_{6b}), 4.60 (dd, 1H, J = 3.8 Hz, J = 2.6 Hz, H_2), 5.14 (dd, 1H, J = 9.7 Hz, J = 3.8 Hz, H_3), 5.29 (t, 1H, J = 9.7 Hz, H_4), 5.45 (d, 1H, J = 2.6 Hz, H_1), 6.58 (d, 2H, J = 8.6 Hz, H_{14}), 7.21 (d, J = 8.6 Hz, H_{15}).

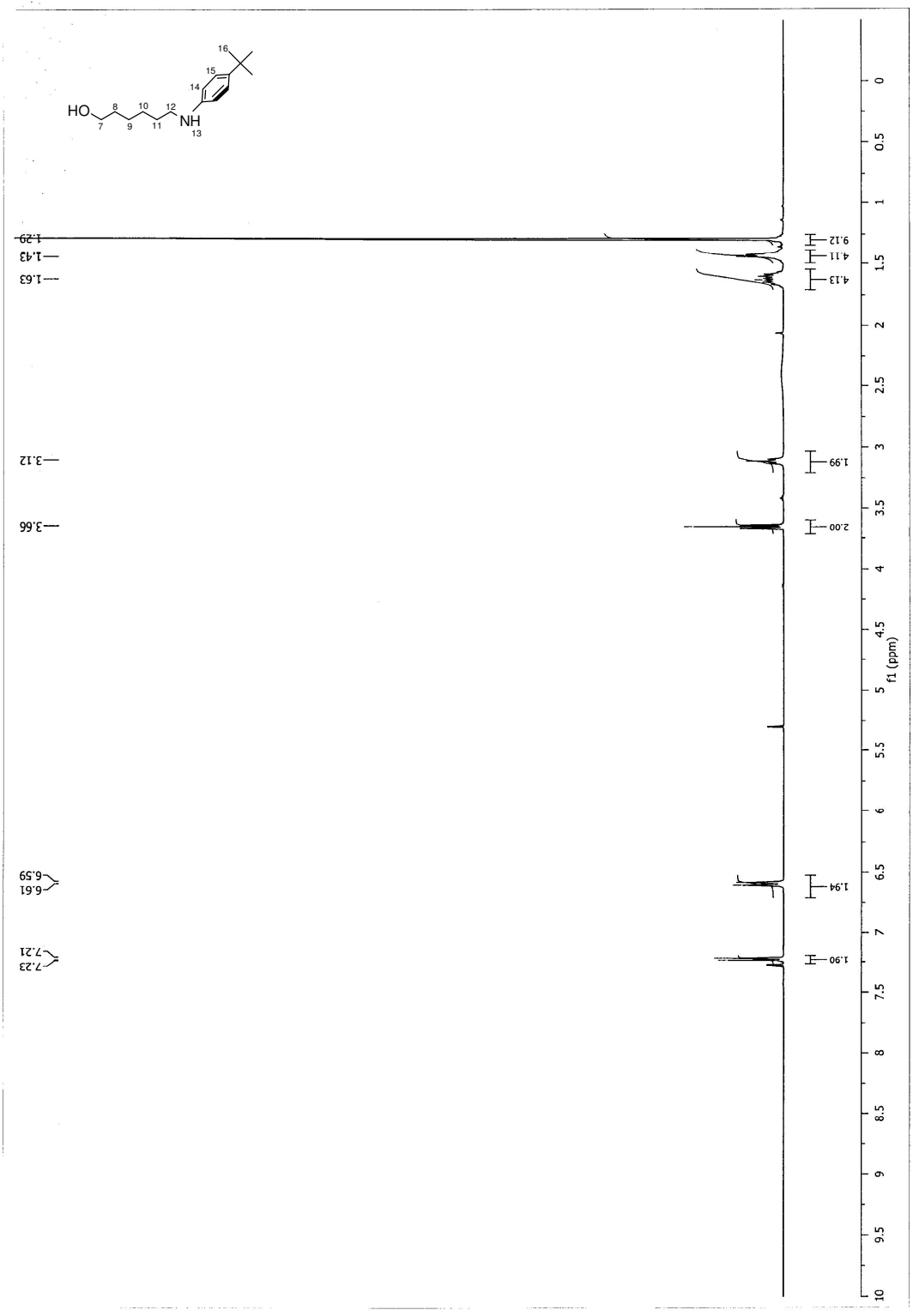
^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ ppm 20.7 & 20.7 & 20.8 ($\underline{C}H_3CO$), 24.6 ($CH_{3\ orthoester}$), 25.8 & 26.8 (C_9 C_{10}), 29.3 & 29.5 (C_8 C_{11}), 31.5 (C_{16}), 33.7 ($C_{q\ tBu}$), 44.0 (C_{12}), 62.2 (C_6), 62.4 (C_7), 65.5 (C_4), 70.6 (C_3) , 71.3 (C_5), 76.3 (C_2), 97.3 (C_1), 112.4 (C_{14}), 124.1 ($C_{q\ orthoester}$), 125.9 (C_{15}), 139.8 & 146.1 ($C_{q\ arom}$), 169.4 & 170.4 & 170.6 ($\underline{C}OCH_3$).

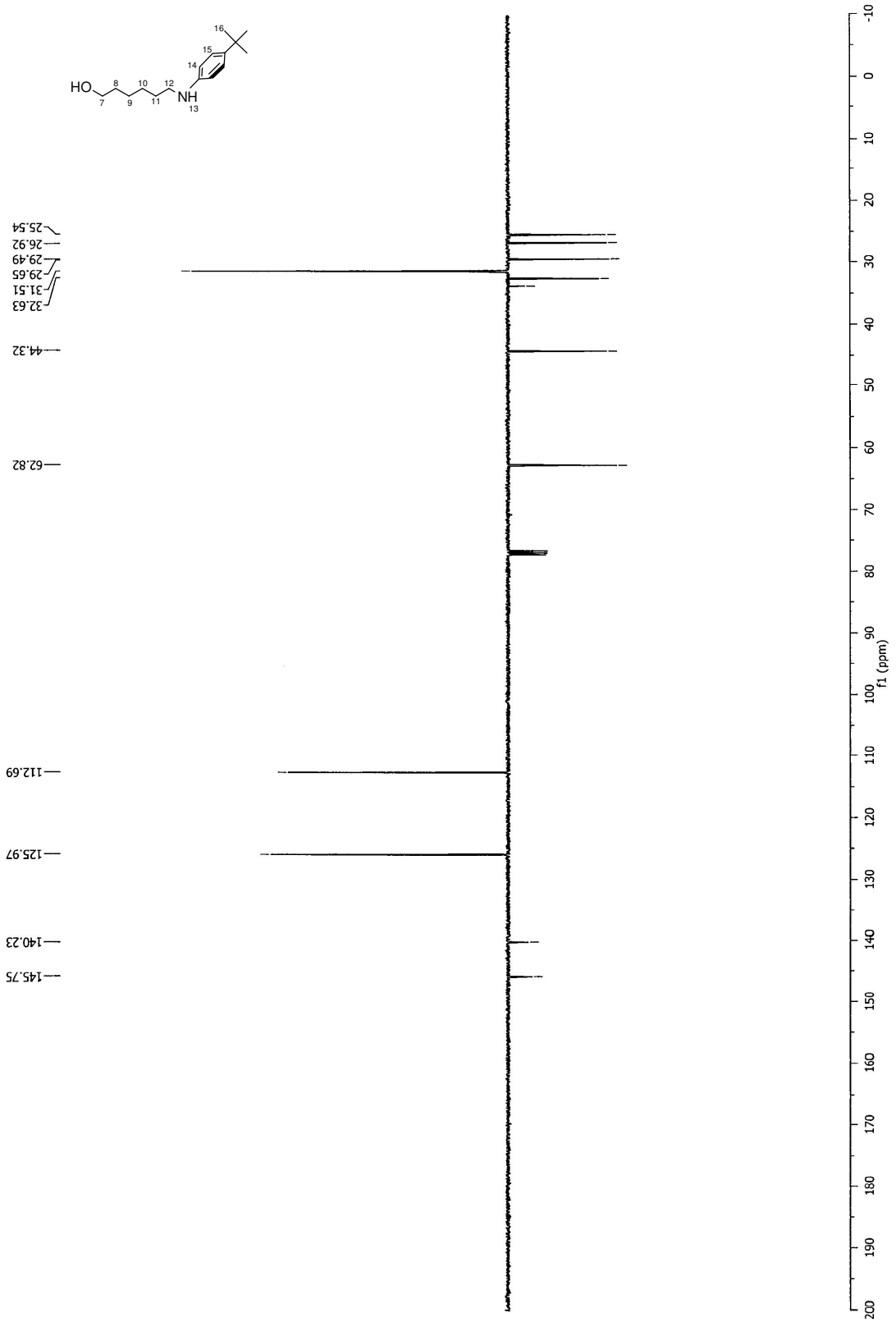
HRMS (ESI): $[M+H]^+$ calcd for $C_{30}H_{46}NO_{10}$: 580.3122, found: 580.3130

