

Desymmetrization of 7-Dimethylphenylsilylcycloheptatriene: Towards The Synthesis of new Aminocycloheptitols

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General considerations

¹H NMR and ¹³C NMR were recorded on a Bruker AC-250 FT (¹H: 250 MHz, ¹³C: 62.9 MHz), Bruker Avance-300 FT (¹H: 300 MHz, ¹³C: 75.5 MHz), and Bruker DPX-400 FT (¹H: 400 MHz, ¹³C: 100.6 MHz) using CDCl₃ as internal reference unless otherwise indicated. The chemical shifts (δ) and coupling constants (J) are expressed in ppm and hertz respectively. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, m = multiplet, br = broad. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer or on a thermo-optek 6700 FTIR spectrometer as neat films on NaCl windows or using a diamond ATR accessory (Golden gate). HRMS were recorded on a Micromass ZABSpec TOF, on a Q-ToF Applied Biosystems and on Waters Q-ToF 2 apparatus (for ESI). Melting points were determined by using a Stuart scientific digital 7SMP3 apparatus and are uncorrected. Microanalysis were determined by using a Flash EA1112 microanalysis apparatus. VWR geduran Si 60 (0.040-0.063 mm) silica gel was used for flash chromatography. All reactions were carried out under nitrogen atmosphere unless specified. THF and CH₂Cl₂ were dried on a MB SPS-800. All other solvents were used without further purification. All reagent-grade chemicals were obtained from commercial suppliers and were used as received, unless otherwise stated.

Yields refer to chromatographically and spectroscopically (¹H NMR) homogeneous materials.

DOWEX CO₃²⁻ was prepared by stirring overnight DOWEX Cl⁻ 1-10 in a Na₂CO₃ 2 M aqueous solution (N.B. the stirring was insured by the rotatory-evaporator turning without vacuum; magnetic stirring was avoided in order to not degrade the resin). The resin was then filtered and rinsed to neutrality with

water. Water was removed by washing thoroughly the resin with methanol. The resin was kept in methanol, and was rinsed with methanol before each use.

The sulfonate resin amberlite IRA120 was reactivated by stirring it with a 10% HCl aqueous solution during 4 hours (N.B. the stirring was insured by the rotatory-evaporator turning without vacuum; magnetic stirring was avoided in order to not degrade the resin). The resin was then filtered and rinsed to neutral with water. Water was removed by washing thoroughly the resin with methanol. The resin was kept in methanol, and was rinsed with methanol before each use.

Experimental protocol:

A three step sequence from the tropylium tetrafluoroborate can be carried out without purification. Each step was considered as complete and a yield of 34 % was obtained over three steps.

If it is not the case, the diol **7** is purified and fully characterized as followed:

7-(dimethyl(phenyl)silyl)cyclohepta-3,5-diene-1,2-diol (7):

The crude mixture was first filtrated on silica gel chromatography (70:30 petroleum ether/EtOAc eluent), secondly purified by silica gel column flash chromatography (60:40 petroleum ether/EtOAc) to obtain **7** as a sticky oil (904 mg, 31 %). **Rf** 0.23 (60:40 petroleum ether/EtOAc). **FTIR** (film, NaCl): 3393, 3019, 2956, 1603, 1428, 1252, 832 cm^{-1} . **$^1\text{H NMR}$** (CDCl_3 , 300 MHz): δ (ppm) = 7.55-7.46 (m, 2H, CH_{ar}), 7.43-7.32 (m, 3H, CH_{ar}), 5.87-5.76 (m, 2H, $\text{CH}_{\text{olefinic}}$), 5.71-5.60 (m, 1H, $\text{CH}_{\text{olefinic}}$), 5.52-5.41 (m, 1H, $\text{CH}_{\text{olefinic}}$), 4.29 (broad s, 1H, CH-O), 4.01 (broad s, 1H, CH-O), 2.81 (broad s, 0.6H, OH), 2.68 (t, $J = 5.7$ Hz, 1H, CH-Si), 2.25 (broad s, 0.8H, OH), 0.35 (s, 6H, CH_3 -Si). **$^{13}\text{C NMR}$** (CDCl_3 , 75.5 MHz): δ (ppm) = 135.8 (Cq, ar), 134.0 (CH, ar), 132.1 (CH, olefinic), 130.8 (CH, olefinic), 129.7 (CH, ar), 128.2 (CH, ar), 123.6 (CH, olefinic), 122.7 (CH, olefinic), 72.9 (CH, CH-O), 70.9 (CH, CH-O), 40.0 (CH, CH-Si), -3.9 (CH_3 , CH_3 -Si), -4.8 (CH_3 , CH_3 -Si). **HRMS** (ESI): calc. for $\text{C}_{15}\text{H}_{20}\text{O}_2\text{SiNa}$ $[\text{M}+\text{Na}]^+$: 283.1130, found : 283.1127.

7-(dimethyl(phenyl)silyl)cyclohepta-3,5-diene-1,2-diyl diacetate (9) 3-steps sequence synthesis:

Hammered lithium wire (1 g, 146 mmol, 13 eq) was added to THF (50 mL). The mixture was cooled to 0 °C and chlorodimethyl(phenyl)silane (5 mL, 30 mmol, 2.7 eq) was added. The mixture turned dark red within 30 minutes. The reaction was allowed to warm to room temperature overnight and the resulting lithiated specie was titrated using phenolphthaleine as color indicator and a 0.120 M solution of HCl. The concentration was found to be 0.52 M (27 mmol, 2.4 eq)). In parallel, ZnCl_2 (1.8 g, 13.49

mmol, 1.2 eq) was gun-heated under vacuum until complete melting. After complete cooling the flask was placed under argon and THF (37.5 mL) was added, sonication helped the dissolution of ZnCl₂. The mixture was cooled to 0 °C and the lithiated species was transferred *via* a cannula, the reaction mixture turned immediately green. The mixture was stirred during half an hour and a suspension of tropylium tetrafluoroborate (**I**) (ALFA AESAR 2 g, 11.2 mmol, 1 eq) in THF (37.5 mL) was prepared. It was stirred during half an hour more and then the zinc reagent was poured into it *via* a cannula. The resulting solution was dark green and was left stirring until the coloration turned bright yellow (from 4 to 14 days).

The reaction was quenched using saturated aqueous NH₄Cl solution and extracted with EtOAc (3x50 mL). Combined organic layers were washed with brine and dried over MgSO₄. The solvent was evaporated under reduced pressure to provide an orange oily product which could be purified by chromatography on silica gel (petroleum ether). See ref 14 for description.

“AD-mix like” mixture was prepared by dry mixing K₂CO₃ (2.9 g, 22.5 mmol, 2 eq), K₂OsO₄·2H₂O (ALDRICH, 166 mg, 0.45 mmol, 0.04 eq), K₃Fe(CN)₆ (7.4 g, 22.5 mmol, 3 eq), quinuclidine (50 mg, 0.45 mmol, 0.04 eq) in a round bottomed flask for 10 minutes. A mixture of *t*-BuOH/H₂O (1:1, 56 mL/56 mL) and methanesulfonamide (1 g, 11.2 mmol, 1 eq) were added. After 10 minutes the resulting orange mixture was added in one portion onto the cycloheptatriene **6** (11.2 mmol, 1 eq). The reaction mixture quickly thickened and turned brown. After 3h, no starting material remained and the reaction was quenched with solid sodium sulfite (Na₂SO₃). Extraction was carried out with EtOAc (3x50 mL). The combined organic layers were washed with brine and dried over Na₂SO₄. The solvent was evaporated under reduced pressure (*t*BuOH was co-evaporated with hexane) to provide a brown pasty residue mixture of **7** and **8**.

The crude product (11.2 mmol, 1 eq) was dissolved CH₂Cl₂ (112 mL). Pyridine (7.3 mL, 90 mmol, 8 eq), acetic anhydride (6.5 mL, 90 mmol, 8 eq) and DMAP (catalytic amount) were then added. No starting material remained in the orange solution after 9 hours (TLC control), and quench was performed using saturated aqueous NH₄Cl solution. Extraction was carried out using CH₂Cl₂ (3x50 mL), the combined organic layers were washed with brine and dried over MgSO₄. The solvent was evaporated under reduced pressure (pyridine and acetic anhydride were co-evaporated with toluene) to provide a yellow oil. The residue was then purified by column chromatography on silica gel (90:10, Petroleum ether/EtOAc) to provide the acetylated product **9** (1.3 g, 34 %) as a yellow oil.

Rf 0.61 (80:20 Petroleum ether/EtOAc). **FTIR** (film, NaCl): 3070, 3022, 2960, 1737, 1607, 1428, 1372, 1248, 1028 cm⁻¹. **¹H NMR** (CDCl₃, 300 MHz): δ(ppm) = 7.59-7.51 (m, 2H, CH_{ar}), 7.39-7.30 (m, 3H, CH_{ar}), 5.92-5.82 (m, 1H, CH_{olefinic}), 5.81-5.72 (m, 1H, CH_{olefinic}), 5.65-5.52 (m, 2H, 1CH_{olefinic} + 1CH-O), 5.45-5.40 (m, 1H, CH-O), 5.36-5.28 (m, 1H, CH_{olefinic}), 2.68 (t, J = 5.3 Hz, 1H, CH-Si), 2.03

(s, 3H, CH₃ of acetate), 1.98 (s, 3H, CH₃ of acetate), 0.45 (s, 6H, CH₃-Si). ¹³C NMR (CDCl₃, 75.5 MHz): δ (ppm) = 170.8 (C_q, C=O of acetate), 170.2 (C_q, C=O of acetate), 135.9 (C_q, ar), 134.2 (CH, ar), 131.0 (CH, olefinic), 129.6 (CH, ar), 128.0 (CH, ar), 126.4 (CH, olefinic), 125.4 (CH, olefinic), 122.2 (CH, olefinic), 72.9 (CH, CH-O), 70.3 (CH, CH-O), 37.3 (CH, CH-Si), 21.3 (CH₃, acetate), 21.1 (CH₃, acetate), -4.2 (CH₃, CH₃-Si), -4.4 (CH₃, CH₃-Si). HRMS (ESI): calc. for C₁₉H₂₄O₄SiNa [M+Na]⁺: 367.1342, found: 367.1339.

General procedure for cycloaddition

NaIO₄ (4.2 g, 31.3 mmol, 10 eq) was added to a solution of the diacetate **9** (1 g, 3.13 mmol, 1 eq) in a mixture of methanol/water (100 mL/39 mL). A solution of hydroxamic acid (6.7 g, 31.3 mmol, 10 eq) in methanol (17 mL) was then added slowly over 6 hours using a syringe pump leading to a very thick orange mixture. The medium was stirred overnight and then the reaction was buffered using a saturated aqueous solution of NaHCO₃ (40 mL) and quenched using a saturated aqueous Na₂SO₃ solution (40 mL). Extraction was carried out using EtOAc (3x40 mL). The combined organic layers were washed with brine and dried over Na₂SO₄. Evaporation of the organic solvents led to a biphasic mixture, insoluble salts were removed by a quick filtration over silica gel pad using EtOAc as eluent. After evaporation, ¹H NMR spectra of the resulting residue was performed in C₂D₆CO to split the signals and allowed the ratio measurement by integration of the relevant signals. The crude products were then purified by column chromatography on silica gel (85:15 Petroleum ether/EtOAc) and 3 compounds (**10/11/12**) were isolated.

7-(tert-butoxycarbonyl)-4-(dimethyl(phenyl)silyl)-6-oxa-7-azabicyclo[3.2.2]non-8-ene-2,3-diyl diacetate (**10**): Major cycloadduct

The product was obtained as a yellow powder (431 mg, 29 %). R_f 0.29 (80:20 Petroleum ether/EtOAc) mp: 92-93°C. FTIR (film, NaCl): 3068, 2977, 1744, 1427, 1368, 1248, 1029 cm⁻¹. ¹H NMR (CDCl₃, 250 MHz): δ (ppm) = 7.66-7.53 (m, 2H, CH_{ar}), 7.42-7.30 (m, 3H, CH_{ar}), 6.44-6.23 (m, 2H, CH_{olefinic}), 5.52 (t, J = 4.2 Hz, 1H, CH-O), 5.25 (t_{appearing}, J₁ = 3.8 Hz, J₂ = 3.6 Hz, 1H, CH-O), 4.84-4.73 (m, 1H, CH-N), 4.70-4.59 (m, 1H, CH-O), 2.02 (s, 3H, CH₃ of acetate), 1.86 (s, 3H, CH₃ of acetate), 1.72-1.61 (m, 1H, CH-Si), 1.48 (s, 9H, CH₃ of Boc), 0.50 (s, 3H, CH₃-Si), 0.47 (s, 3H, CH₃-Si). ¹³C NMR (CDCl₃, 75.5 MHz): δ (ppm) = 169.9 (C_q, C=O of acetate), 169.3 (C_q, C=O of acetate), 155.5 (C_q, C=O of Boc), 136.5 (C_q, ar), 134.2 (CH, ar), 132.2 (CH, olefinic), 129.5 (CH, ar), 128.0 (CH, ar or olefinic), 127.9 (CH, ar or olefinic), 82.2 (C_q, Boc), 73.6 (CH, CH-O), 72.7 (CH, CH-O), 69.4 (CH, CH-O), 55.4 (CH, CH-N), 36.5 (CH, CH-Si), 28.3 (CH₃, Boc), 21.0 (CH₃, acetate), 20.8 (CH₃, acetate), -3.2 (CH₃, CH₃-Si), -3.6 (CH₃, CH₃-Si). HRMS (ESI): calc. for C₂₄H₃₃NO₇SiNa [M+Na]⁺ = 498.1924, found: 498.1923.

7-(tert-butoxycarbonyl)-2-(dimethyl(phenyl)silyl)-6-oxa-7-azabicyclo[3.2.2]non-8-ene-3,4-diyl diacetate (11): Second major cycloadduct

The product was obtained as a white solid (312 mg, 21 %). **Rf** 0.22 (80:20 Petroleum ether/EtOAc) **Anal. calcd.** for C₂₄H₃₃NO₇Si, C, 60.61; H, 6.99; N, 2.94 found C, 60.35; H, 6.92; N, 2.88. **mp:** 118-119°C. **FTIR** (film, NaCl): 2978, 1742, 1428, 1368, 1248, 1051 cm⁻¹. **¹H NMR** (CDCl₃, 300 MHz): δ (ppm) = 7.64-7.48 (m, 2H, CH_{ar}), 7.41-7.30 (m, 3H, CH_{ar}), 6.52 (t, J = 7.9 Hz, 1H, CH_{olefinic}), 6.16 (t_{appearing}, J₁ = 8.7 Hz, J₂ = 7.0 Hz, 1H, CH_{olefinic}), 5.58 (t_{appearing}, J₁ = 4.7, J₂ = 4.5 Hz, 1H, CH-O), 5.20 (t_{appearing}, J₁ = 4.3 Hz, J₂ = 4.1 Hz, 1H, CH-O), 4.83-4.67 (m, 2H, CH-O and CH-N), 2.00 (s, 3H, CH₃ of acetate), 1.82 (s, 3H, CH₃ of acetate), 1.76 (t_{appearing}, J = 4.5 Hz, 1H, CH-Si), 1.38 (s, 9H, CH₃ of Boc), 0.49 (s, 3H, CH₃-Si), 0.44 (s, 3H, CH₃-Si). **¹³C NMR** (CDCl₃, 75.5 MHz): δ (ppm) = 169.8 (Cq, C=O of acetate), 169.6 (Cq, C=O of acetate), 157.2 (Cq, C=O of Boc), 136.9 (Cq, ar), 135.0 (CH, ar), 134.1 (CH, olefinic), 129.4 (CH, ar), 128.0 (CH, olefinic), 125.7 (CH, ar), 82.2 (Cq, Boc), 72.9 (CH, CH-O), 72.8 (CH, CH-O), 69.3 (CH, CH-O), 54.2 (CH, CH-N), 32.1 (CH, CH-Si), 28.2 (CH₃, Boc), 21.0 (CH₃, acetate), 20.8 (CH₃, acetate), -3.2 (CH₃, CH₃-Si), -3.6 (CH₃, CH₃-Si). **HRMS** (ESI): calc. for C₂₄H₃₃NO₇SiNa [M+Na]⁺ = 498.1924, found: 498.1927.