8. NMR spectra

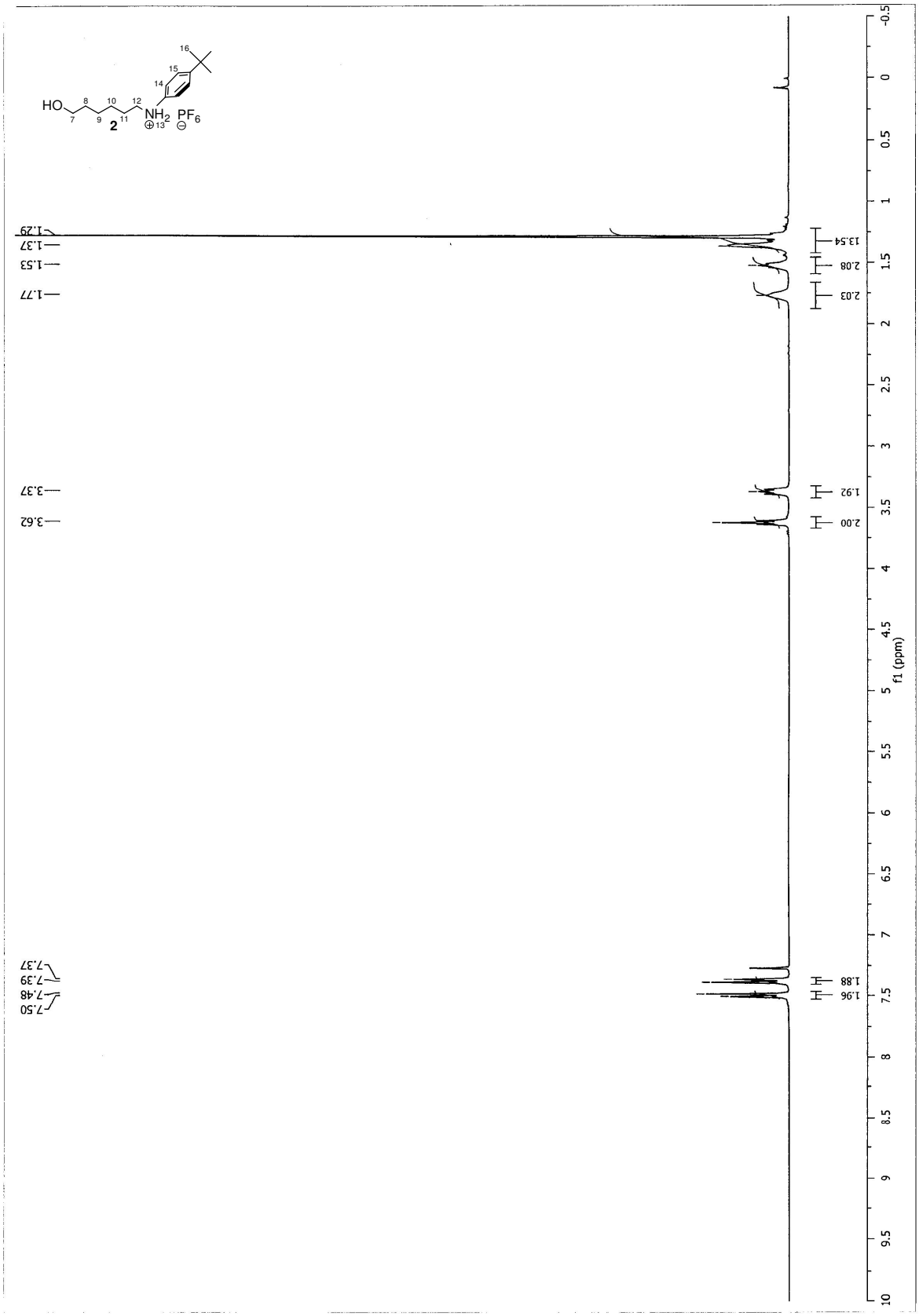
*8.1 NMR spectra of compound **2***

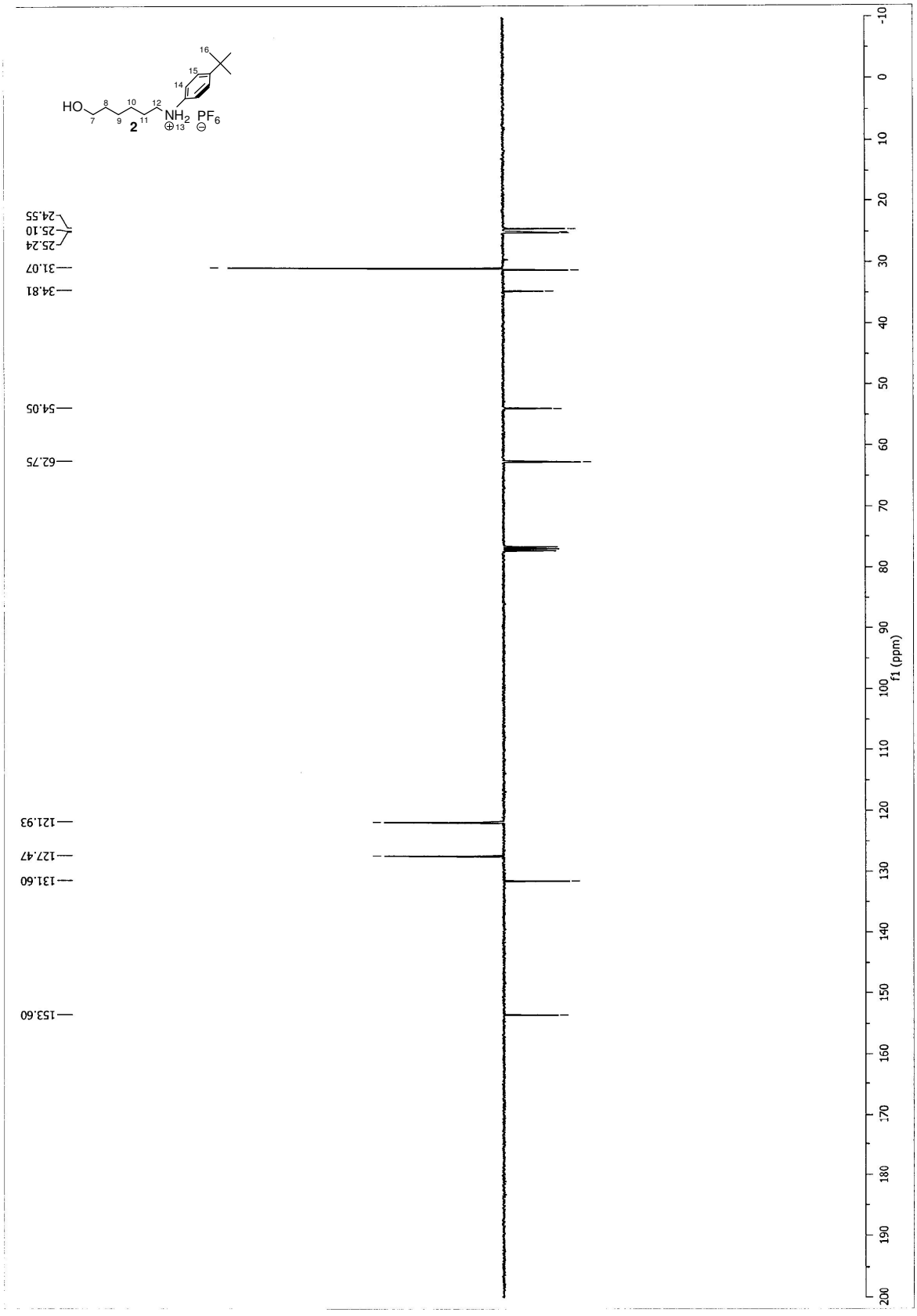
a. NMR spectra of the intermediary deprotonated aminoalcohol (first step)