7-(tert-butoxycarbonyl)-2-(dimethyl(phenyl)silyl)-6-oxa-7-azabicyclo[3.2.2]non-8-ene-3,4-diyl diacetate (12): Minor cycloadduct

The product was obtained as a white powder (119 mg, 8 %). **Rf** 0.16 (80:20 Petroleum ether/EtOAc) **mp:** 99-102°C. **FTIR** (film, NaCl): 2977, 1744, 1427, 1368, 1246, 1056 cm⁻¹. **¹H NMR** (CDCl₃, 250 MHz): δ (ppm) = 7.58-7.41 (m, 2H, CH_{ar}), 7.41-7.29 (m, 3H, CH_{ar}), 6.24 (t_{appearing}, J₁ = 8.7 Hz, J₂ = 6.5 Hz, 1H, CH_{olefinic}), 6.01 (t_{appearing}, J₁ = 7.5 Hz, J₂ = 8.5 Hz, 1H, CH_{olefinic}), 5.22 (t_{appearing}, J₁ = 4.8 Hz, J₂ = 5.0 Hz, 1H, CH-O), 5.04 (dd, J₁ = 4.3 Hz, J₂ = 11.9 Hz, 1H, CH-O), 4.90-4.74 (m, 2H, CH-O and CH-N), 2.13 (s, 3H, CH₃ of acetate), 1.71 (s, 3H, CH₃ of acetate), 1.41 (s, 9H, CH₃ of Boc), 1.26-1.10 (m, 1H, CH-Si), 0.38 (s, 3H, CH₃-Si), 0.34 (s, 3H, CH₃-Si). **¹³C NMR** (CDCl₃, 100.6 MHz): δ (ppm) = 170.9 (Cq, C=O of acetate), 169.9 (Cq, C=O of acetate), 155.0 (Cq, C=O of Boc), 136.5 (Cq, ar), 133.8 (CH, ar), 131.1 (CH, olefinic), 129.7 (CH, ar), 128.2 (CH, ar), 127.6 (CH, olefinic), 81.8 (Cq, Boc), 71.6 (CH, CH-O), 70.4 (CH, CH-O), 70.0 (CH, CH-O), 53.6 (CH, CH-N), 29.1 (CH, CH-Si), 28.4 (CH₃, CH₃ of Boc), 21.0 (CH₃, acetate), 20.8 (CH₃, acetate), -3.2 (CH₃, CH₃-Si), -3.5 (CH₃, CH₃-Si). **HRMS** (ESI): calc. for C₂₄H₃₃NO₇SiNa [M+Na]⁺ = 498.1924, found: 498.1928.

7-(tert-butoxycarbonyl)-6-oxa-7-azabicyclo[3.2.2]nonane-2,3,4-triyl triacetate (17) 3 steps-sequence synthesis:

To a solution of the olefinic compound **10** (1281 mg, 2.69 mmol, 1 eq) in a 2:1 mixture of

EtOAc/MeOH (0.12 M, 15 mL+7.5 mL), 10 % Pd/C (287 mg of the mixture, 0.27 mmol of palladium, 0.1 eq) was added. Vacuum followed by nitrogen refill was performed 3 times. Then vacuum followed by dihydrogen was performed twice and the mixture was stirred overnight under dihydrogen atmosphere. Palladium was removed by filtration on celite pad, using ethyl acetate as eluent. **13** was obtained as a white sticky foam.

KBr (640 mg, 5.38 mmol, 2 eq) and NaOAc (927 mg, 11.3 mmol, 4.2 eq) at 0 °C, acetic acid (6.1 mL, 0.44M) was added to **13** (2.69 mmol, 1 eq). The mixture solidified and peracetic acid (9.78 mL, 0.275 M, 32 %) was added over 10 minutes, the liquid mixture then bubbled and turned orange. 5 minutes after the addition, the ice bath was removed, and the mixture was stirred overnight. The reaction was quenched using a 25 % aqueous solution of Na₂S₂O₃ at 0 °C, followed by saturation of the aqueous phase with Na₂S₂O₃. The two phases were separated and the aqueous phase was extracted with EtOAc (3x20 mL). The combined organic layers were then washed first with a saturated aqueous solution of NaHCO₃, secondly with brine and were then dried over sodium sulfate. An orange crude mixture containing **15** was obtained.

To a solution of this residue (2.69 mmol, 1 eq) in dichloromethane (27 mL, 0.1M), pyridine (0.9 mL, 10.76 mmol, 4 eq), acetic anhydride (0.8 mL, 10.76 mmol, 4 eq) and DMAP (catalytic amount) were added. The reaction mixture was stirred overnight. It was then quenched using NH₄Cl saturated aqueous solution and extracted with CH₂Cl₂ (2x10 mL). The combined organic fractions were washed successively with H₂O and brine and were dried over Na₂SO₄. Solvents were evaporated under reduced pressure (pyridine and acetic anhydride were co-evaporated with toluene). The crude was purified on silica gel column chromatography (60:40 Pentane/ EtOAc) providing **17** as a vitrified colorless oil (604 mg, 56 %).

FTIR (film, NaCl): 2979, 1751, 1460, 1370, 1228, 1048 cm⁻¹. **¹H NMR** (CDCl₃, 250 MHz): δ (ppm) = 5.57-5.40 (m, 2H, CH-O or/and CH-N), 4.95 (d, J = 8.1 Hz, 1H, CH-O or CH-N), 4.52 (t_{appearing}, J₁ = 5.3 Hz, J₂ = 5.8 Hz, 1H, CH-O or CH-N), 4.33 (d_{appearing}, J = 5.2 Hz, 1H, CH-O or CH-N), 2.14-1.86 (m, 13H, 2CH₂ + CH₃ of 3 acetate), 1.43 (s, 9H, CH₃ of Boc). **¹³C NMR** (CDCl₃, 62.9 MHz): δ (ppm) = 170.3 (Cq, C=O of acetate), 169.3 (Cq, C=O of acetate), 154.2 (Cq, C=O of Boc), 82.3 (Cq, Boc), 76.8 (CH, CH-O), 76.2 (CH, CH-O), 69.3 (CH, CH-O), 68.3 (CH, CH-O), 51.5 (CH, CH-N), 28.2 (CH₃, Boc), 20.8 (CH₃ or CH₂), 20.71 (CH₃ or CH₂), 20.68 (CH₃ or CH₂), 20.6 (CH₃ or CH₂), 16.2 (CH₂). **HRMS** (ESI): calc. for C₁₈H₂₇NO₉Na [M+Na]⁺ = 424.15835 found: 424.1582.

When the sequence was performed step by step, the intermediate **13** and **15** were purified and fully characterized as followed:

(7-(tert-butoxycarbonyl)-4-(dimethyl(phenyl)silyl)-6-oxa-7-azabicyclo[3.2.2]nonane-2,3-diyl diacetate (13) :

To a solution of the olefinic compound **10** (86 mg, 0.18 mmol, 1 eq) in a 2:1 mixture of EtOAc/MeOH (0.12 M, 1 mL+0.5 mL), 10 % Palladium on Charcoal (19 mg of the mixture, 0.018 mmol of palladium, 0.1 eq) was added. Vacuum followed by nitrogen refill was performed 3 times. Then vacuum followed by H₂ refill was performed twice and the mixture was left stirring overnight under H₂ atmosphere. Palladium was removed by filtration on celite pad, using ethyl acetate as eluent. Purification was performed by chromatography on silica gel (85:15 Pentane/EtOAc) providing the product **13** as colorless oil (84 mg, 98 %).

Rf 0.11 (85:15, Petroleum ether/EtOAc). **FTIR** (film, NaCl): 3049, 2977, 1744, 1688, 1427, 1367, 1247, 1024 cm⁻¹. **¹H NMR** (CDCl₃, 300 MHz): δ (ppm) = 7.65-7.56 (m, 2H, CH_{ar}), 7.47-7.30 (m, 3H, CH_{ar}), 5.58 (appearing t, J₁ = 4.1 Hz, J₂ = 2.6 Hz, 1H, CH-O), 5.21-5.10 (m, 1H, CH-O), 4.46-4.24 (m, 2H, CH-N and CH-O), 2.45-2.28 (m, 1H, CH₂), 2.22-2.07 (m, 1H, CH₂), 2.07-1.97 (m, 1H, CH₂), 2.02 (s, 3H, CH₃ of acetate), 1.99 (s, 3H, CH₃ of acetate), 1.97-1.88 (m, 1H, CH₂), 1.68 (t_{appearing}, J₁ = 3.4 Hz, J₂ = 3 Hz, 1H, CH-Si), 1.52 (s, 9H, CH₃ of Boc), 0.47 (s, 3H, CH₃-Si), 0.46 (s, 3H, CH₃-Si). **¹³C NMR** (CDCl₃, 75.5 MHz): δ (ppm) = 169.8 (Cq, C=O of acetate), 169.2 (Cq, C=O of acetate), 153.3 (Cq, C=O of Boc), 136.5 (Cq, ar), 134.2 (CH, ar), 129.5 (CH, ar), 128.0 (CH, ar), 81.8 (Cq, Boc), 74.8 (CH, CH-O), 74.1 (CH, CH-O), 69.5 (CH, CH-O), 53.5 (broad CH, CH-N), 39.5 (CH, CH-Si), 28.5 (CH₃, Boc), 24.2 (CH₂), 21.2 (CH₃, acetate), 20.8 (CH₃, acetate), 17.9 (CH₂), -3.4 (CH₃, CH₃-Si), -3.5 (CH₃, CH₃-Si). **HRMS** (ESI): calc. for C₂₄H₃₆NO₇SiNa [M+Na]⁺ = 500.2080 found: 500.2088

7-(tert-butoxycarbonyl)-4-hydroxy-6-oxa-7-azabicyclo[3.2.2]nonane-2,3-diyl diacetate (15):

To a mixture of reduced cycloadduct **13** (1.31 mmol, 627 mg, 1 eq), KBr (2.62 mmol, 312 mg, 2 eq) and NaOAc (5.5 mmol, 451 mg, 4.2 eq) at 0 °C, acetic acid (2.98 mL, 0.44 M) was added. peracetic acid (4.76 mL, 0.275 M, 32 %) was added over 10 minutes to the solid mixture, which turned into liquid, bubbled, and turned orange. 5 minutes after the addition, the ice bath was removed, and the mixture was stirred overnight. The reaction was quenched using a 25 % weight aqueous solution of Na₂S₂O₃ at 0 °C, followed by saturation of the aqueous phase with solid Na₂S₂O₃. The two phases were separated and the aqueous phase was extracted with EtOAc (3x20 mL). The combined organic layers were then washed first with a saturated aqueous solution of NaHCO₃, secondly with brine and were then dried over

sodium sulfate. Purification was performed by chromatography on silica gel (99:1 CH₂Cl₂/MeOH) to provide the following product **15** as a colorless oil (206 mg, 44 %).

Rf 0.22 (98:2 CH₂Cl₂/MeOH). **FTIR** (film, NaCl): 3463, 2979, 1751, 1371, 1244, 1069 cm⁻¹. **¹H NMR** (CDCl₃, 400 MHz): δ (ppm) = 5.41 (t, J = 5.3 Hz, 1H, CH-O), 5.21 (t_{appearing}, J₁ = 5.7 Hz, J₂ = 5.3 Hz, 1H, CH-O), 4.38 (broad s, 2H, CH-O and CH-N), 3.81 (d, J = 4.7 Hz, 1H, CH-O), 2.13-1.92 (m, 2H, CH₂), 1.99 (s, 3H, CH₃ of acetate), 1.98 (s, 3H, CH₃ of acetate), 1.92-1.77 (m, 2H, CH₂), 1.41 (s, 9H, CH₃ of Boc). **¹³C NMR** (CDCl₃, 100.6 MHz): δ (ppm) = 169.9 (Cq, C=O of acetate), 169.3 (Cq, C=O of acetate), 154.3 (Cq, C=O of Boc), 82.4 (Cq, Boc), 78.6 (CH, CH-O), 74.6 (CH, CH-O), 72.5 (CH, CH-O), 69.3 (CH, CH-O), 52.3 (CH, CH-N), 28.1 (CH₃, Boc), 20.7 (CH₃, acetate), 20.6 (CH₃ acetate), 20.3 (CH₂), 16.7 (CH₂). **HRMS** (ESI): calc. for C₁₆H₂₅NO₈Na [M+Na]⁺ 382.1478 found: 382.1470

7-(tert-butoxycarbonyl)-6-oxa-7-azabicyclo[3.2.2]nonane-2,3,4-triyl triacetate (18) 3 steps sequence synthesis:

To a solution of **11** (581 mg, 1.22 mmol, 1 eq) in a 2:1 mixture of EtOAc/MeOH (0.12 M, 6.8/3.4 mL), 10 % Palladium on charcoal (ALDRICH, 129 mg of the mixture, 0.122mmol of palladium, 0.1 eq) was added. Vacuum followed by nitrogen refill was performed 3 times. Then vacuum followed by dihydrogen was performed twice and the mixture was stirred overnight under dihydrogen atmosphere. Palladium was removed by filtration on celite pad, using ethyl acetate as eluent. **14** was obtained as a sticky foam.

KBr (229 mg, 1.92 mmol, 2 eq) and sodium acetate (331 mg, 4.03 mmol, 4.2 eq), acetic acid (2.18 mL, 0.44M) was added to **14** (460 mg, 0.96 mmol, 1 eq), at 0 °C. peracetic acid (3.5 mL, 0.275 M) was added dropwise over 10 minutes to the solid medium which then became liquid and orange upon the addition. The reaction was stirred 5 more minutes at 0 °C and was then allowed to warm at room temperature. After 8 hours the reaction was quenched at 0 °C using a 25 % aqueous solution of Na₂S₂O₃ (the mixture turned light yellow and gas was produced), followed by Na₂S₂O₃ solid until saturation was reached. Extraction was carried out with EtOAc (3x20 mL) and the combined organic layers were washed successively with a saturated aqueous solution of NaHCO₃ and with brine. The organic layer was then dried over sodium sulfate. Solvent was evaporated under reduced pressure providing **16** which was used without further purification in the following step.

The alcohol **16** (0.96 mmol, 1 eq) was dissolved in dichloromethane (9.2 mL, 0.1M) and pyridine (0.3 mL, 3.68 mmol, 3.8 eq), acetic anhydride (0.27 mL, 3.68 mmol, 3.8 eq) and DMAP (11 mg, 0.09 mmol, 0.09 eq) were added. The colorless solution was stirred overnight and turned yellow. The reaction was quenched using NH₄Cl aqueous saturated solution, and was extracted with CH₂Cl₂ (3x20 mL). The combined organic layers were then washed successively with H₂O and brine and were dried over

Na₂SO₄. Solvent was evaporated under reduced pressure (pyridine and acetic anhydride were co-evaporated with toluene). The crude was purified on silica gel column chromatography (80:20 Pentane/EtOAc) providing **18** as a white crystalline solid (196 mg, 40 %).

Rf 0.08 (60:40, Petroleum ether/EtOAc) **Anal. calcd.** for C₁₈H₂₇NO₉, C, 53.86; H, 6.78; N, 3.49, found C, 53.81; H, 6.81; N, 3.30. **mp**: 133-134°C. **FTIR** (film, NaCl): 2979, 1746, 1699, 1430, 1370, 1226, 1047, 918 cm⁻¹. **¹H NMR** (CDCl₃, 250 MHz): δ (ppm) = 5.66-5.51 (m, 2H, 2 CH-O), 5.07-4.97 (m, 1H, CH-O), 4.64-4.50 (m, 2H, CH-O and CH-N), 2.27-2.12 (m, 1H, 1H of CH₂), 2.05 (s, 1.5H, CH₃ of acetate), 2.04 (s, 1.5H, CH₃ of acetate), 2.00 (s, 1.5H, CH₃ of acetate), 1.99 (s, 1.5H, CH₃ of acetate), 1.96 (s, 1.5H, CH₃ of acetate), 1.95 (s, 1.5H, CH₃ of acetate), 1.92-1.79 (m, 3H, CH₂), 1.43 (s, 4.5H, CH₃ of Boc), 1.42 (s, 4.5H, CH₃ of Boc). **¹³C NMR** (CDCl₃, 75.5 MHz): δ (ppm) = 170.3 (Cq, C=O of acetate), 169.6 (Cq, C=O of acetate), 169.5 (Cq, C=O of acetate), 155.1 (Cq, C=O of Boc), 82.0 (Cq, Boc), 76.6 (CH, CH-O), 73.4 (CH, CH-O), 70.9 (CH, CH-O), 70.6 (CH, CH-O), 53.7 (CH, CH-N), 28.2 (CH₃, Boc), 20.9 (CH₃, acetate), 20.7 (CH₃, acetate), 19.9 (CH₂), 19.3 (CH₂). **HRMS** (ESI): calc. for C₁₈H₂₇NO₉Na [M+Na]⁺ = 424.15835 found: 424.1577.

When the sequence was performed step by step, the intermediate **14** and **16** were purified and fully characterized as followed:

7-(tert-butoxycarbonyl)-2-(dimethyl(phenyl)silyl)-6-oxa-7-azabicyclo[3.2.2]nonane-3,4-diyl diacetate (14) :

The olefinic compound (654 mg, 1.38 mmol, 1 eq) was dissolved in a 2:1 mixture of EtOAc/MeOH (0.12 M, 8 mL + 4 mL). 10 % Palladium on charcoal (147 mg of the mixture, 0.138 mmol of palladium, 0.1 eq) was then added. Vacuum followed by nitrogen refill was performed 3 times. Then vacuum followed by dihydrogen was performed twice and the mixture was stirred overnight under dihydrogen atmosphere. Palladium was removed by filtration on celite pad, using ethyl acetate as eluent. No further purification was necessary; the product **14** was obtained as white powder (645 mg, 98 %)

Rf 0.16 (85:15 Petroleum ether/EtOAc). **FTIR** (film, NaCl): 2976, 1743, 1428, 1368, 1246, 1038. **¹H NMR** (CDCl₃, 300 MHz): δ (ppm) = 7.57-7.42 (m, 2H, CH_{ar}), 7.39-7.27 (m, 3H, CH_{ar}), 5.64 (t, J = 4.5 Hz, 1H, CH-O), 5.30 (t, J = 4.5 Hz, 1H, CH-O), 4.41 (broad, 1H, CH-N), 4.26 (broad, 1H, CH-O), 2.13-1.90 (m, 7H, CH₃ of acetate + 2CH₂), 1.86 (s, 3H, CH₃ of acetate), 1.79 (t, J = 4.53 Hz, 1H, CH-Si) 1.41 (s, 9H, CH₃ of Boc), 0.42 (s, 3H, CH₃-Si), 0.40 (s, 3H, CH₃-Si). **¹³C NMR** (CDCl₃, 75.5 Mhz): δ (ppm) = 169.7 (Cq, C=O of acetate), 169.4 (Cq, C=O of acetate), 155.8 (Cq, C=O of Boc), 136.9 (Cq, ar), 133.9 (CH, ar), 129.3 (CH, ar), 127.8 (CH, ar), 81.5 (Cq, Boc), 73.7 (CH, CH-O), 73.6 (CH, CH-O), 69.5 (CH, CH-O), 52.3 (CH, CH-N), 36.4 (CH, CH-Si), 28.2 (CH₃, Boc), 22.8 (CH₂), 21.0 (CH₃, CH₃ of

acetate), 20.8 (CH₃, CH₃ of acetate), 18.7 (CH₂), -3.40 (CH₃, CH₃-Si), -3.6 (CH₃, CH₃-Si). **HRMS** (ESI): [M+H]⁺ 500.20805 found 500.2085

7-(tert-butoxycarbonyl)-2-hydroxy-6-oxa-7-azabicyclo[3.2.2]nonane-3,4-diyl diacetate (16):

To a mixture of **14** (114 mg, 0.24 mmol, 1 eq), KBr (57 mg, 0.48 mmol, 2 eq) and NaOAc (82 mg, 1 mmol, 4.2 eq), acetic acid (0.55 mL, 0.44 M) was added at 0 °C. Peracetic acid (0.9 mL, 0.275M) was added drop wise over 10 minutes to the solid mixture, the mixture became then liquid and orange upon the addition. The reaction was stirred 5 more minutes at 0 °C and was then allowed to warm at room temperature. After 8 hours the reaction was quenched at 0 °C using a 25 % aqueous solution of Na₂S₂O₃ (the mixture turned light yellow and gas was produced), solid Na₂S₂O₃ was then added until saturation was reached. Extraction was carried out with EtOAc (3 x 10mL). The combined organic fractions were washed successively with a saturated aqueous solution of NaHCO₃ and with brine. The organic layers were then dried over sodium sulfate. Solvent was evaporated under reduced pressure. Purification was performed by silica gel chromatography (70:30 Pentane/EtOAc) providing the product **16** as a white solid (56 mg, 65 %)

Rf 0.15 (60:40 Petroleum ether/EtOAc). **mp**: 148-149°C. **FTIR** (film, NaCl): 3456, 2978, 2936, 1746, 1702, 1370, 1250, 1053, 921cm⁻¹. **¹H NMR** (CDCl₃, 250 MHz): δ (ppm) = 5.59-5.42 (m, 2H, CH-O), 4.61-4.50 (m, 2H, CH-O and CH-N), 3.94 (broad s, 1H, CH-O), 3.10 (broad s, 1H, OH), 2.30-1.96 (m, 2H, CH₂), 2.07 (s, 3H, CH₃ of acetate), 2.06 (s, 3H, CH₃ of acetate), 1.86 (broad s, 2H, CH₂), 1.48 (s, 9H, CH₃ of Boc). **¹³C NMR** (CDCl₃, 75.5 MHz): δ (ppm) = 170.5 (Cq, C=O of acetate), 169.8 (Cq, C=O of acetate), 156.7 (Cq, C=O of Boc), 82.5 (Cq, Boc), 76.1 (CH, CH-O), 73.9 (CH, CH-O), 73.8 (CH, CH-O), 71.4 (CH, CH-O), 56.9 (CH, CH-N), 28.3 (CH₃, CH₃ of Boc), 21.0 (CH₃, acetate), 20.9 (CH₃, acetate), 19.6 (CH₂), 19.1 (CH₂). **HRMS** (ESI): calc. for C₁₆H₂₅NO₈Na [M+Na]⁺ 382.14779 found: 382.1479.

Elaboration of original aminocycloheptitols 22 and 24.

4-(tert-butoxycarbonylamino)-7-hydroxycycloheptane-1,2,3-triyl triacetate and regioisomers (19) :

To a solution of hydroxylamine **17** (199 mg, 0.5 mmol, 1 eq) in a 9:1 CH₃CN/H₂O (0.1 M, 4.5/0.5 mL) mixture, Mo(CO)₆ (ALDRICH-98 %, 162 mg, 0.6 mmol, 1.3 eq) was added. The white mixture was refluxed overnight and rapidly turned black when temperature increased. Reflux was then stopped and silica was used to quench the reaction. The mixture was then filtered and the products were eluted with EtOAc. Solvent was evaporated under reduced pressure. The residue was purified on silica gel column

chromatography (60:40 Pentane/EtOAc) affording a mixture of **19** and regioisomers as a white solid (161 mg, 80 %).

tert-butyl-2,3,4,5-tetrahydroxycycloheptylcarbamate (21) :

To a solution of the acetate compounds mixture (**19 and regioisomers**) (482 mg, 1.2 mmol) in methanol, DOWEX CO₃²⁻ (2 spoons) was added. The mixture was stirred overnight. It was then filtered and the resin was rinsed thoroughly with methanol. The clean material **21** was obtained after evaporation as a white solid (320 mg, 96 %). No further purification was performed.

Rf 0.23 (90:10 CH₂Cl₂/MeOH). **mp**: 149-151°C. **FTIR** (neat) : 3334, 1725, 1519, 1455, 1366, 1157 cm⁻¹. **¹H NMR** (CD₃OD, 300 MHz): δ (ppm) = 4.05-3.91 (m, 3H, 3 CH-O), 3.82-3.78 (m, 1H, CH-O), 3.78-3.65 (m, 1H, CH-N), 1.96-1.79 (m, 2H, CH₂), 1.79-1.61 (m, 2H, CH₂), 1.47 (s, 9H, CH₃ of Boc). **¹³C NMR** (CD₃OD, 75.5 MHz): δ (ppm) = 158.0 (Cq, C=O of Boc), 80.0 (Cq, Boc), 74.7 (CH, CH-O), 73.9 (CH, CH-O), 73.2 (CH, CH-O), 71.8 (CH, CH-O), 54.1 (CH, CH-N), 28.8 (CH₃, CH₃ of Boc), 28.4 (CH₂), 27.2 (CH₂). **HRMS** (ESI): calc. for C₁₂H₂₃NO₆Na [M+Na]⁺ = 300.14231 found: 300.1419

5-aminocycloheptane-1,2,3,4-tetraol (22) :

To a solution of carbamate **21** (180 mg, 0.65 mmol) in methanol (8 mL) Amberlite IRA 120 (2 spoons) was added. The mixture was refluxed during 2 hours, stirred overnight and refluxed again for additional 2 hours. The resin was then separated by filtration and placed in a round bottomed flask. The flask was cooled to 0 °C and a 15 % NH₃ aqueous solution was added. After 15 hours of stirring the resin was eliminated by filtration and the solution was evaporated under reduced pressure providing the colorless oil (63mg, 56 %).

¹H NMR (CD₃OD, 300 MHz): δ (ppm) = 4.15-3.91 (m, 2H, 2 CH-O), 3.91-3.76 (m, 2H, 2 CH-O), 3.14-2.96 (m, 1H, CH-N), 2.05-1.77 (m, 2H, CH₂), 1.77-1.55 (m, 2H, CH₂). **¹³C NMR** (CD₃OD, 75.5 MHz): δ (ppm) = 74.9 (CH, CH-O), 74.8 (CH, CH-O), 74.4 (CH, CH-O), 71.7 (CH, CH-O), 53.2 (CH, CH-N), 28.4 (CH₂), 28.3 (CH₂). **HRMS** (ESI): calc. for C₇H₁₆NO₄ [M+H]⁺ = 178.10793 found: 178.1076.

4-(tert-butoxycarbonylamino)-7-hydroxycycloheptane-1,2,3-triyl triacetate (20):

To a solution of hydroxylamine **18** (152 mg, 0.38 mmol, 1 eq) in a 9:1 CH₃CN/H₂O (0.1 M, 3.4/0.4 mL) mixture, Mo(CO)₆ (ALDRICH-98 %, 112 mg, 0.42 mmol, 1.1 eq) was added. The white mixture was refluxed overnight and rapidly turned black when temperature increased. Heating was then stopped and silica was used to quench the reaction. It was then filtered and the products were eluted with EtOAc. Solvent was evaporated under reduced pressure. The product was purified by silica gel column chromatography (60-40 Pentane/EtOAc) providing **20** as a white solid (152 mg, 99 %, mixture of

regioisomers).

tert-butyl 2,3,4,5-tetrahydrocycloheptylcarbamate (23) :

To a solution of **20** (98 mg, 0.24 mmol) in methanol (about 5 mL), resin DOWEX CO₃²⁻ (2 spoons) was added. The reaction mixture was stirred and the progress of the reaction was followed by TLC. After 4 hours no starting material remained. Resin was removed by filtration and rinsed with methanol. After evaporation, **23** was obtained as a vitrified colorless solid (42 mg, 63 %). No further purification was required.

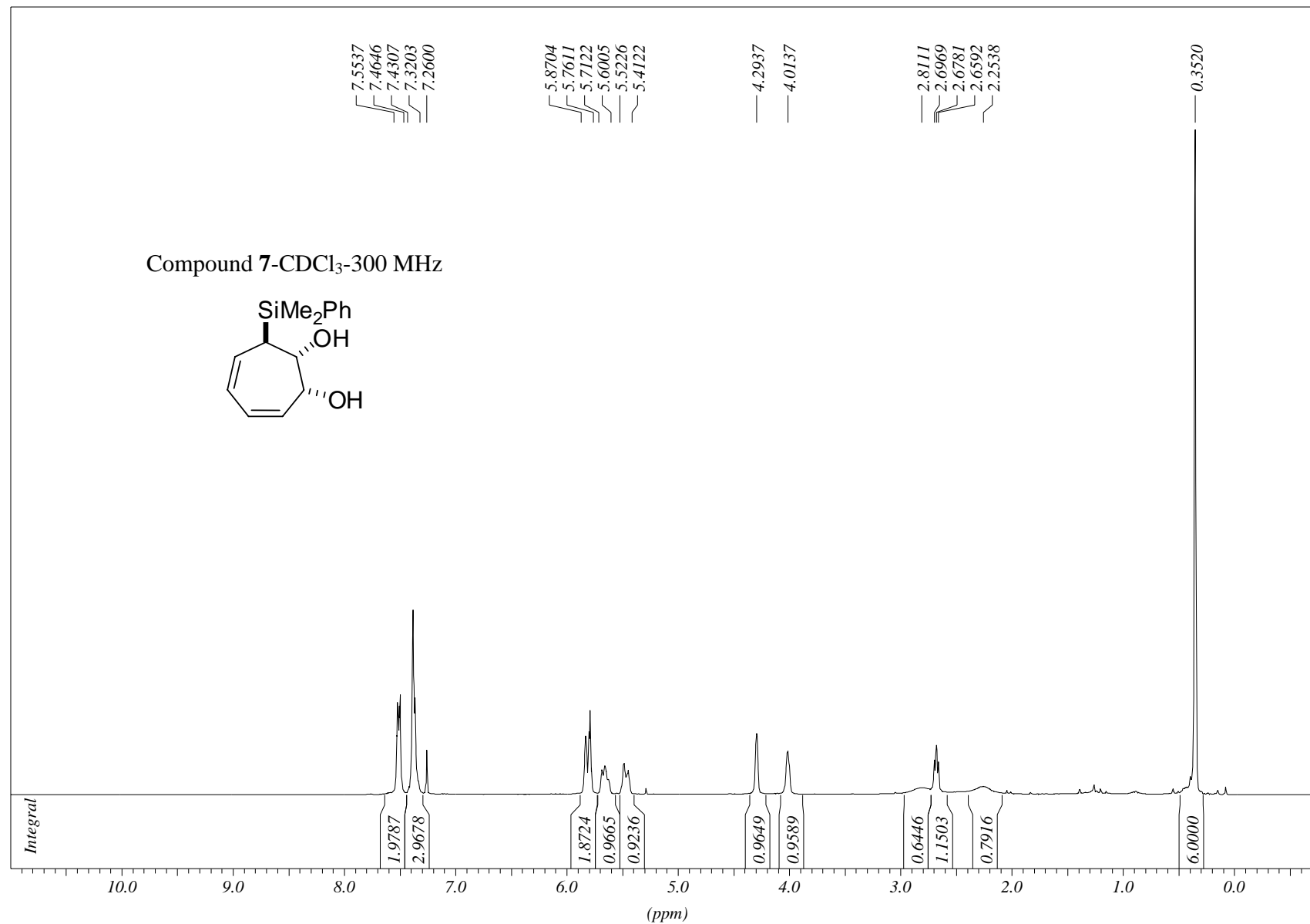
Rf 0.14 (90:10 CH₂Cl₂/MeOH) **mp**: 154-155°C. **FTIR** (film, NaCl): 3351, 3003, 2920, 1686, 1507, 1452, 1363, 1172, 1087 cm⁻¹. **¹H NMR** (CD₃OD, 400 MHz): δ (ppm) = 3.99-3.90 (m, 2H, CH-O), 3.88-3.77 (m, 3H, CH-O and CH-N), 2.11-1.95 (m, 1H, 1H of CH₂), 1.95-1.83 (m, 1H, 1H of CH₂), 1.83-1.68 (m, 1H, 1H of CH₂), 1.45 (s, 10H, 9H of Boc + 1H of CH₂) **¹³C NMR** (CD₃OD, 100.6 MHz): δ (ppm) = 157.5 (Cq, C=O of Boc), 80.1 (Cq, Boc), 76.2 (CH, CH-O), 75.7 (CH, CH-O), 73.8 (CH, CH-O), 72.6 (CH, CH-O), 53.0 (CH, CH-N), 32.0 (CH₂), 28.7 (CH₃, CH₃ of Boc), 25.2 (CH₂). **HRMS** (ESI): calc. for C₁₂H₂₃NO₆Na [M+Na]⁺ = 300.14231 found: 300.1420.