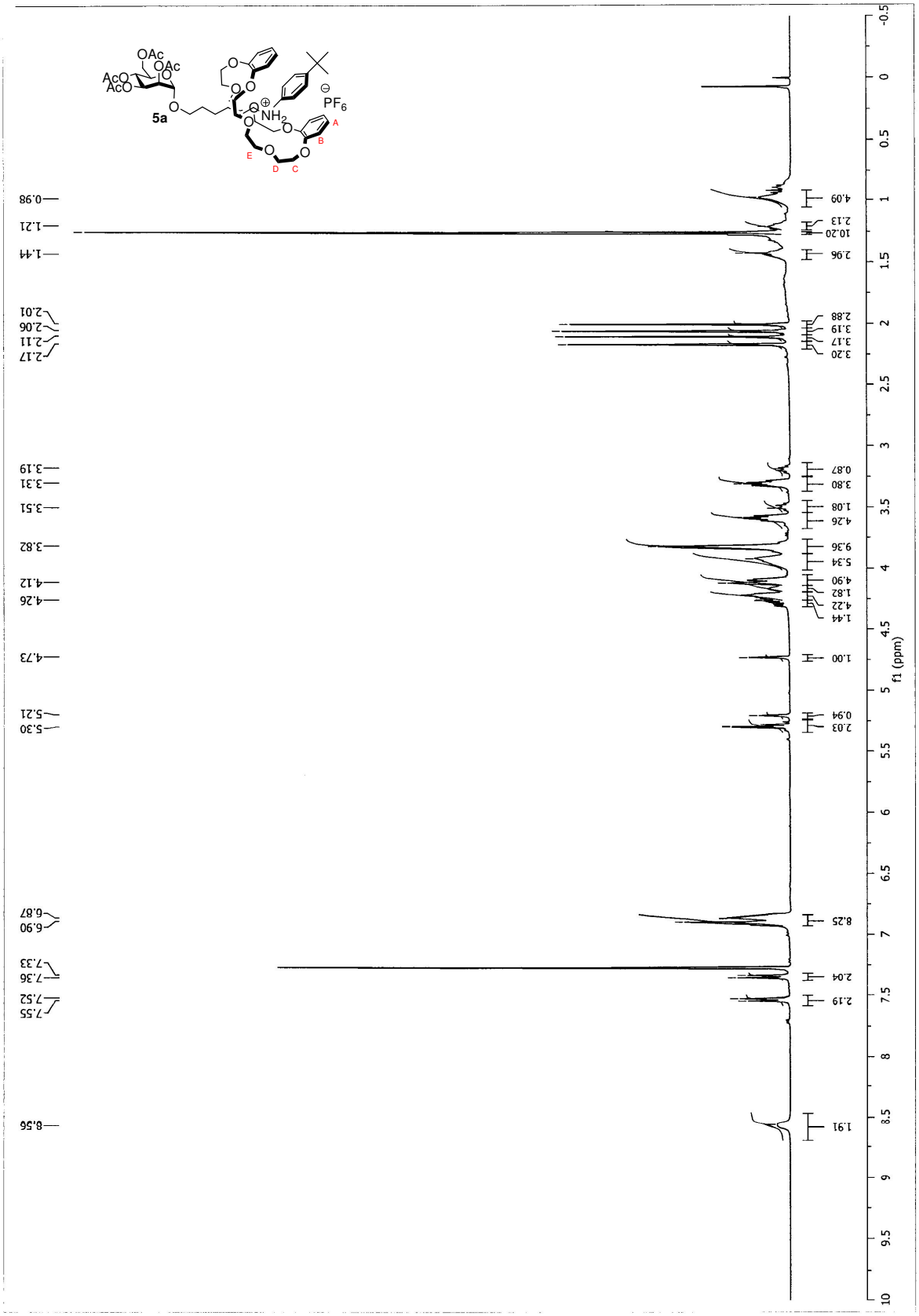

HO
NH
7
8
9
10
11
12
13
14
15
16
25.54
26.92
29.49
29.65
31.51
32.63
44.32
62.82
112.69
125.97
140.23
145.75
f1 (ppm)

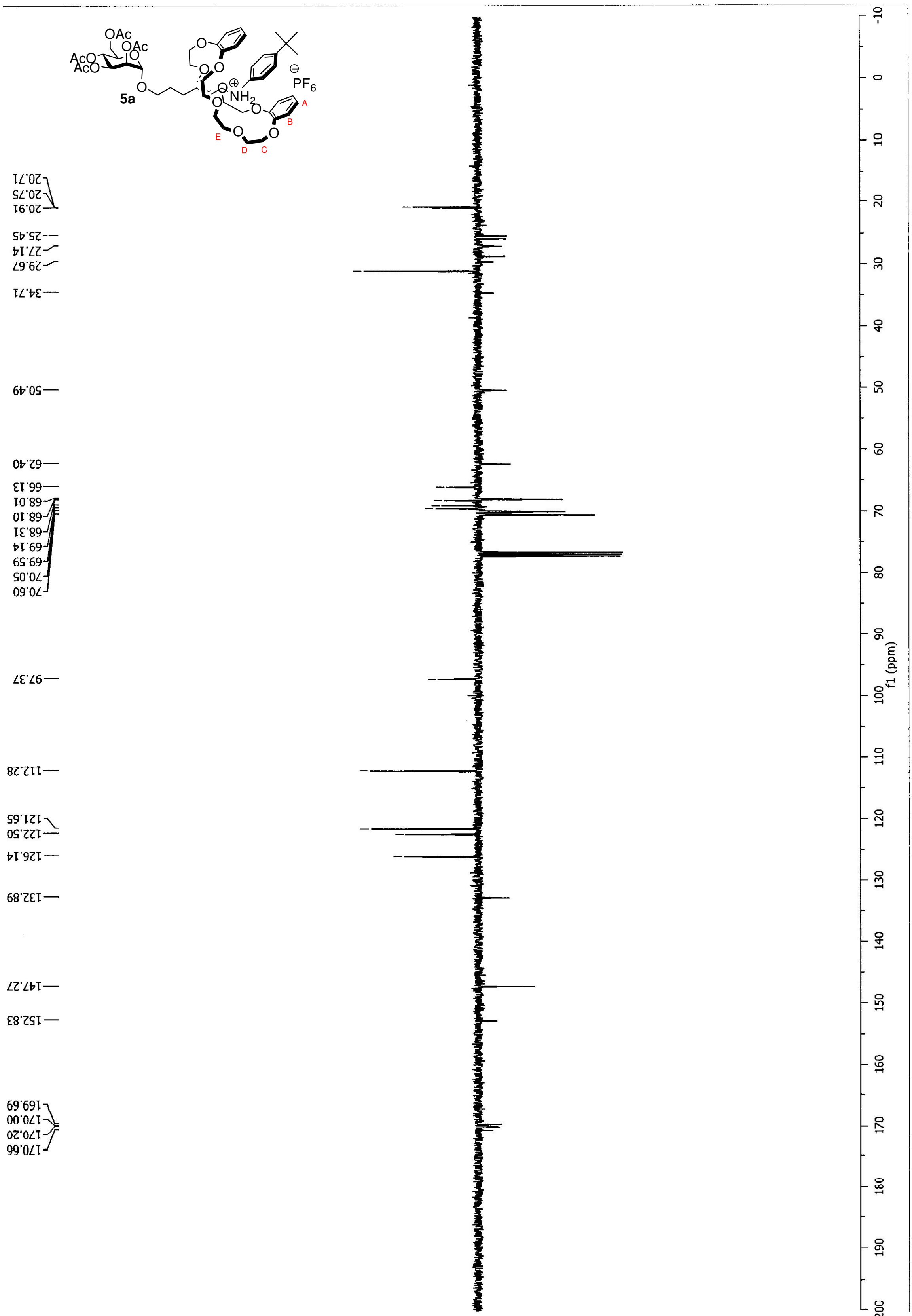
b. NMR spectra of compound 2 (second step)



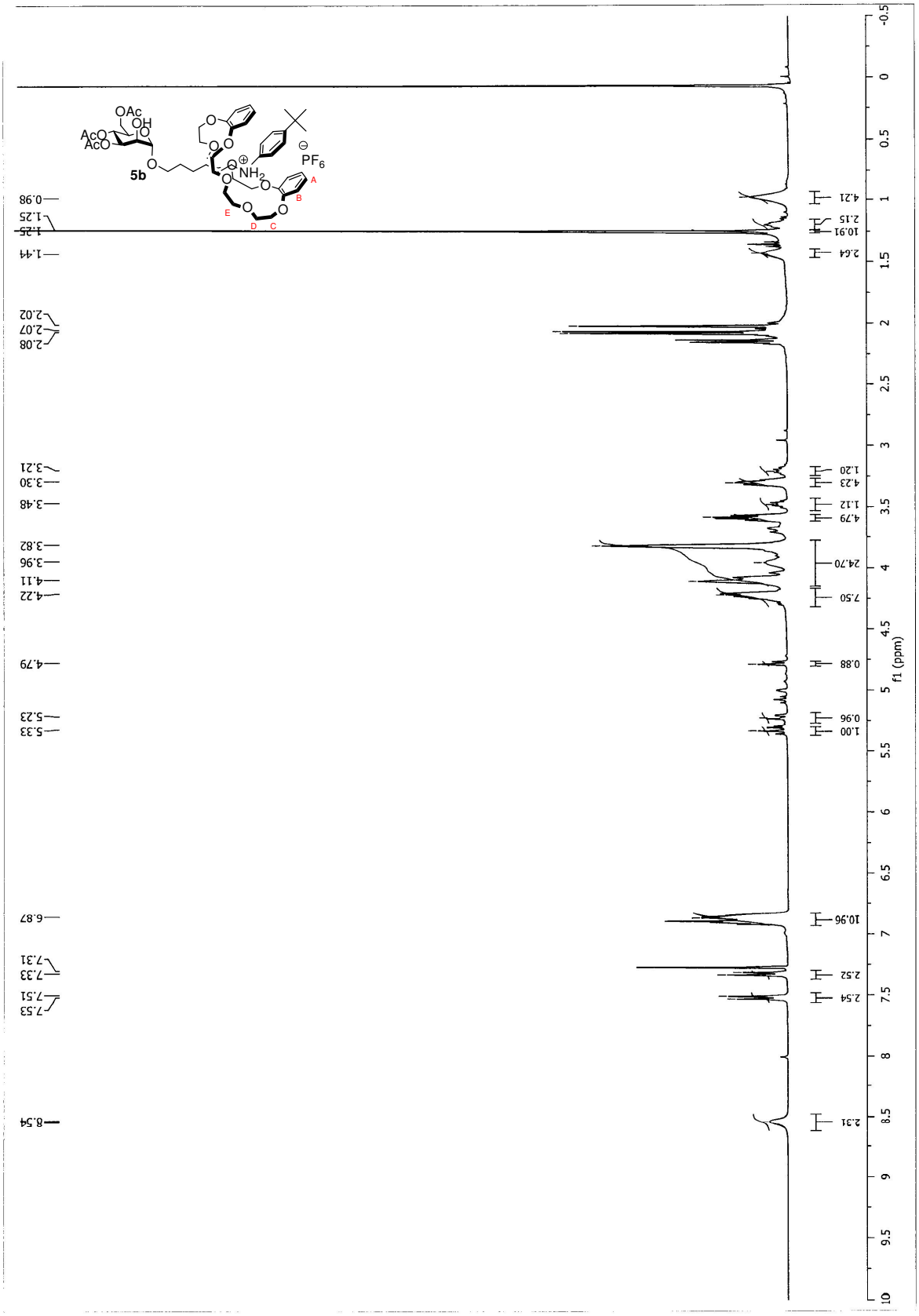

HO
NH2 PF6
2
24.55
25.10
25.24
31.07
34.81
54.05
62.75
121.93
127.47
131.60
153.60
f1 (ppm)

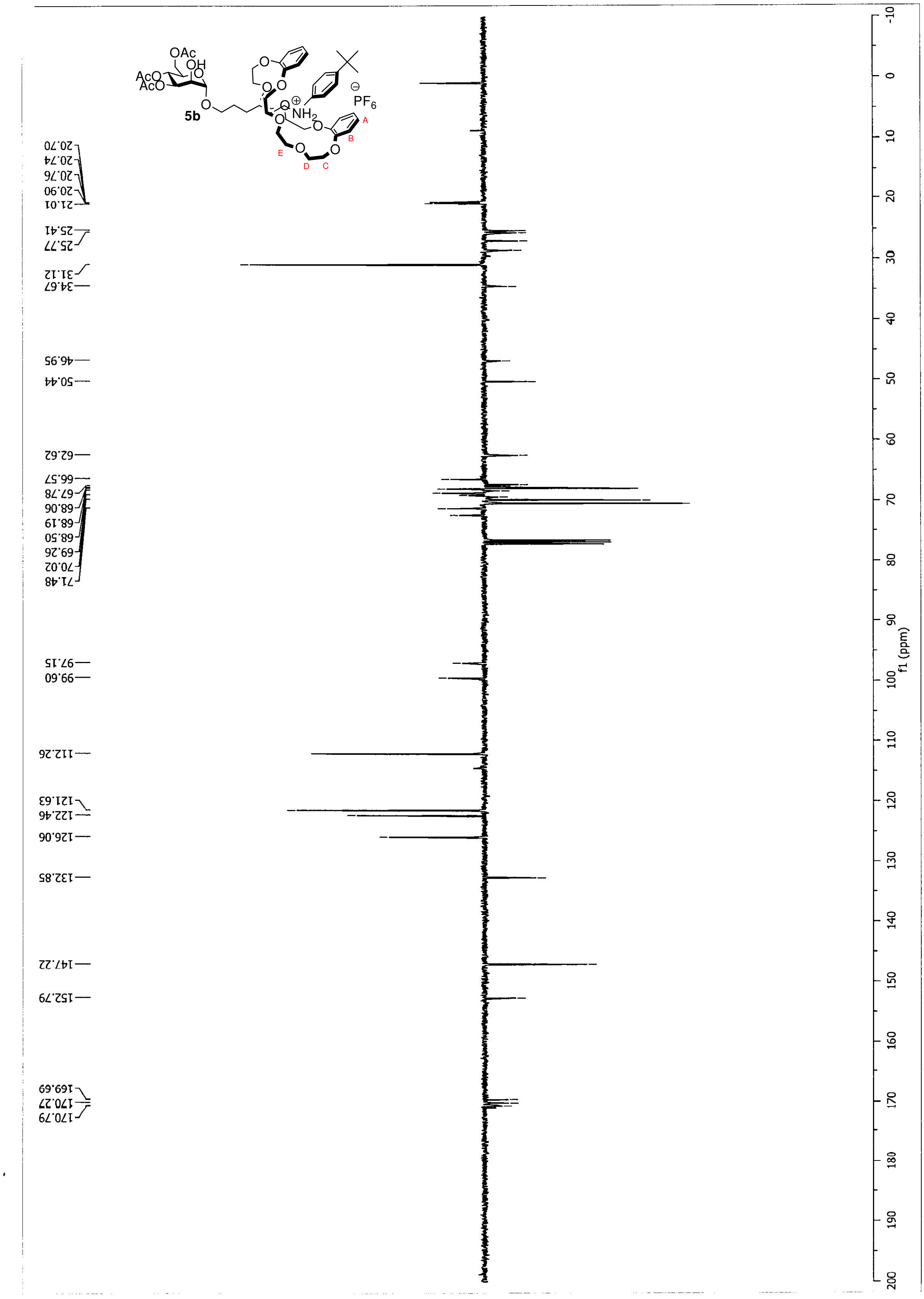
*8.2 NMR spectra of compound **5a***




5a
OAc
AcO
PF6
NH2
A
B
C
D
E
20.71
20.75
20.91
25.45
27.14
29.67
34.71
50.49
62.40
66.13
68.01
68.10
68.31
69.14
69.59
70.05
70.60
97.37
112.28
121.65
122.50
126.14
132.89
147.27
152.83
169.69
170.00
170.20
170.66
f1 (ppm)