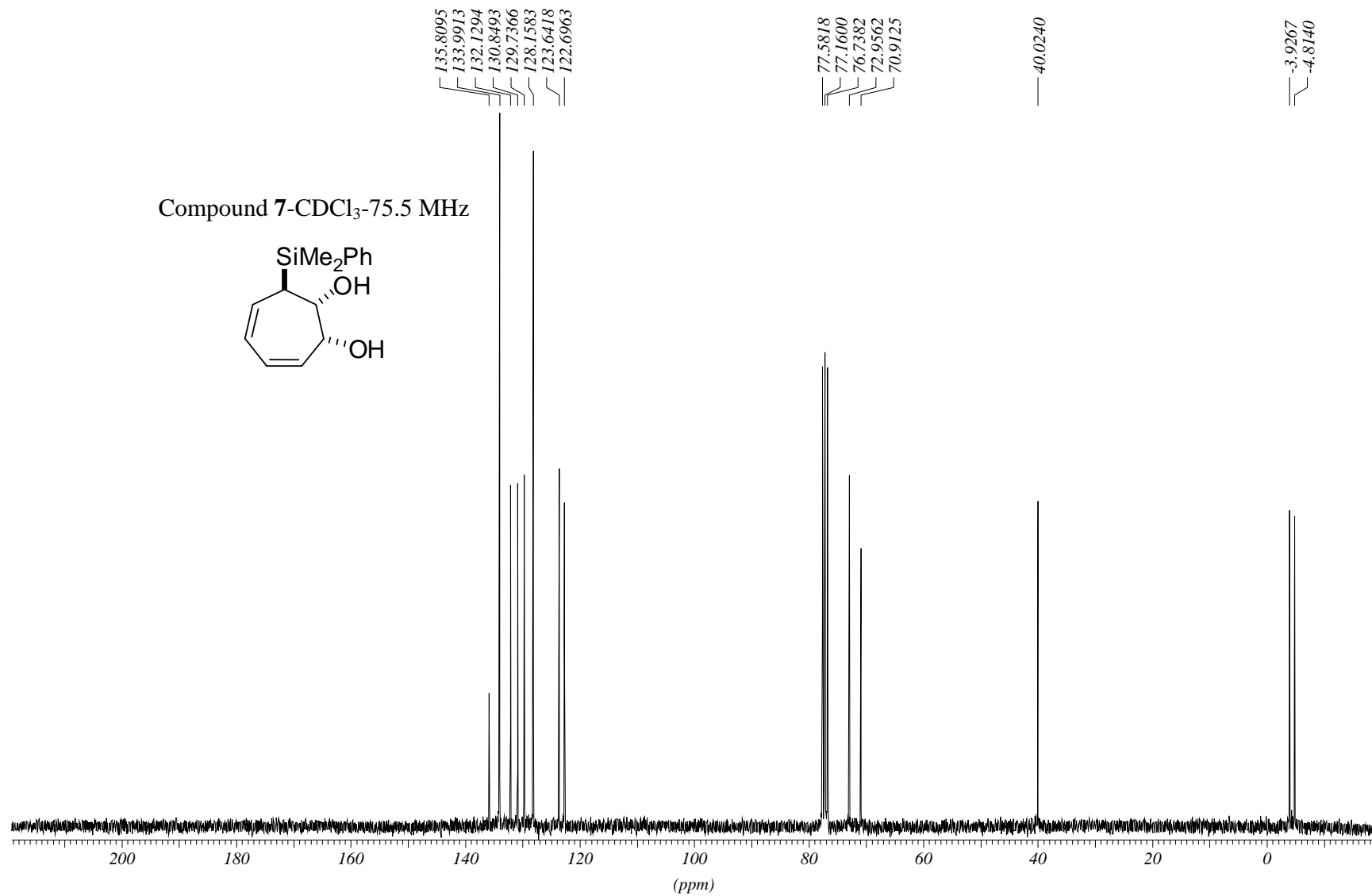
5-aminocycloheptane-1,2,3,4-tetraol (24) :

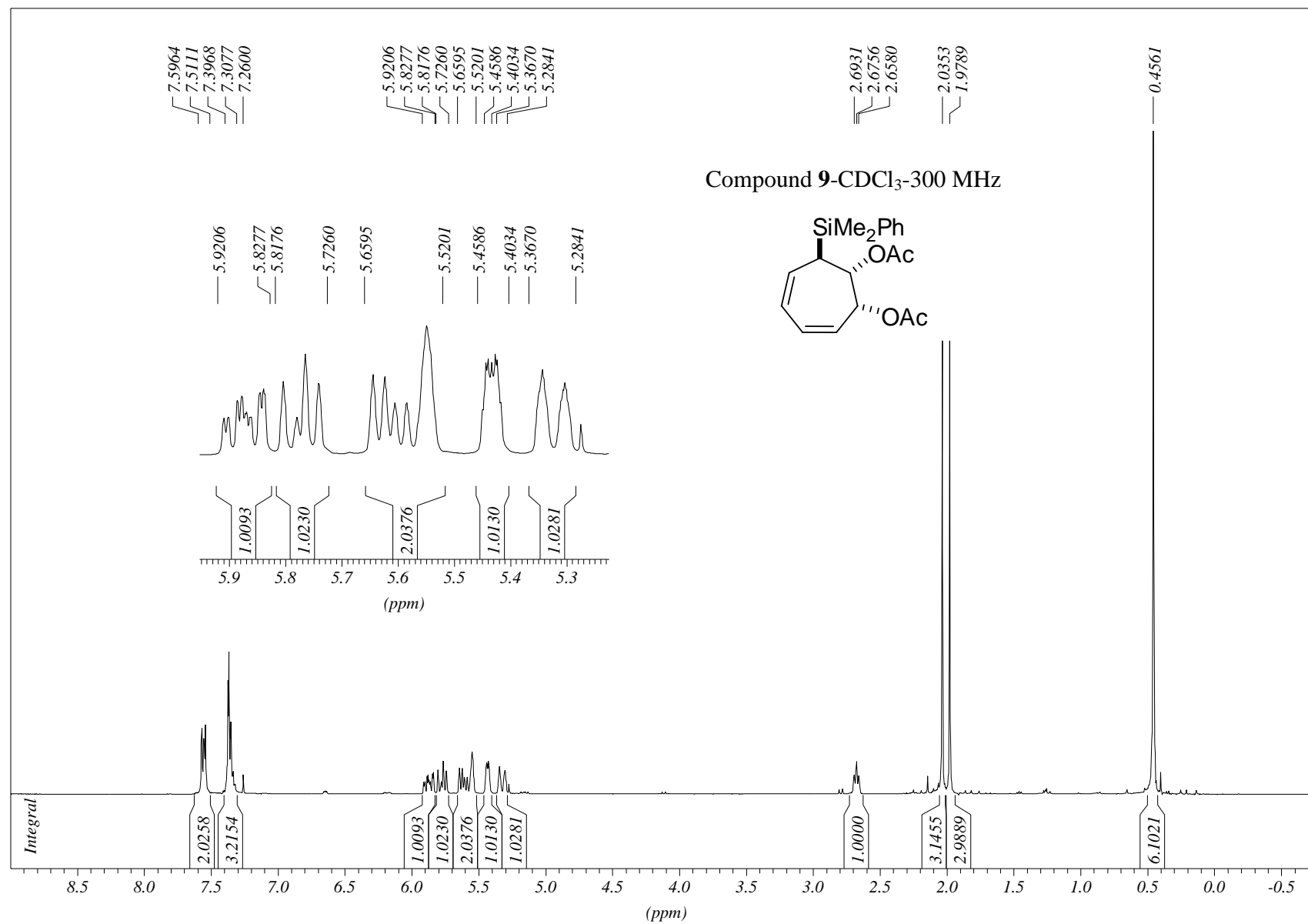
To a solution of **23** (40 mg, 0.14mmol) in methanol (4 mL), Amberlite IRA 120 was added (2 spoons). The mixture was refluxed during 2 hours, stirred overnight and refluxed again for additional 2 hours. The resin was then separated by filtration and placed in a round bottomed flask. The flask was cooled to 0 °C and a 15 % NH₃ aqueous solution was added. After 15 hours of stirring the resin was eliminated by filtration and the solution was evaporated under reduced pressure affording the clean product **24** (8 mg, 32 %) as a colorless oil.

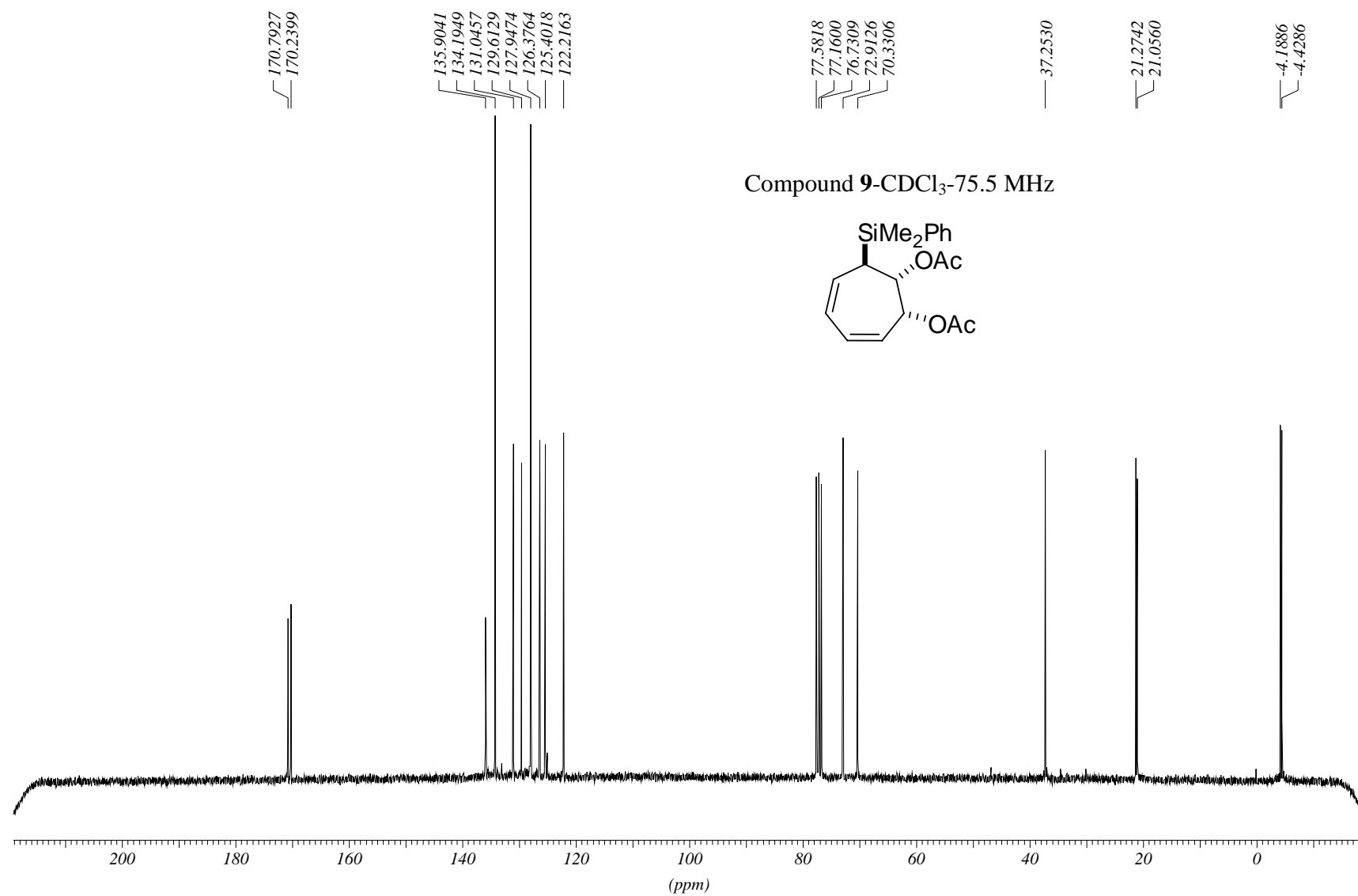
¹H NMR (CD₃OD, 300 MHz): δ (ppm) = 4.01-3.90 (m, 2H, 2 CH-O), 3.86-3.76 (m, 2H, 2 CH-O), 3.13 (dt, J₁ = 9.5 Hz, J₂ = 3.2 Hz, 1H, CH-N), 2.05-1.68 (m, 3H, CH₂), 1.58-1.47 (m, 1H, 1H of CH₂). **¹³C NMR** (CD₃OD, 75.5 MHz): δ (ppm) = 75.6 (CH, CH-O), 74.8 (CH, CH-O), 73.9 (CH, CH-O), 72.1 (CH, CH-O), 52.9 (CH, CH-N), 30.7 (CH₂), 26.3 (CH₂). **HRMS** (ESI): calc. for C₇H₁₆NO₄ [M+H]⁺ = 178.10793 found: 178.1082.