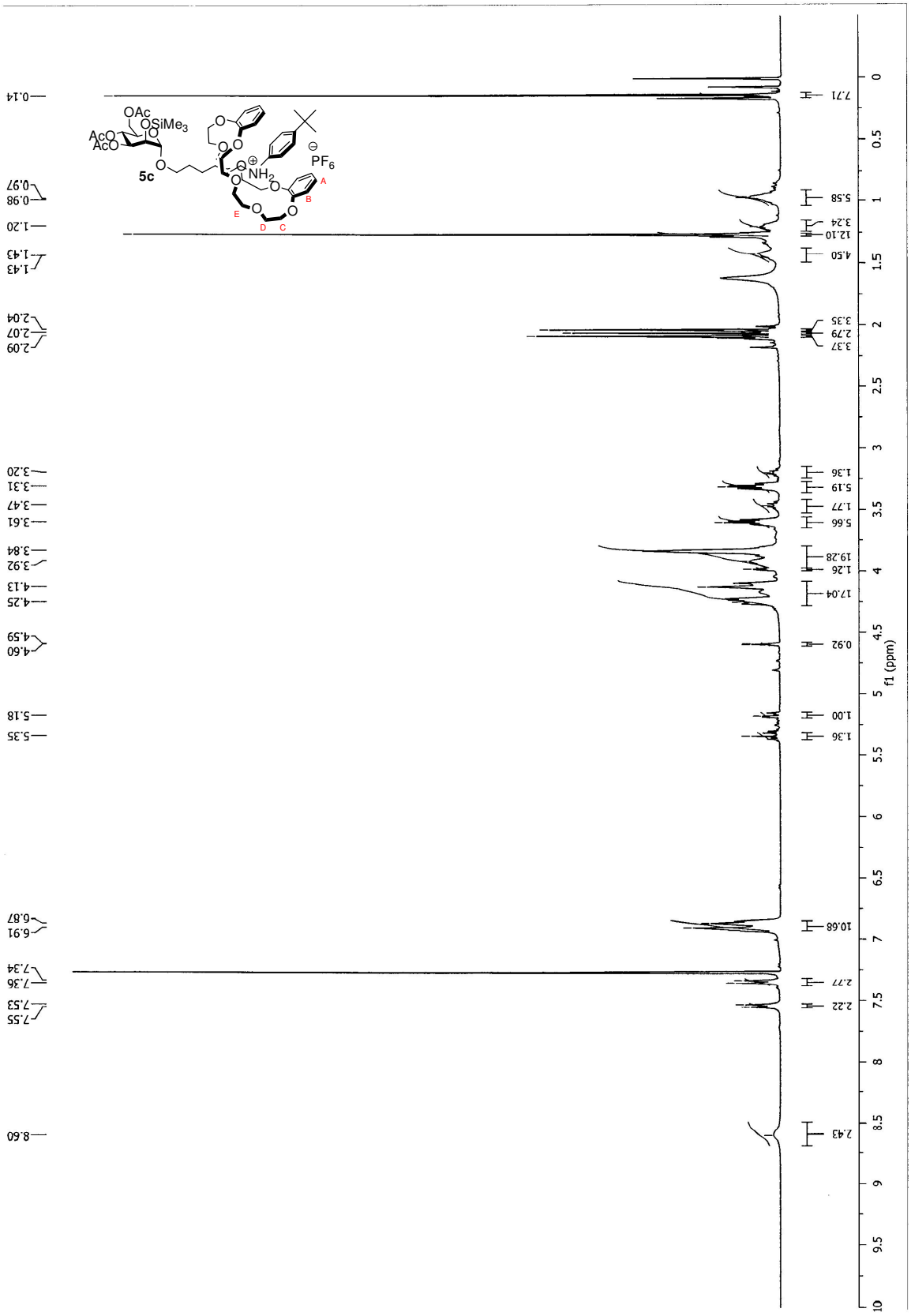
8.3 NMR spectra of compound ***5b***

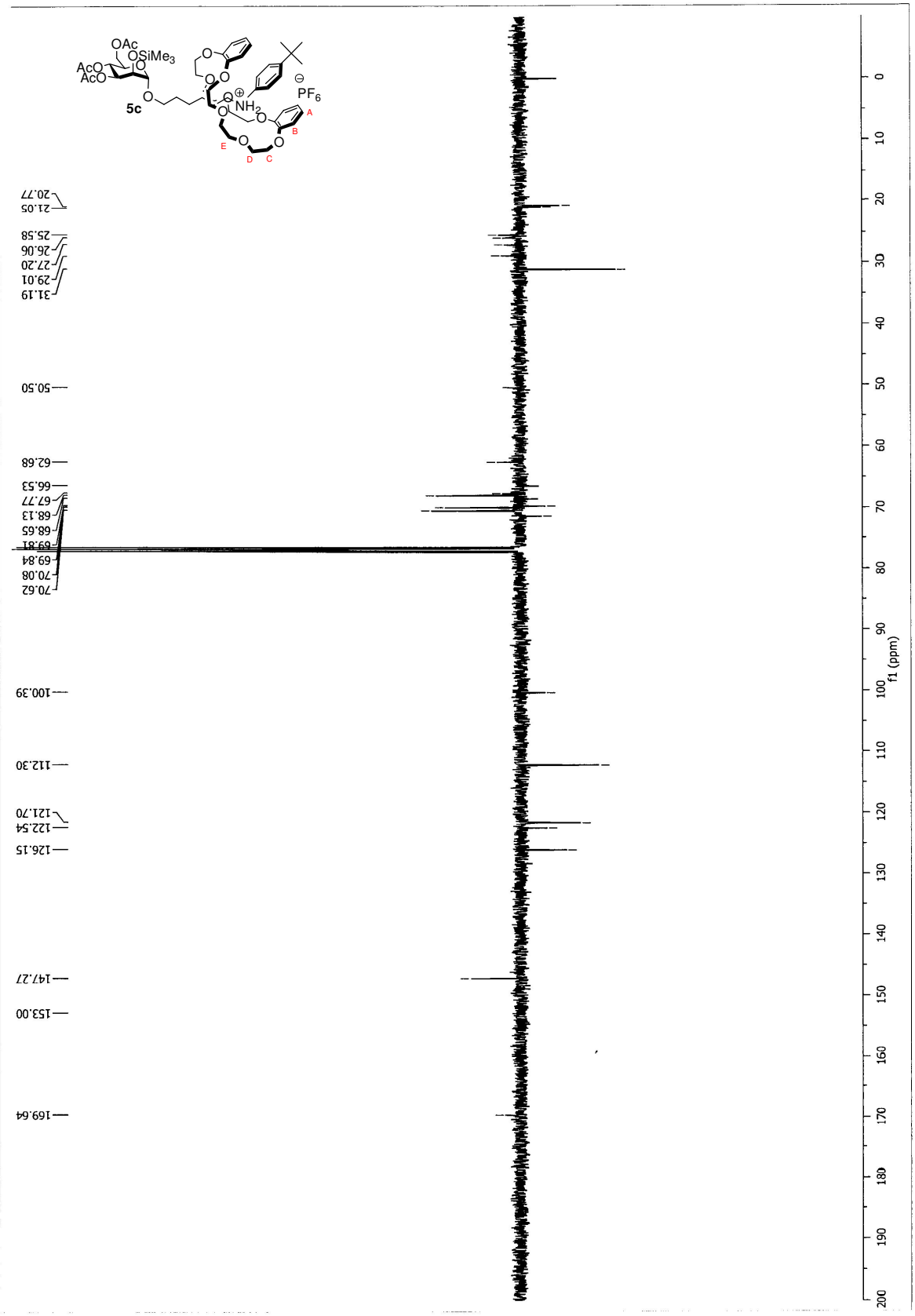




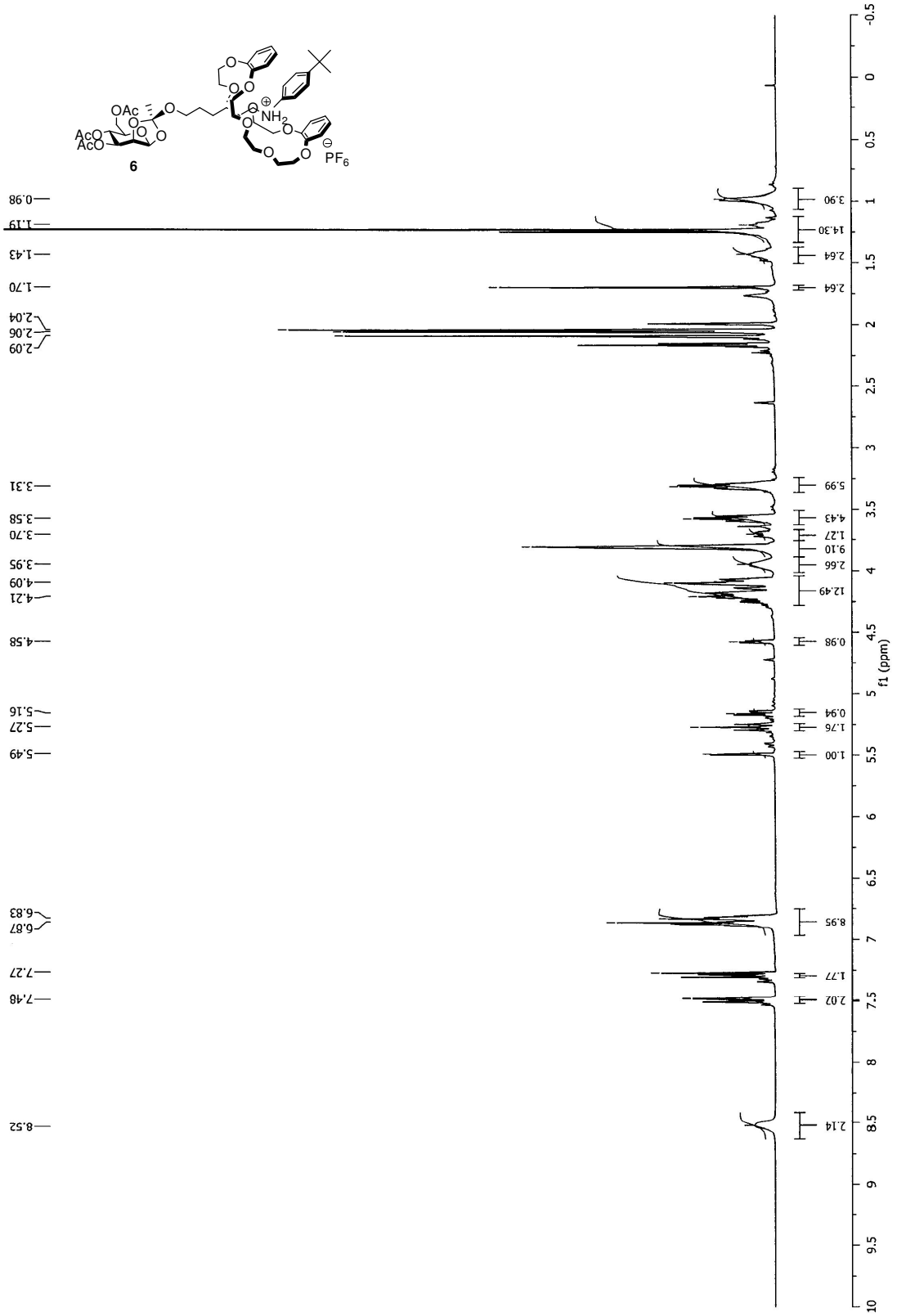
20.70
20.74
20.76
20.90
21.01
25.41
25.77
31.12
34.67
46.95
50.44
62.62
66.57
67.78
68.06
68.19
68.50
69.26
70.02
71.48
97.15
99.60
112.26
121.63
122.46
126.06
132.85
147.22
152.79
169.69
170.27
170.79
f1 (ppm)
5b

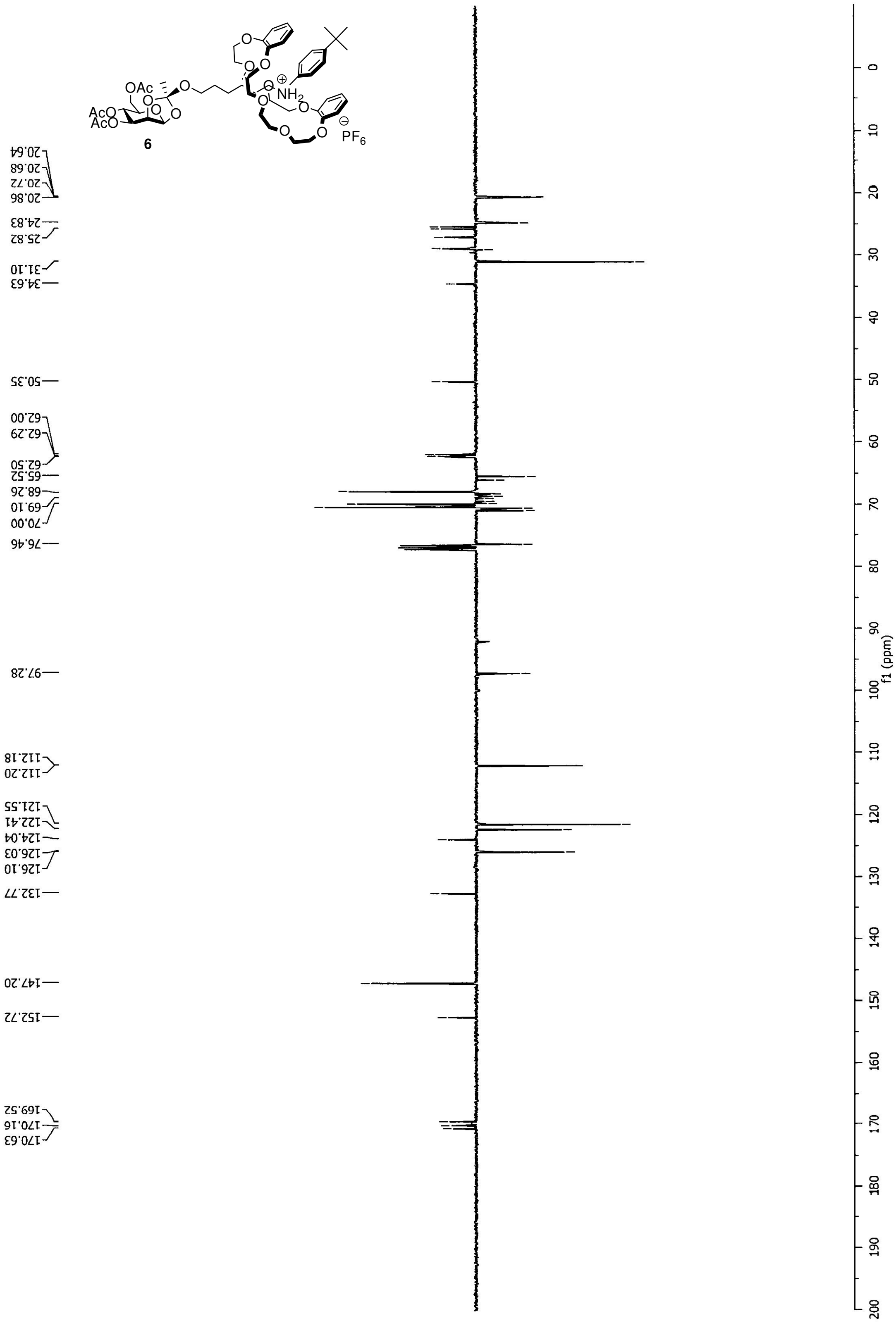
8.4 NMR spectra of compound ***5c***




OAc
OSiMe3
AcO
AcO
O
O
O
O
O
O
O
O
NH2
PF6
A
B
C
D
E
5c
20.77
21.05
25.58
26.06
27.20
29.01
31.19
50.50
62.68
66.53
67.77
68.13
68.65
69.81
69.84
70.08
70.62
100.39
112.30
121.70
122.54
126.15
147.27
153.00
169.64
f1 (ppm)