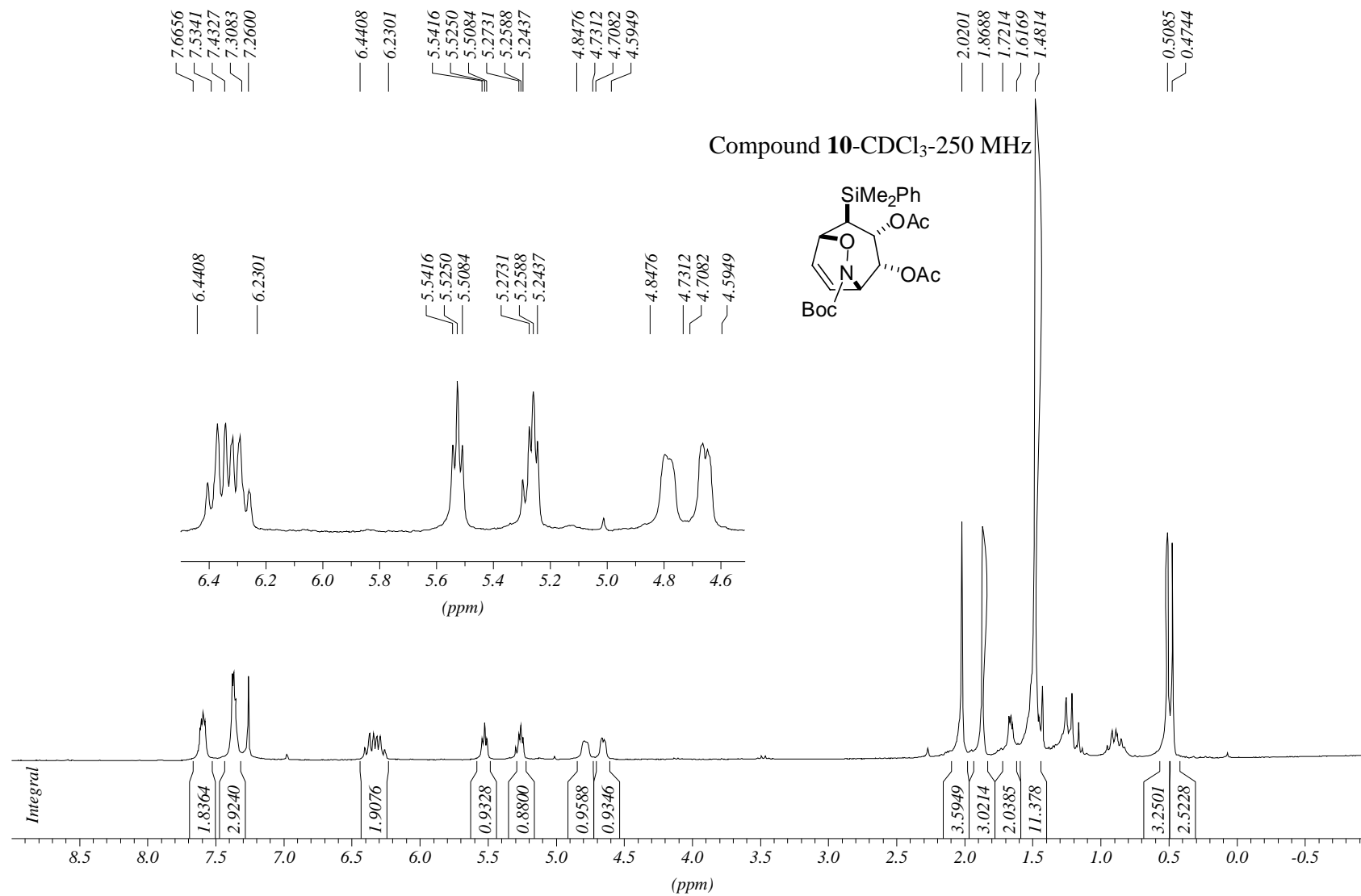
^1H and ^{13}C NMR Spectra

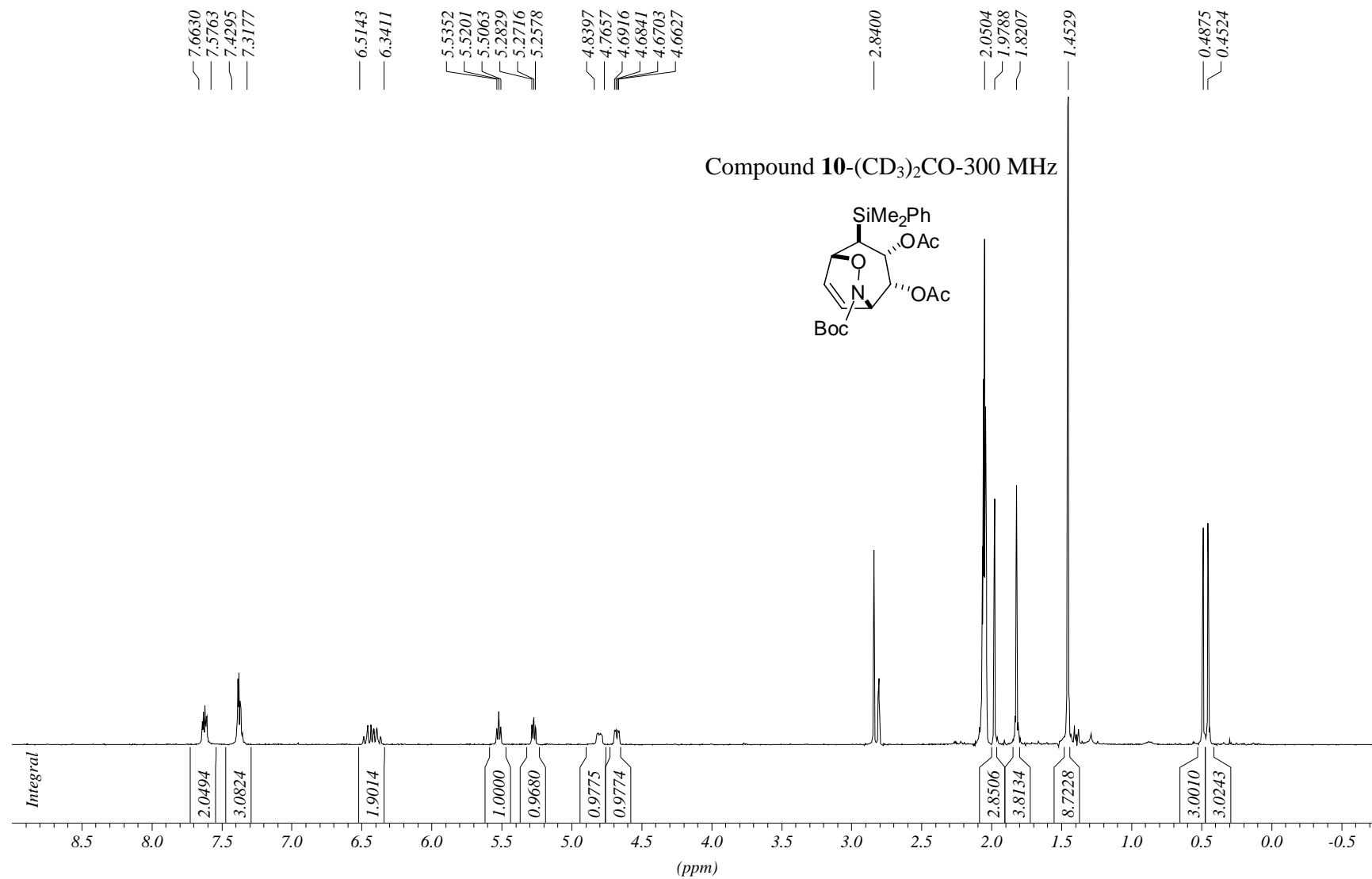


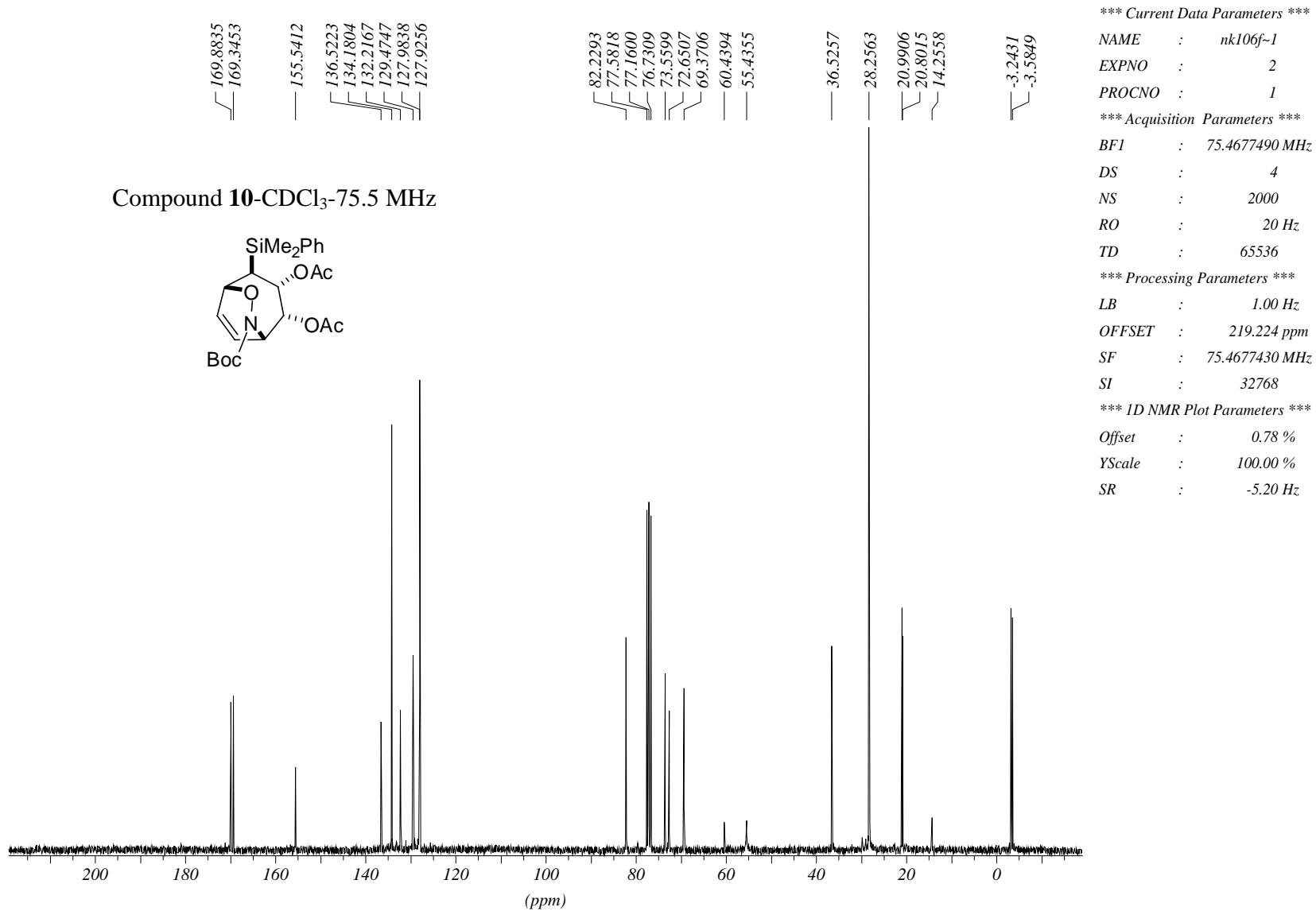


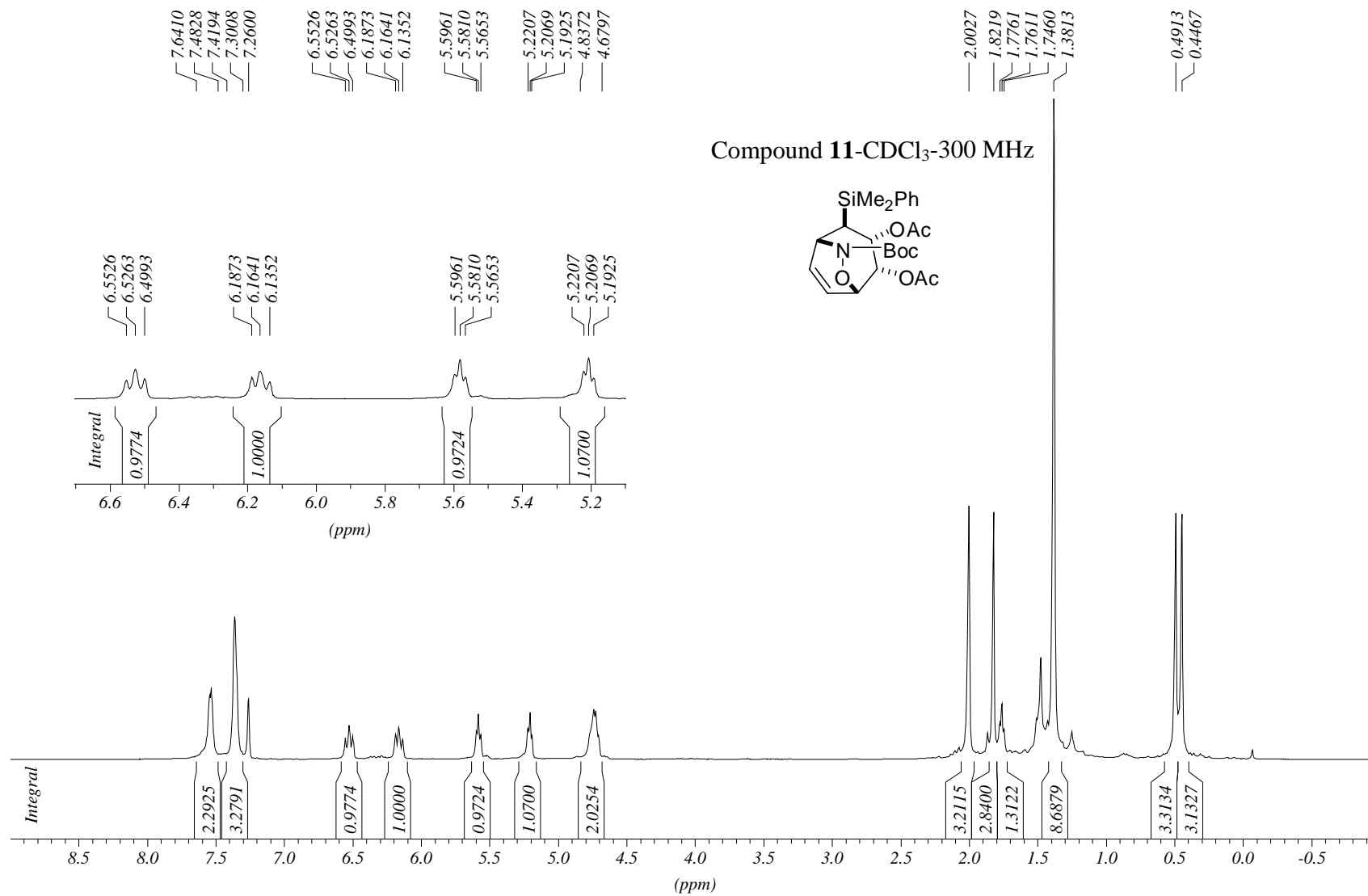


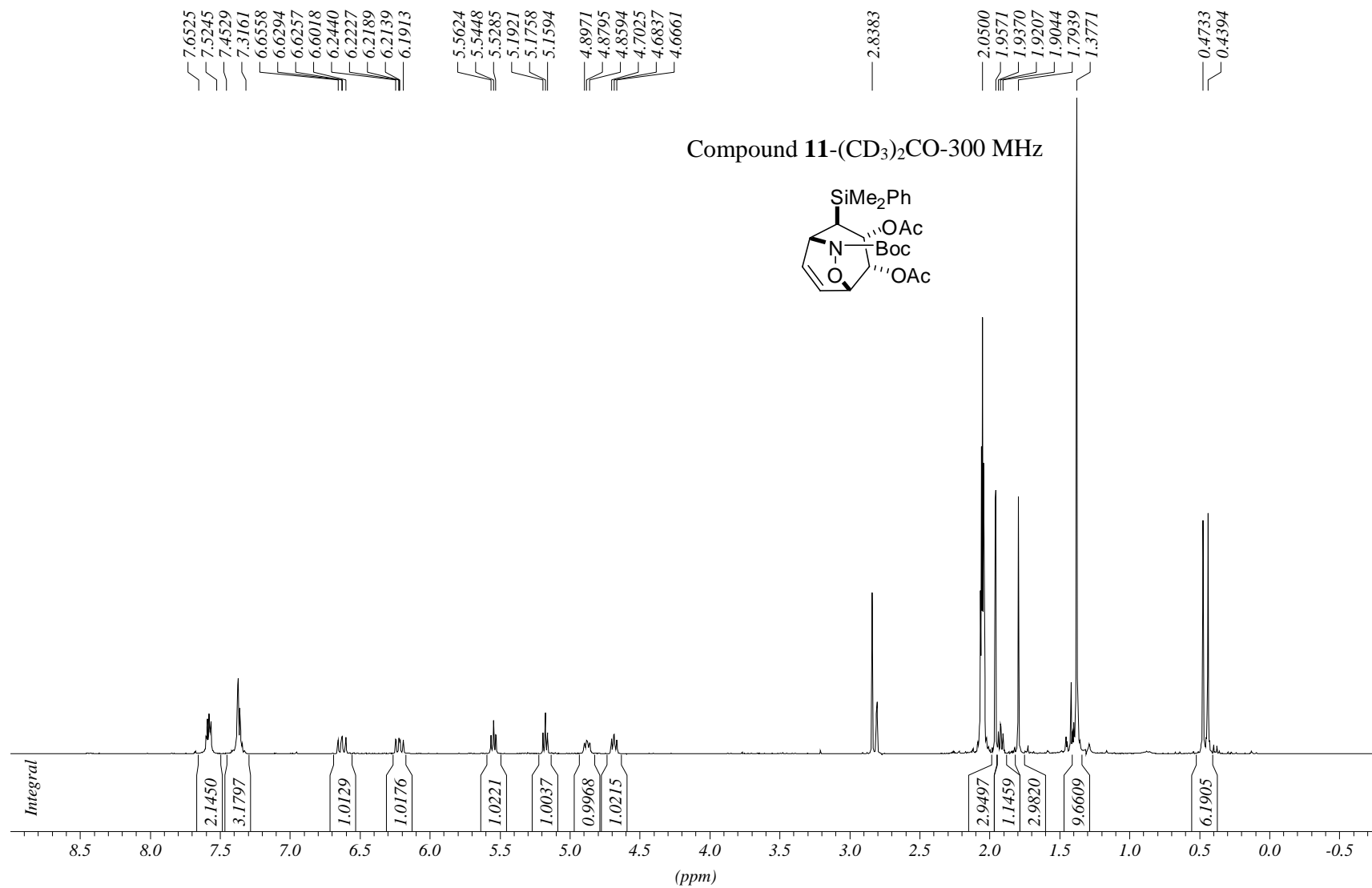