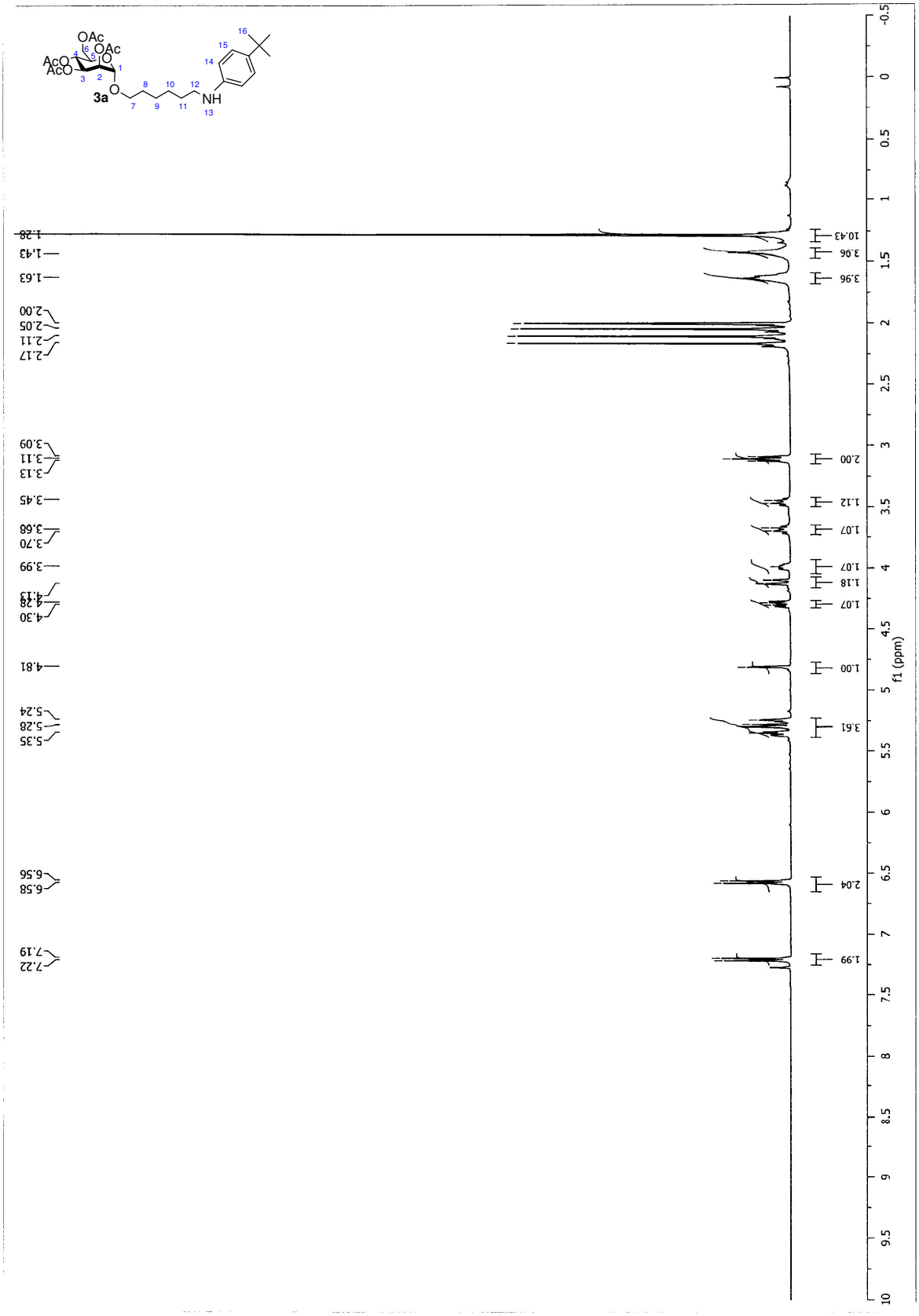
8.5 NMR spectra of compound ***6***

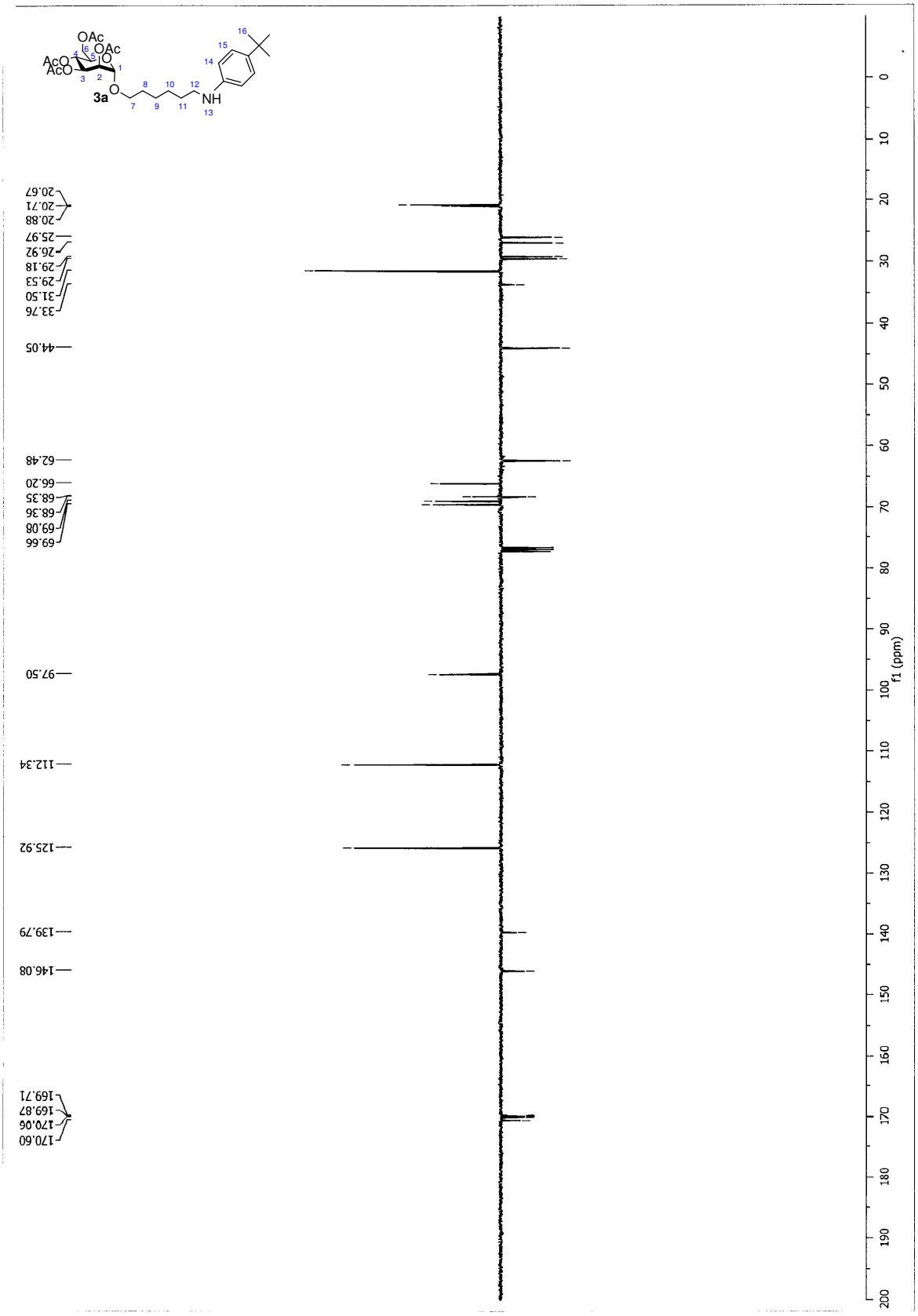




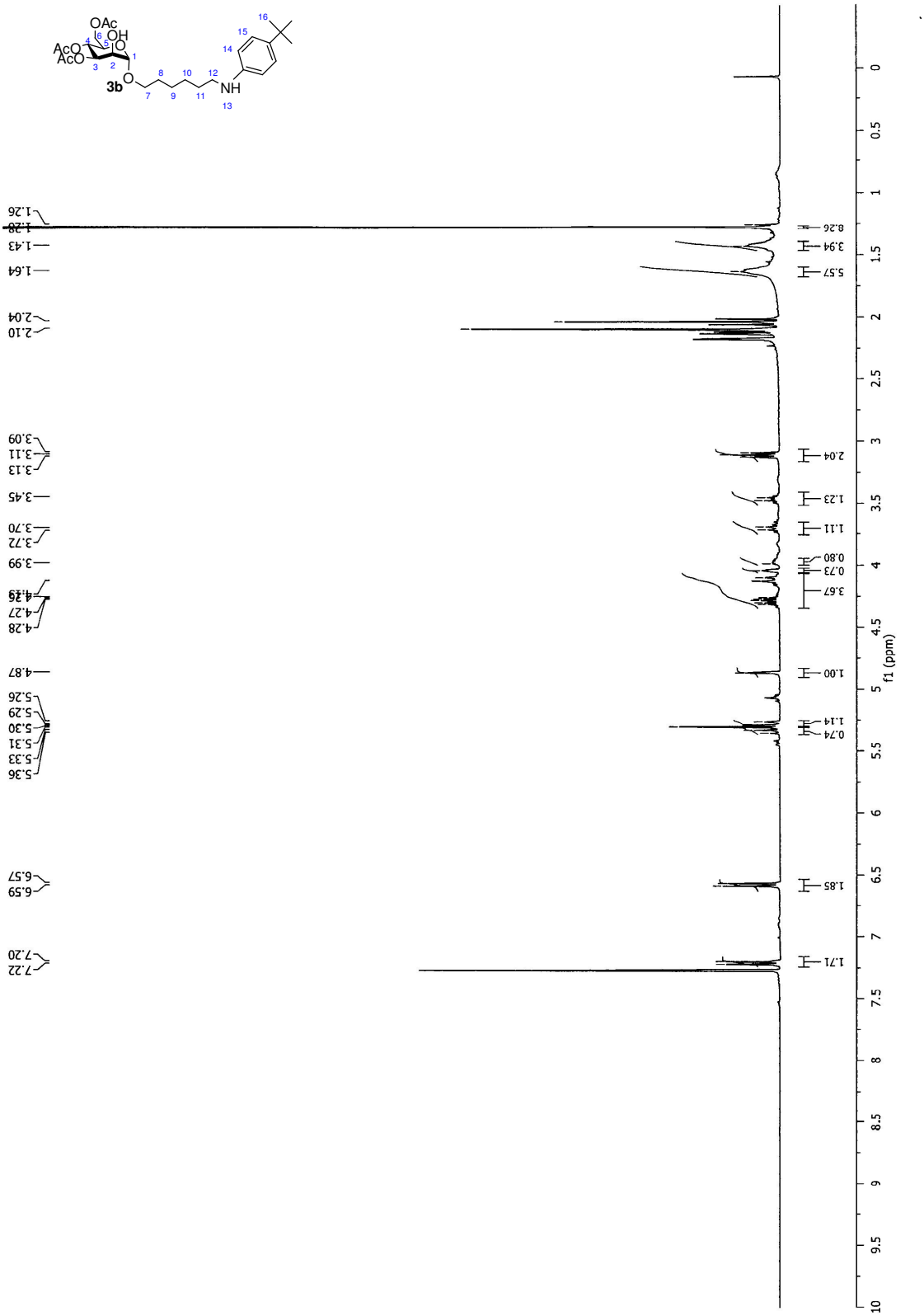
AcO
AcO
OAc
NH2
PF6
6
20.64
20.68
20.72
20.86
24.83
25.82
31.10
34.63
50.35
62.00
62.29
62.50
65.52
68.26
69.10
70.00
76.46
97.28
112.18
112.20
121.55
122.41
124.04
126.03
126.10
132.77
147.20
152.72
169.52
170.16
170.63
f1 (ppm)

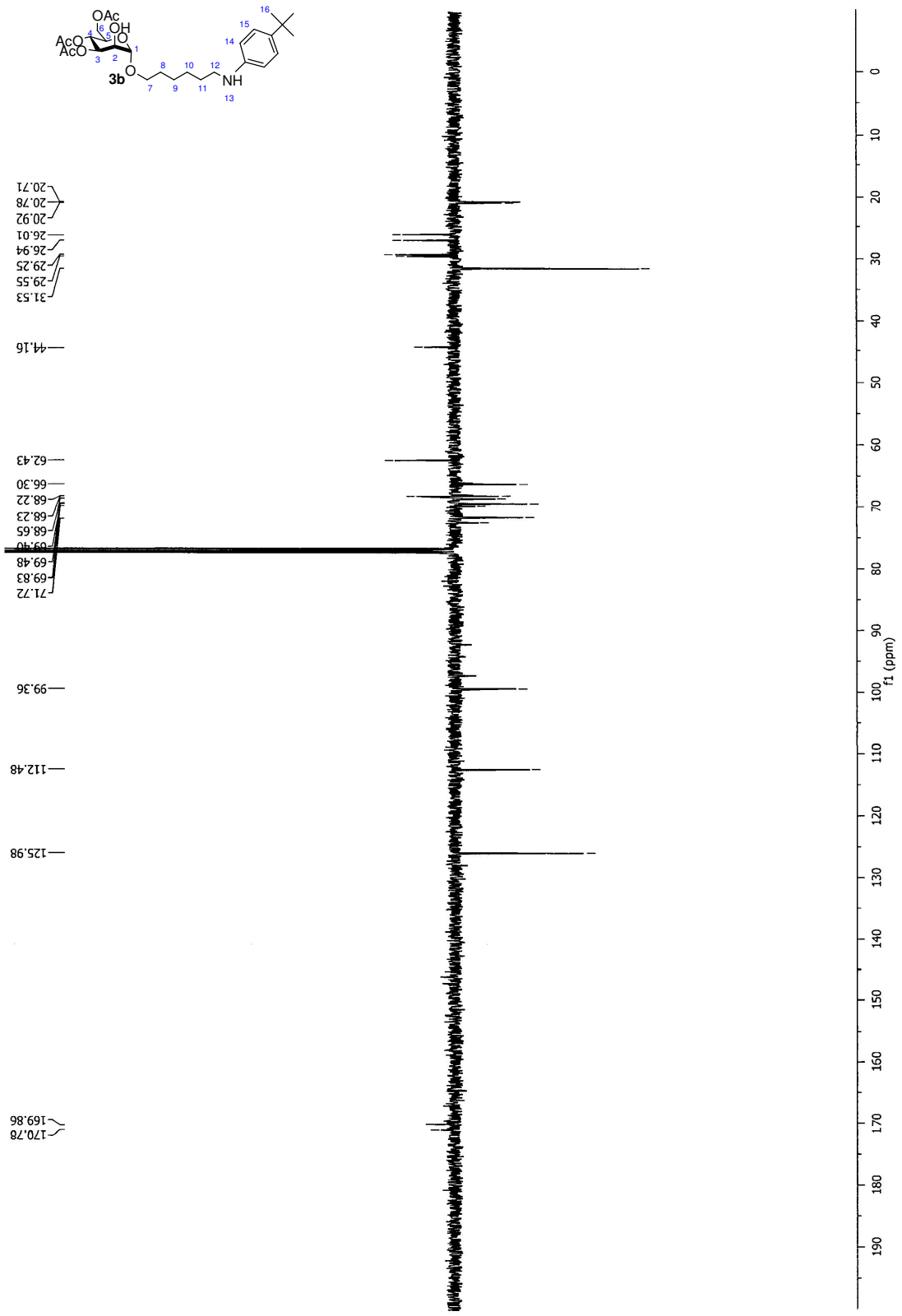
*8.6 NMR spectra of deprotonated compound **3a***