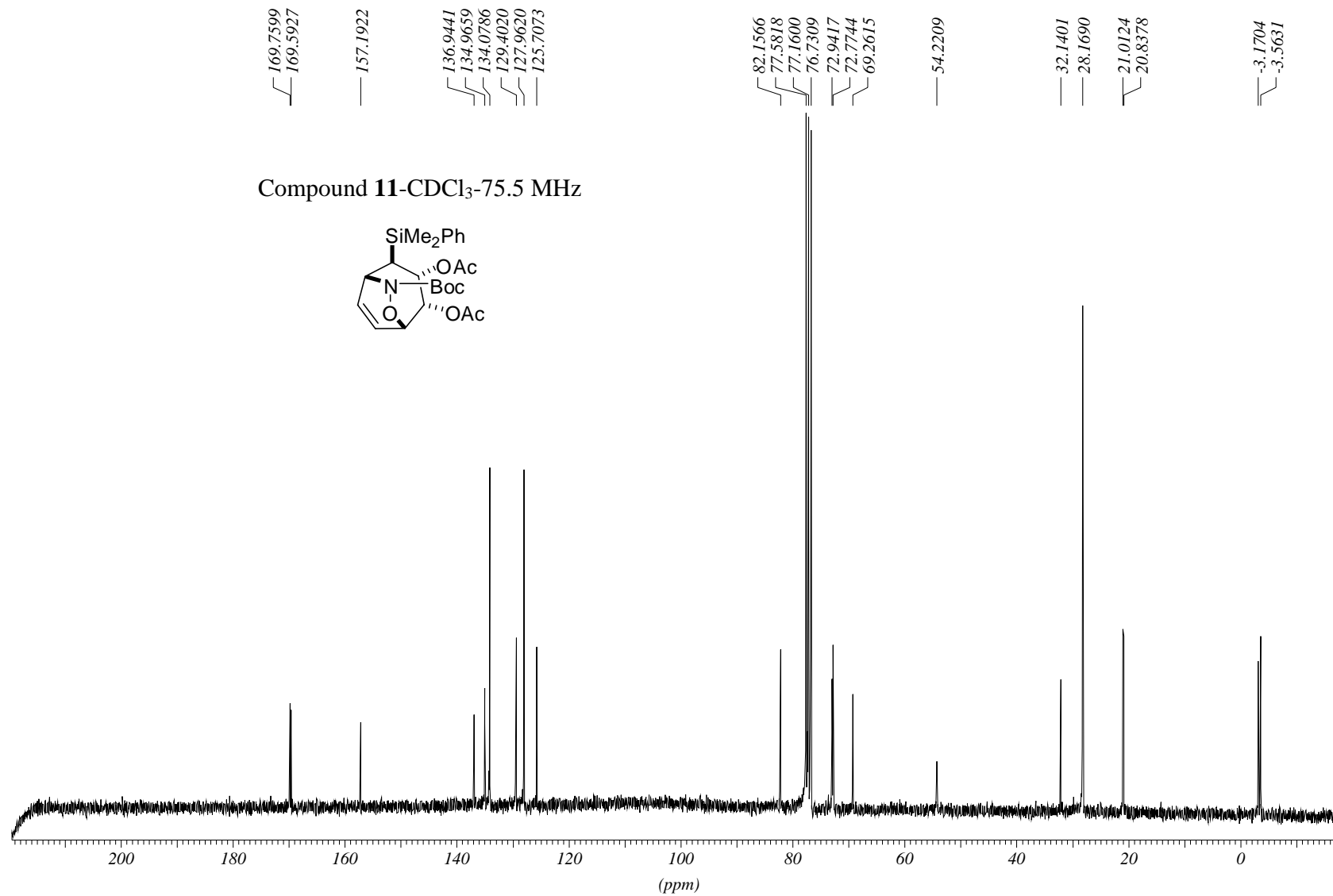


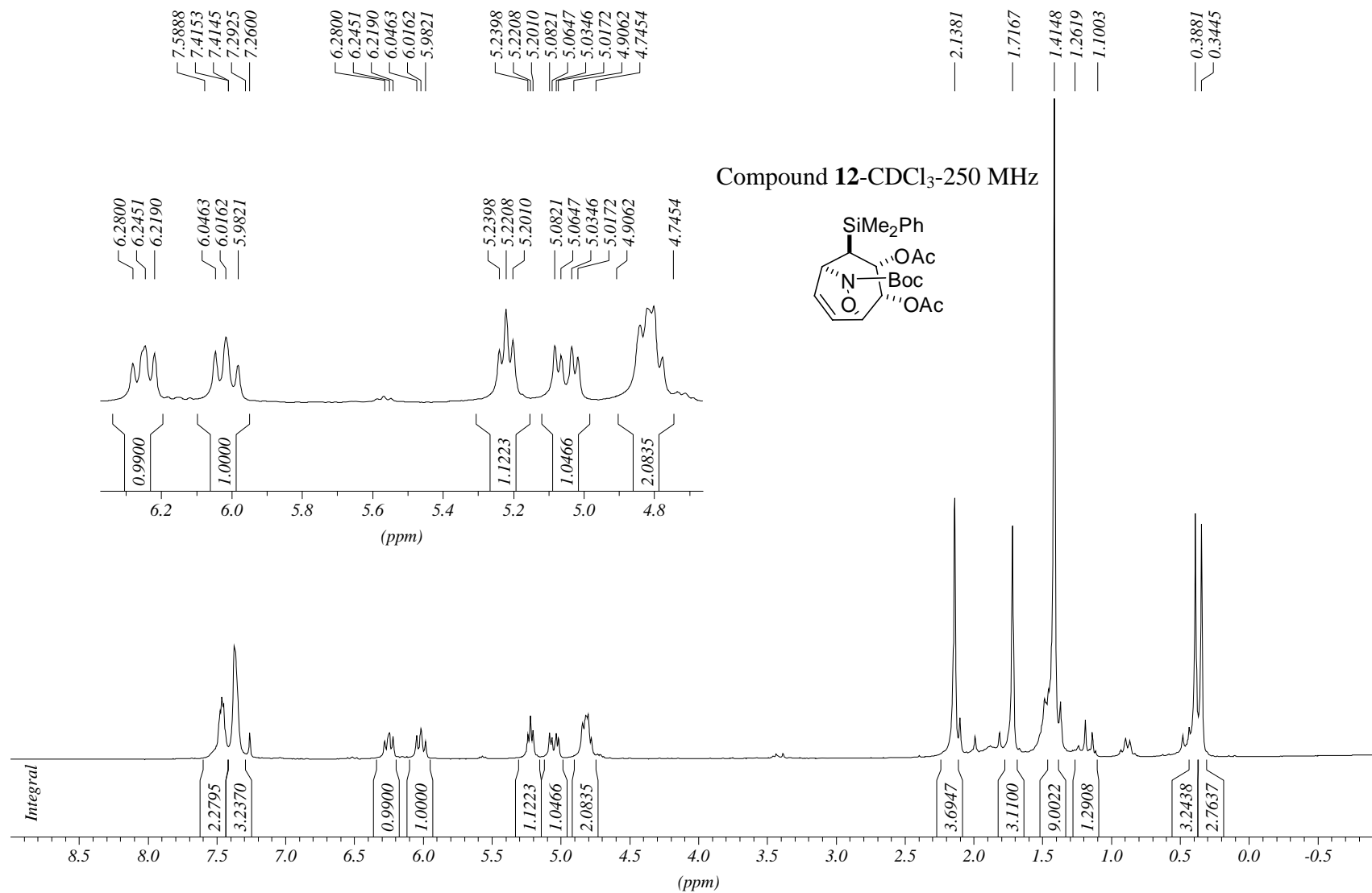


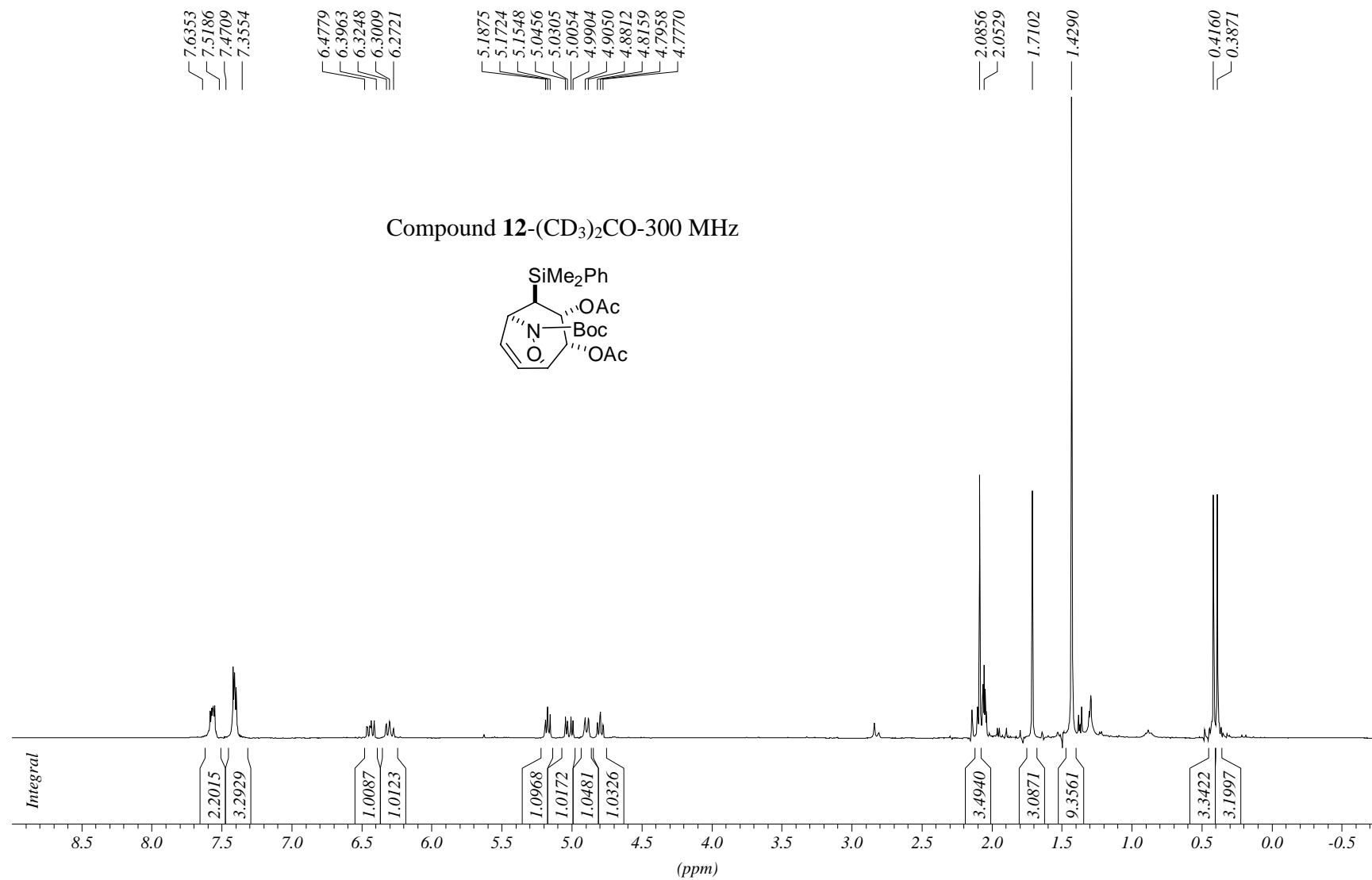


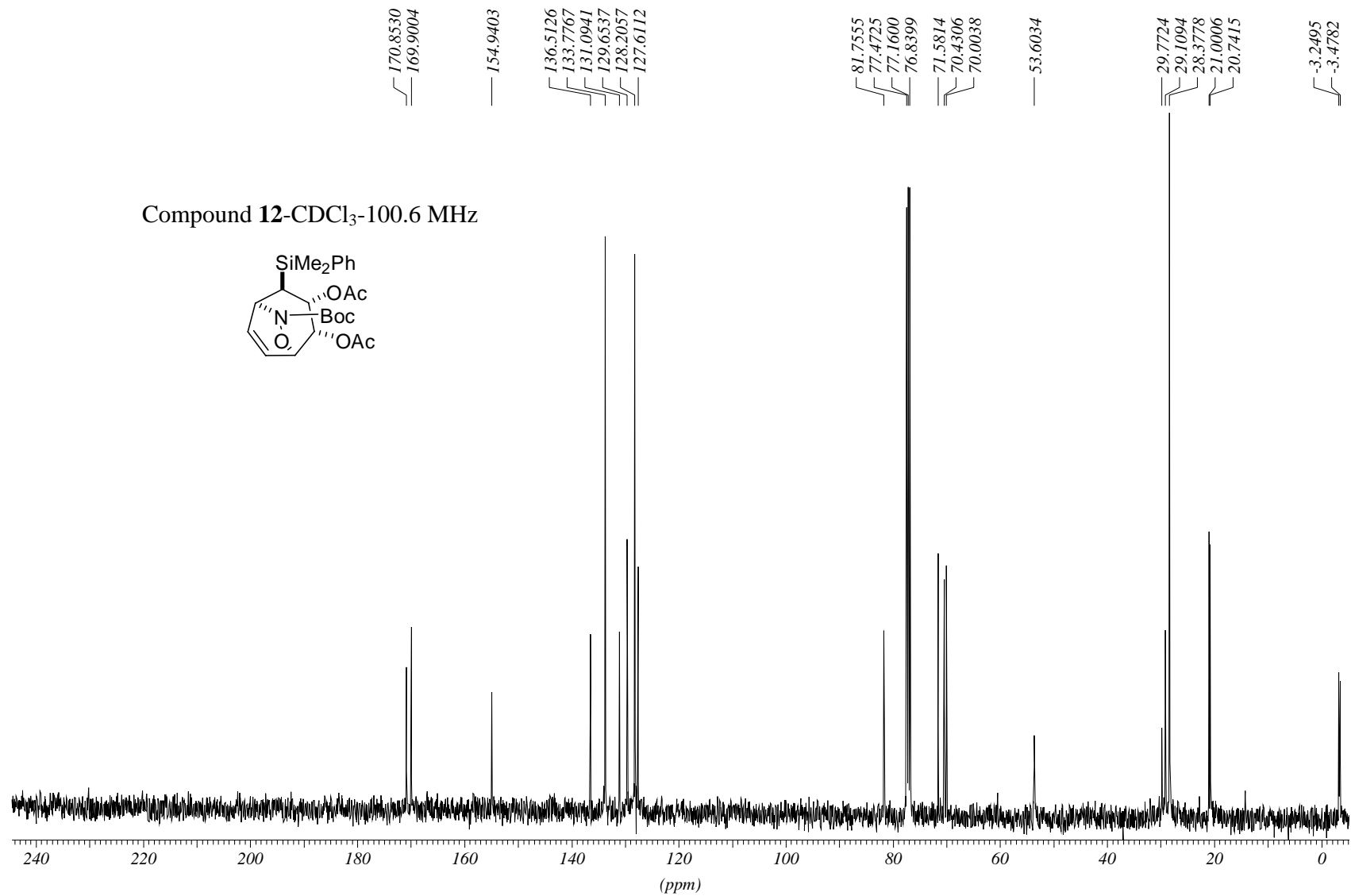


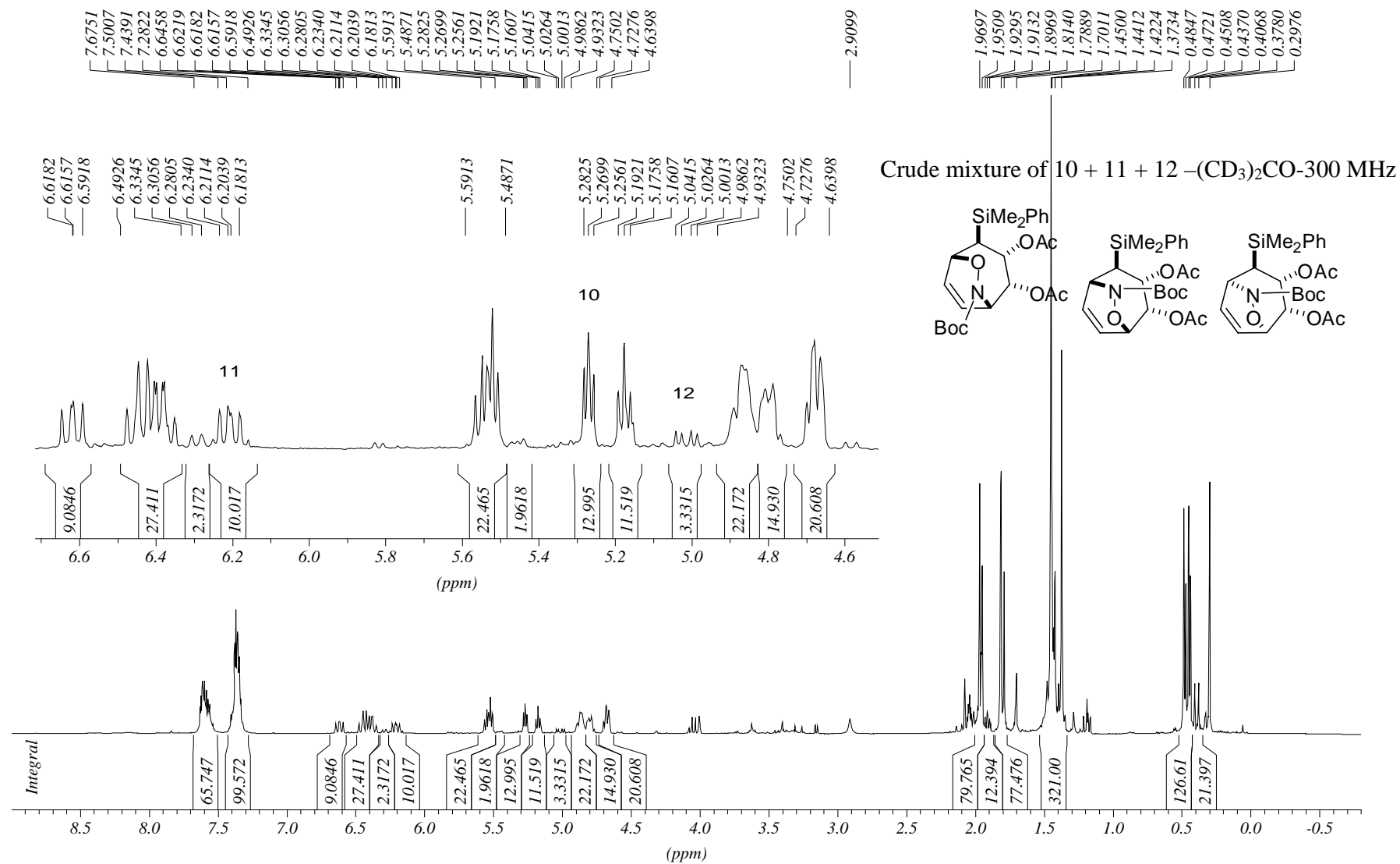