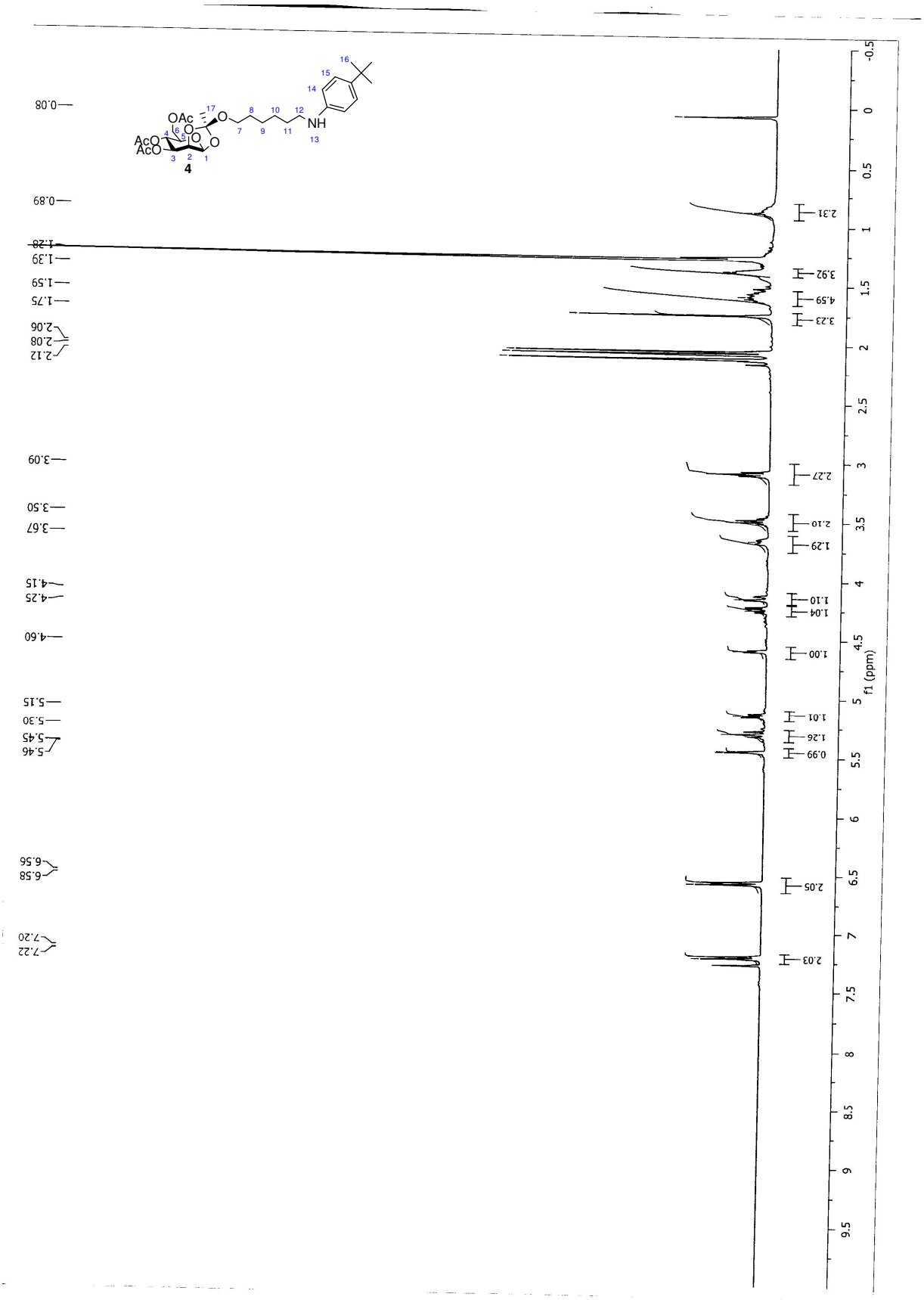

OAc
OAc
AcO
AcO
O
3a
NH
20.67
20.71
20.88
25.97
26.92
29.18
29.53
31.50
33.76
44.05
62.48
66.20
68.35
68.36
69.08
69.66
97.50
112.34
125.92
139.79
146.08
169.71
169.87
170.06
170.60
f1 (ppm)

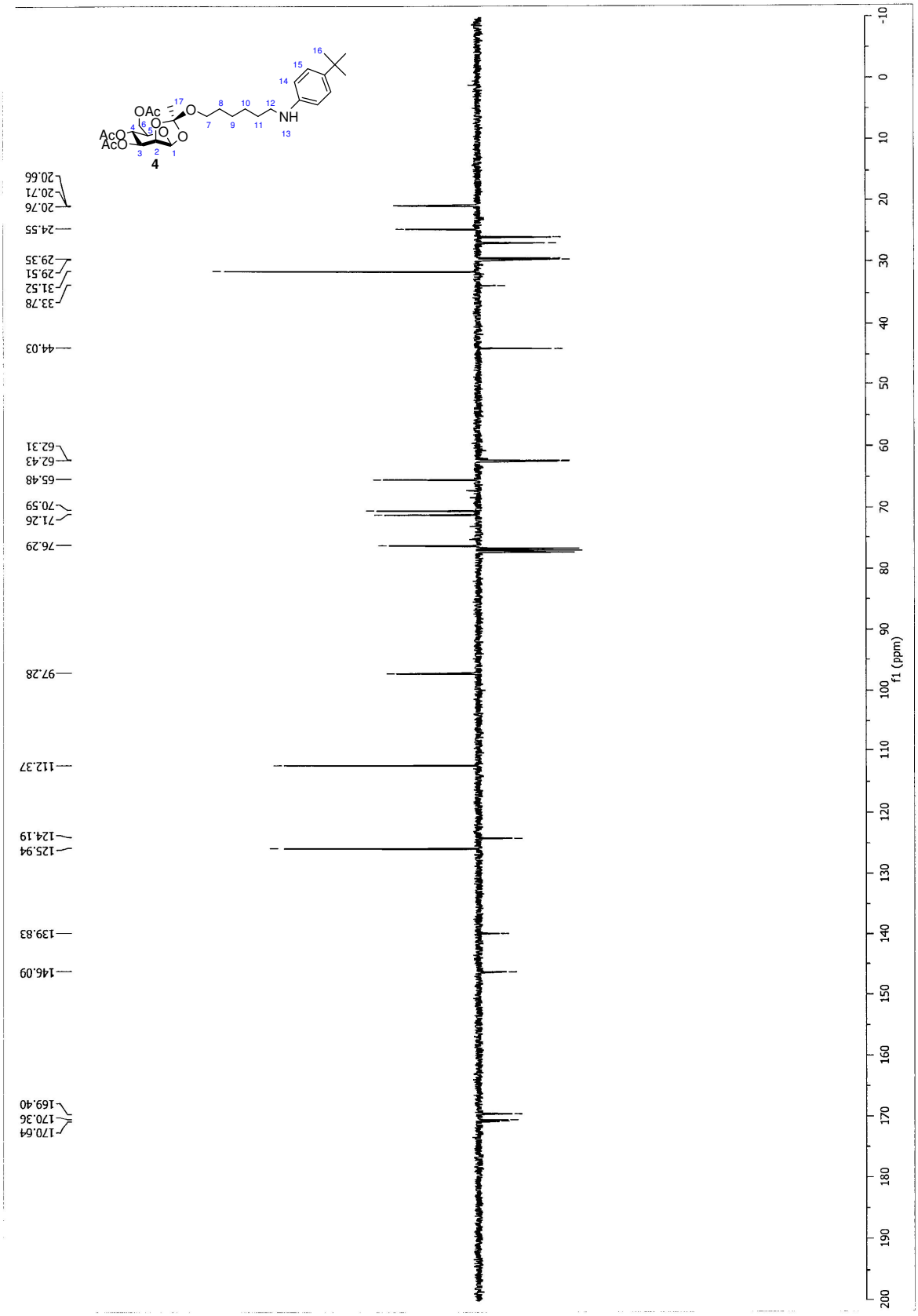
*8.7 NMR spectra of deprotonated compound **3b***




OAc
OH
AcO
AcO
O
1
2
3
4
5
3b
7
8
9
10
11
12
NH
13
14
15
16
20.71
20.78
20.92
26.01
26.94
29.25
29.55
31.53
44.16
62.43
66.30
68.22
68.23
68.65
69.40
69.48
69.83
71.72
99.36
112.48
125.98
169.86
170.78
f1 (ppm)

*8.8 NMR spectra of deprotonated orthoester compound **4***




OAc
AcO
AcO
O
NH
4
20.66
20.71
20.76
24.55
29.35
29.51
31.52
33.78
44.03
62.31
62.43
65.48
70.59
71.26
76.29
97.28
112.37
124.19
125.94
139.83
146.09
169.40
170.36
170.64
f1 (ppm)

9. References

(1) Upreti, M.; Ruhela, D.; Vishwakarma, R. A. *Tetrahedron* **2000**, 56 (35), 6577-6584.

(2) Loeb, S. J.; Tiburcio, J.; Vella, S. J. *Org. Lett.* **2005**, 7 (22), 4923-4926.