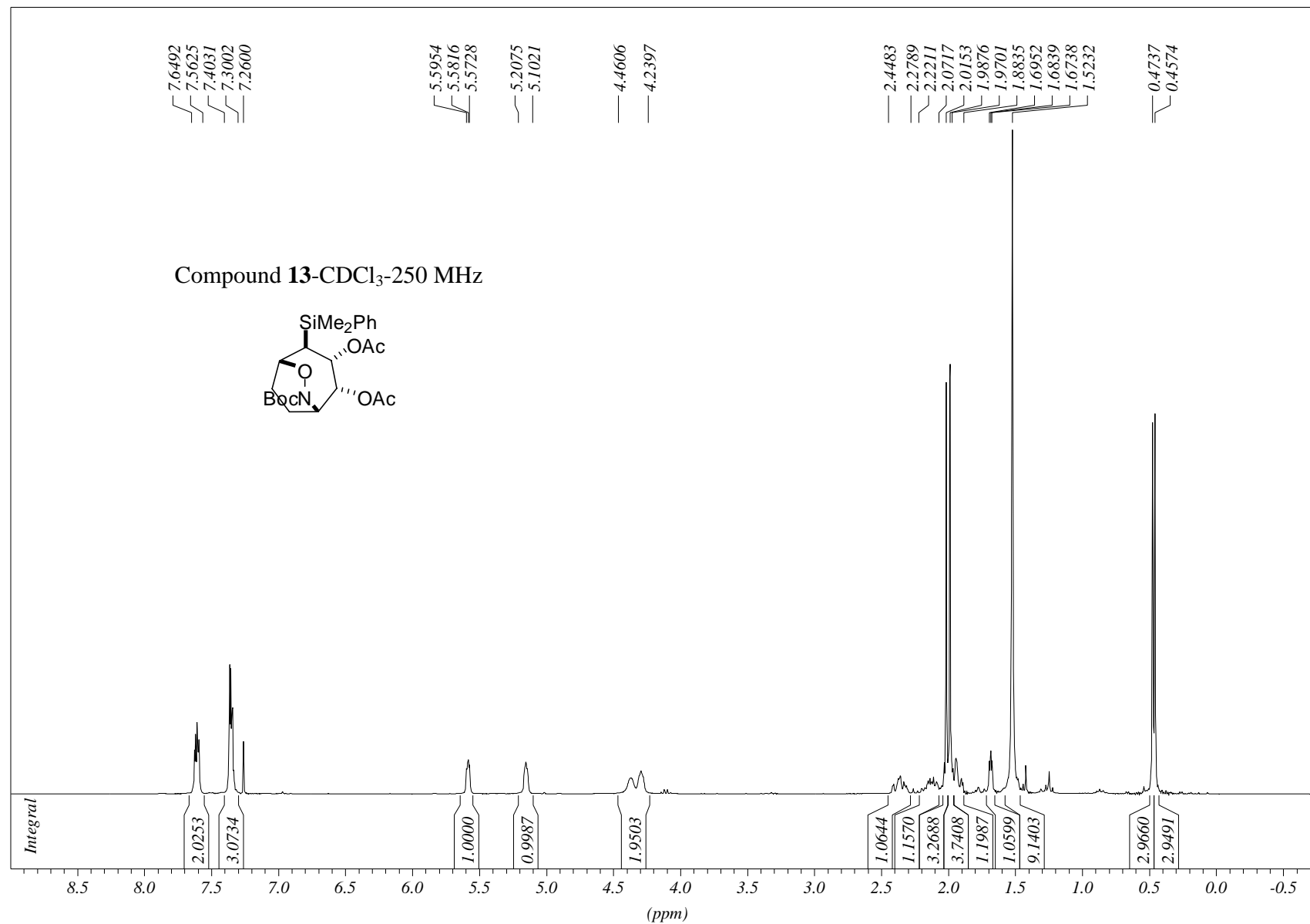


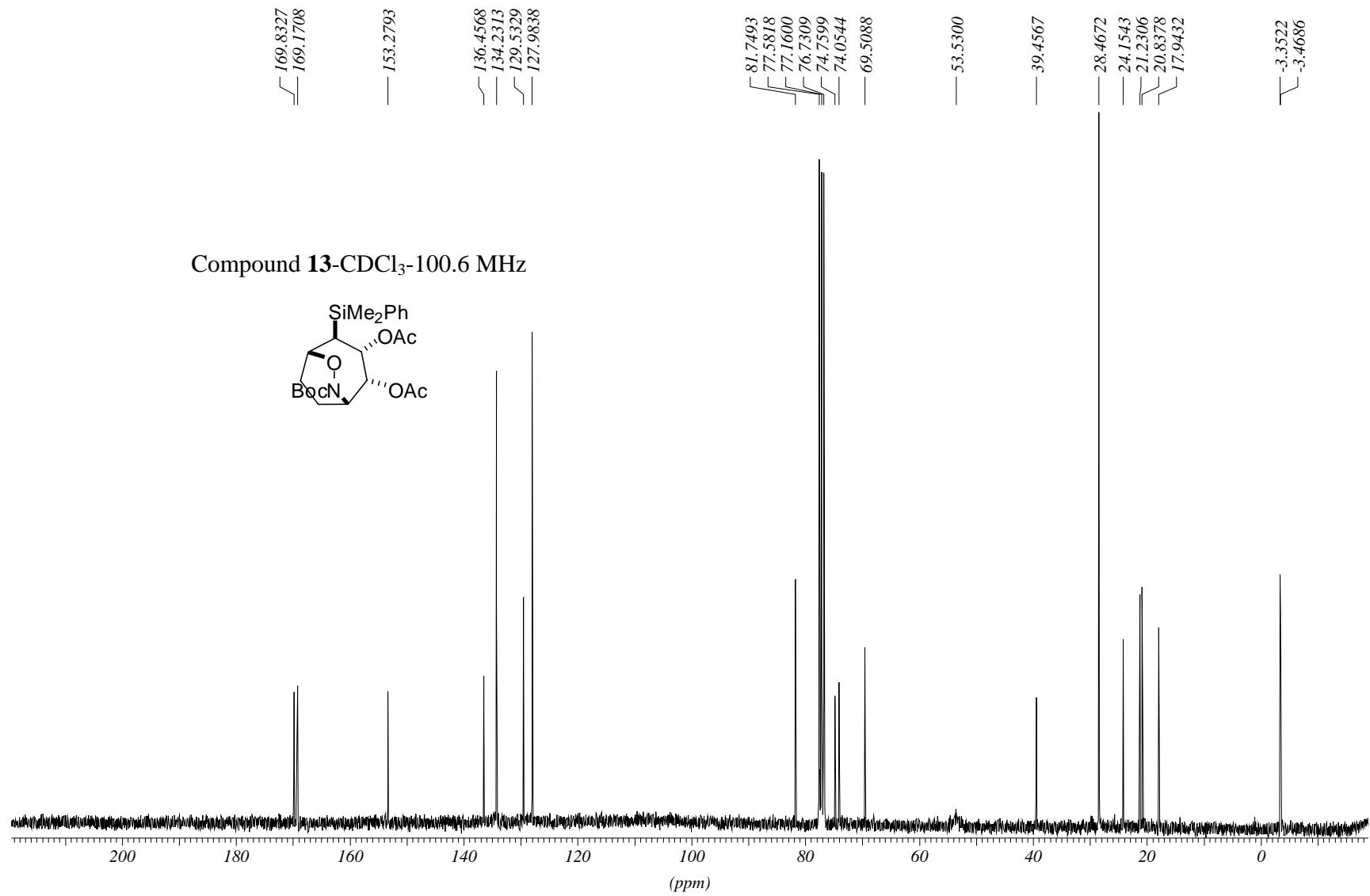


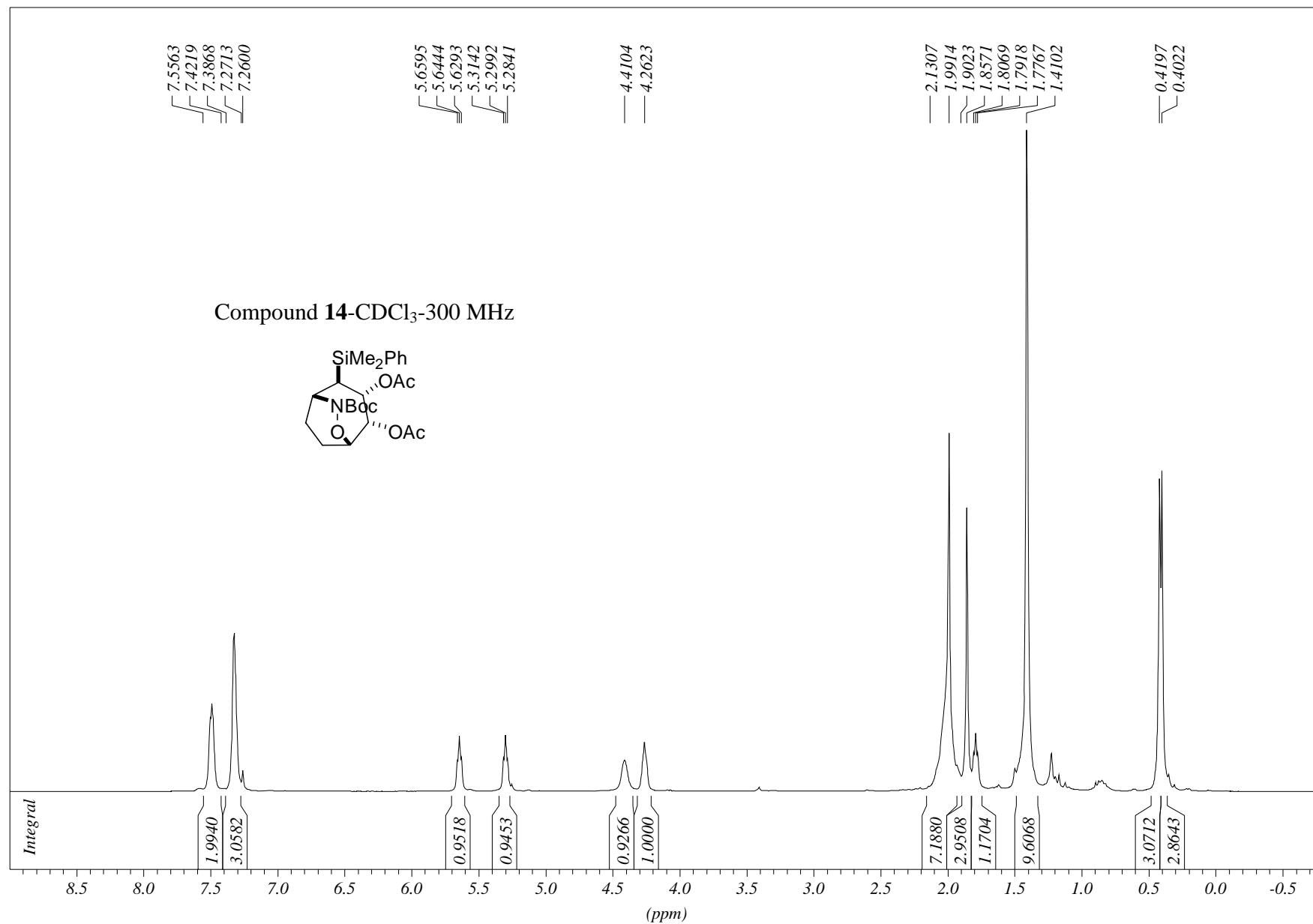


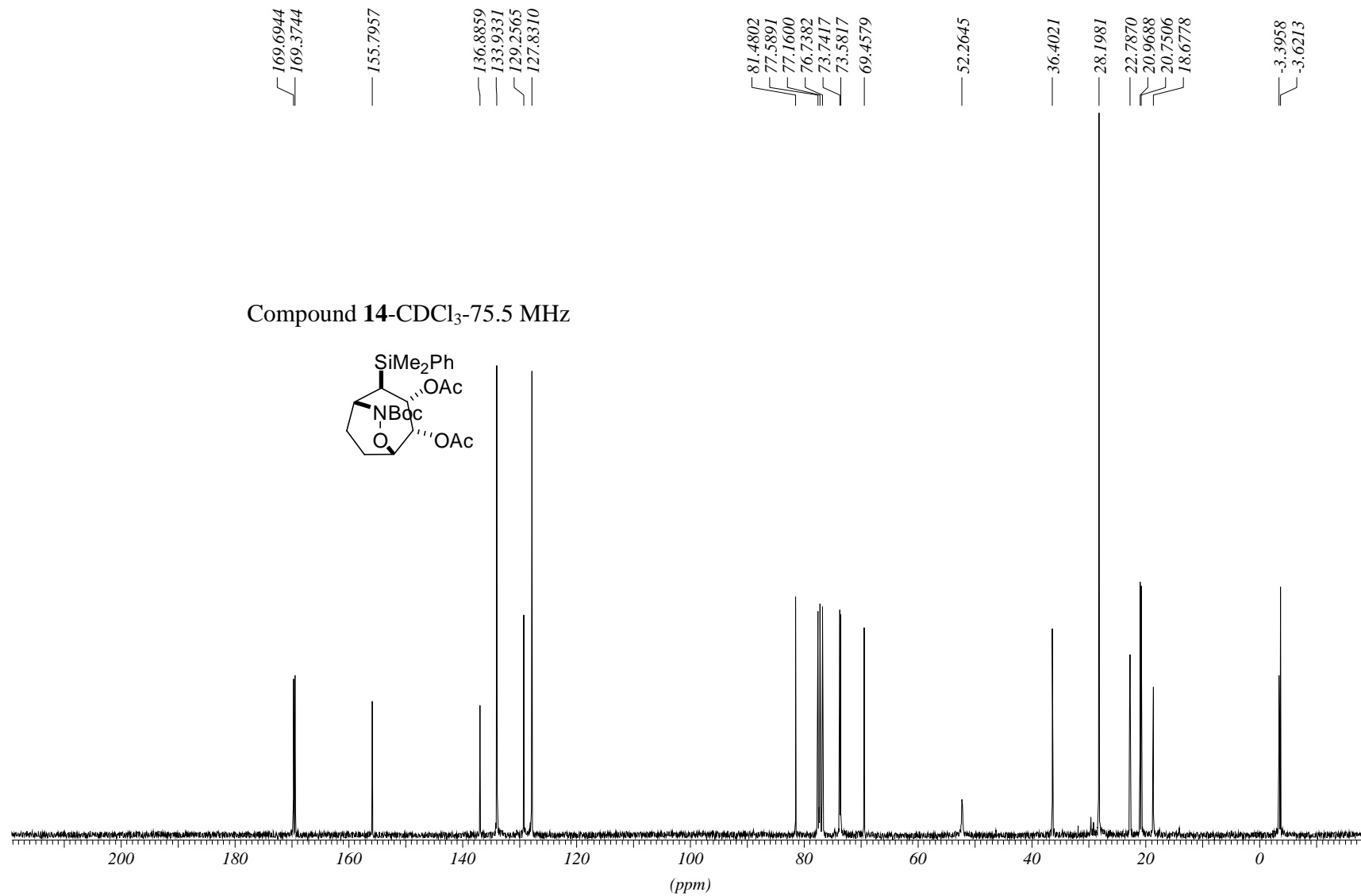


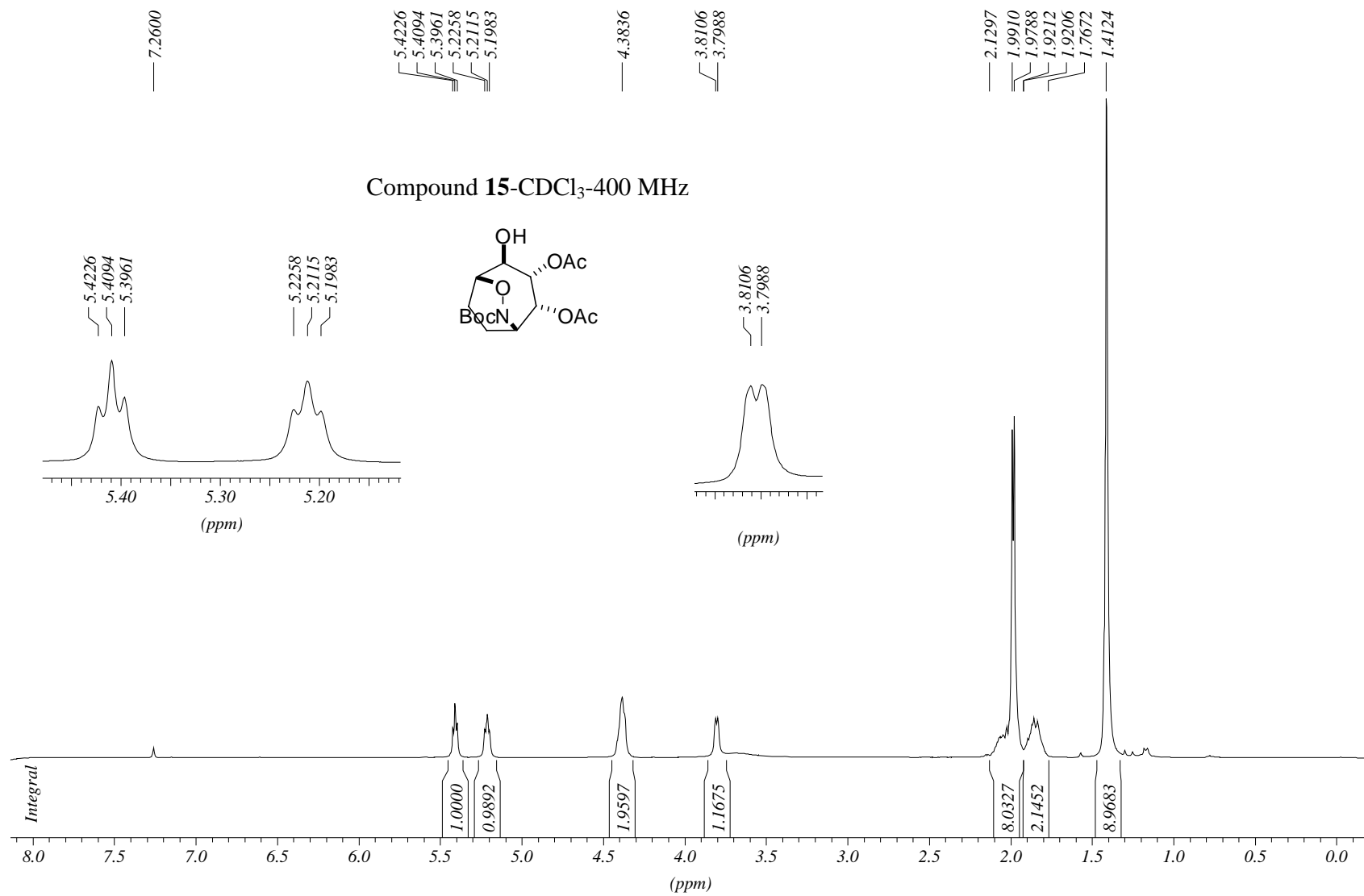


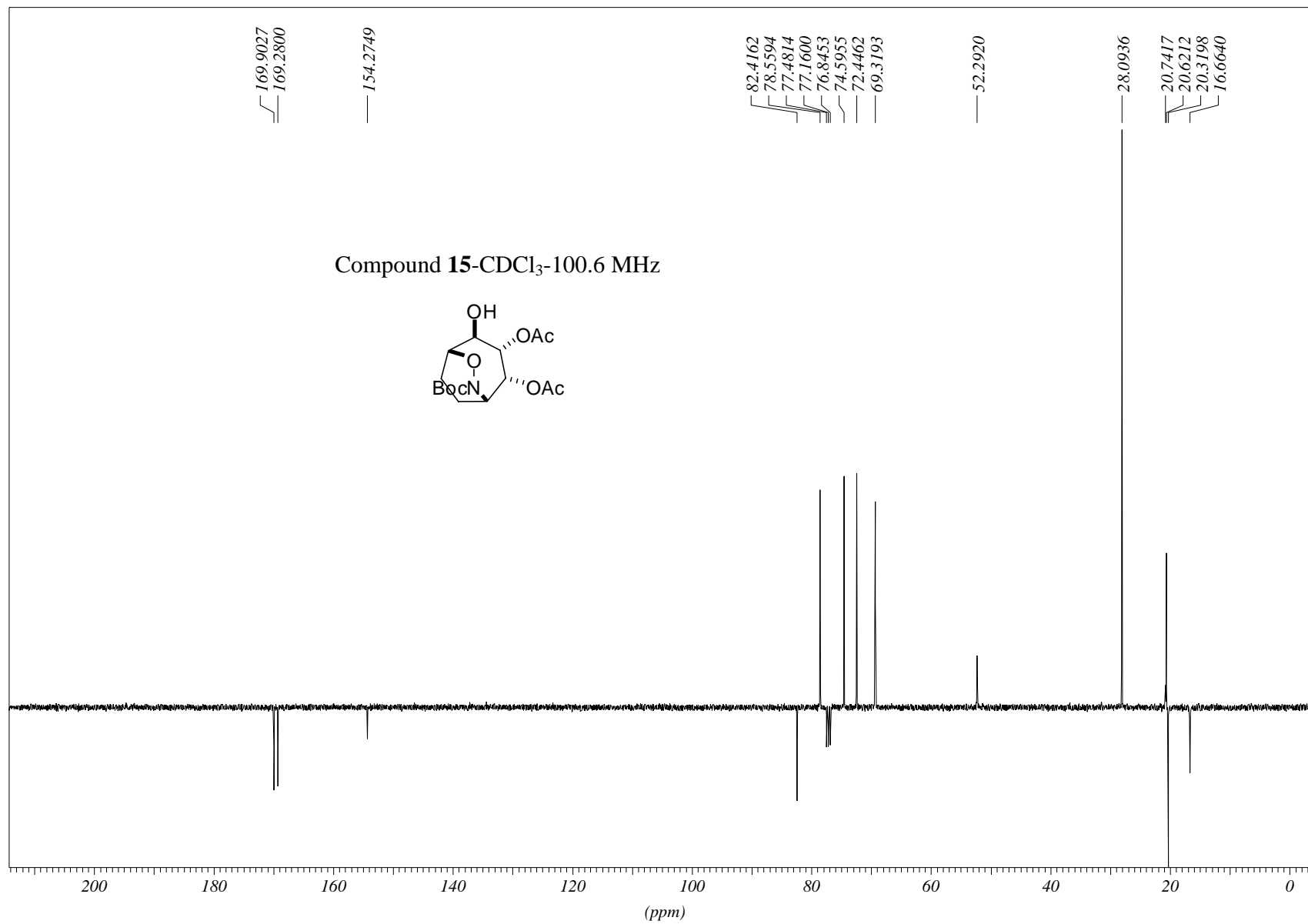


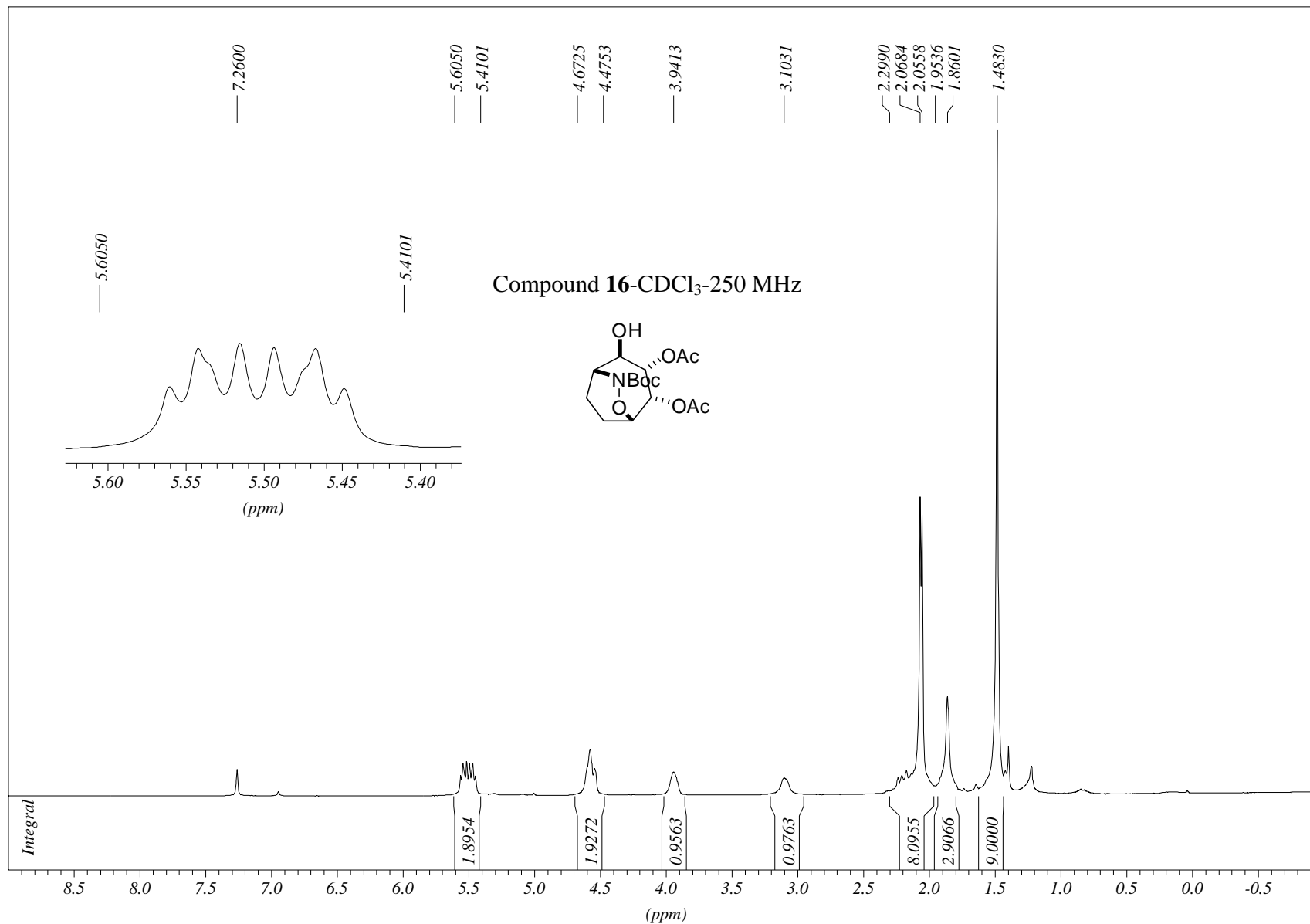


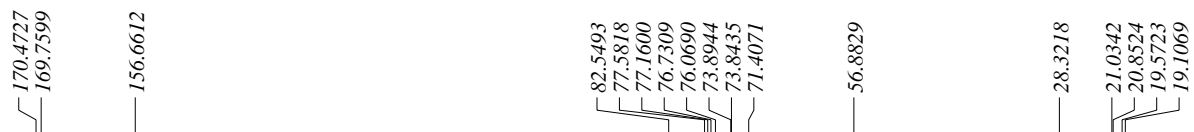




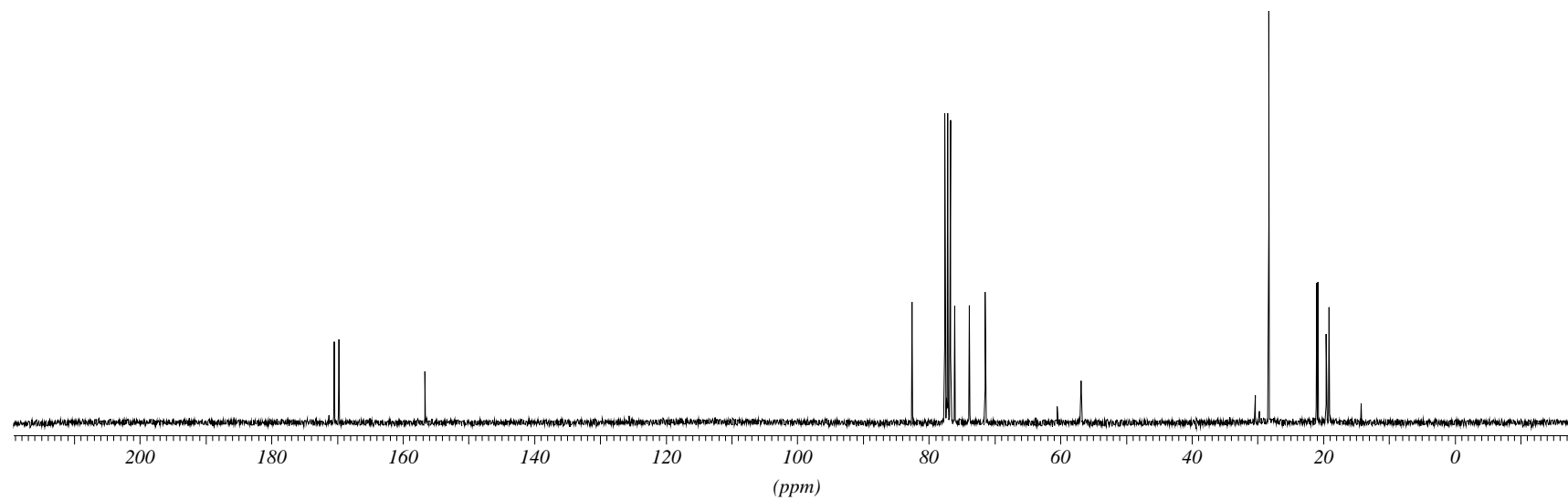
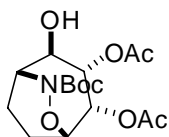


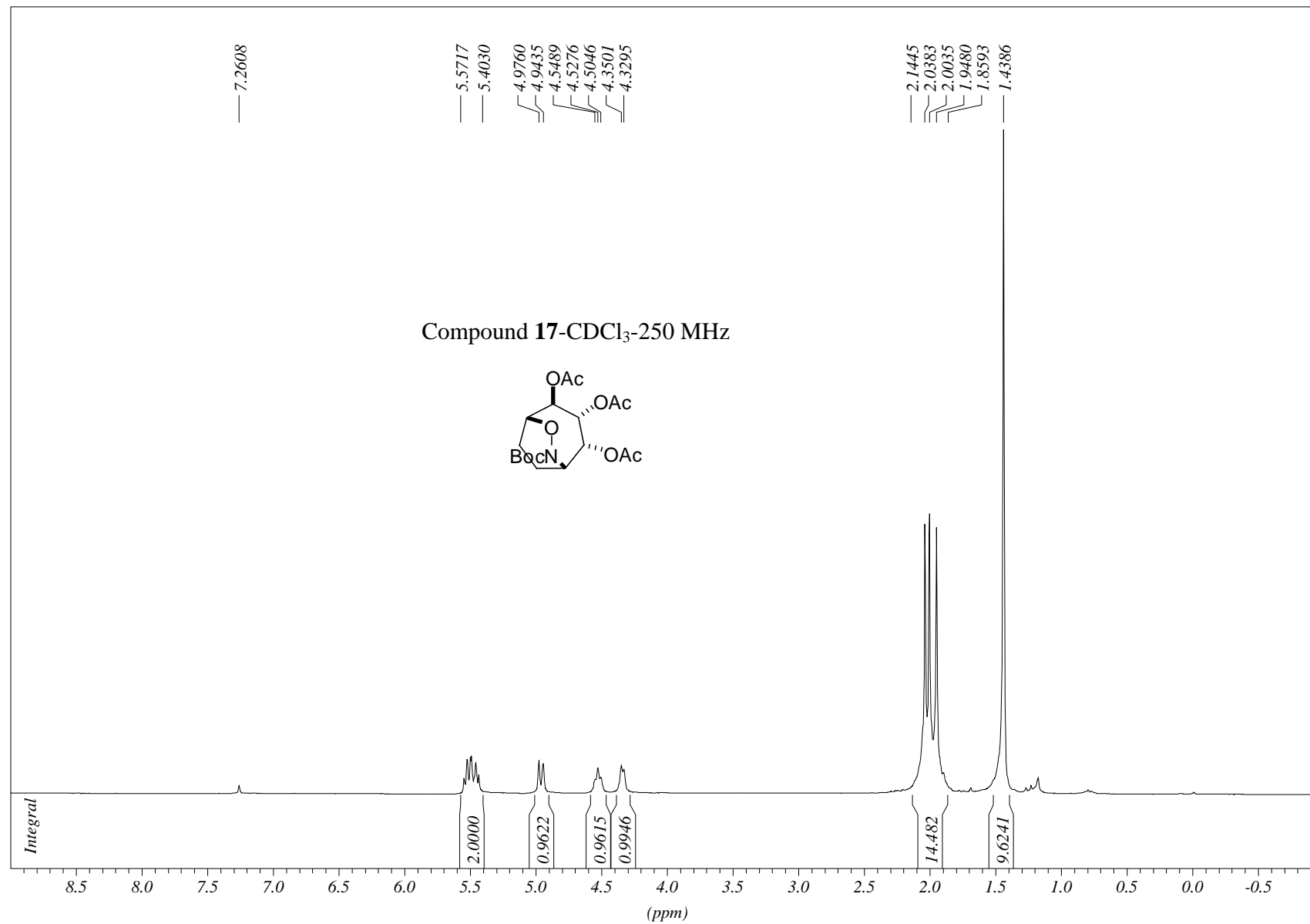


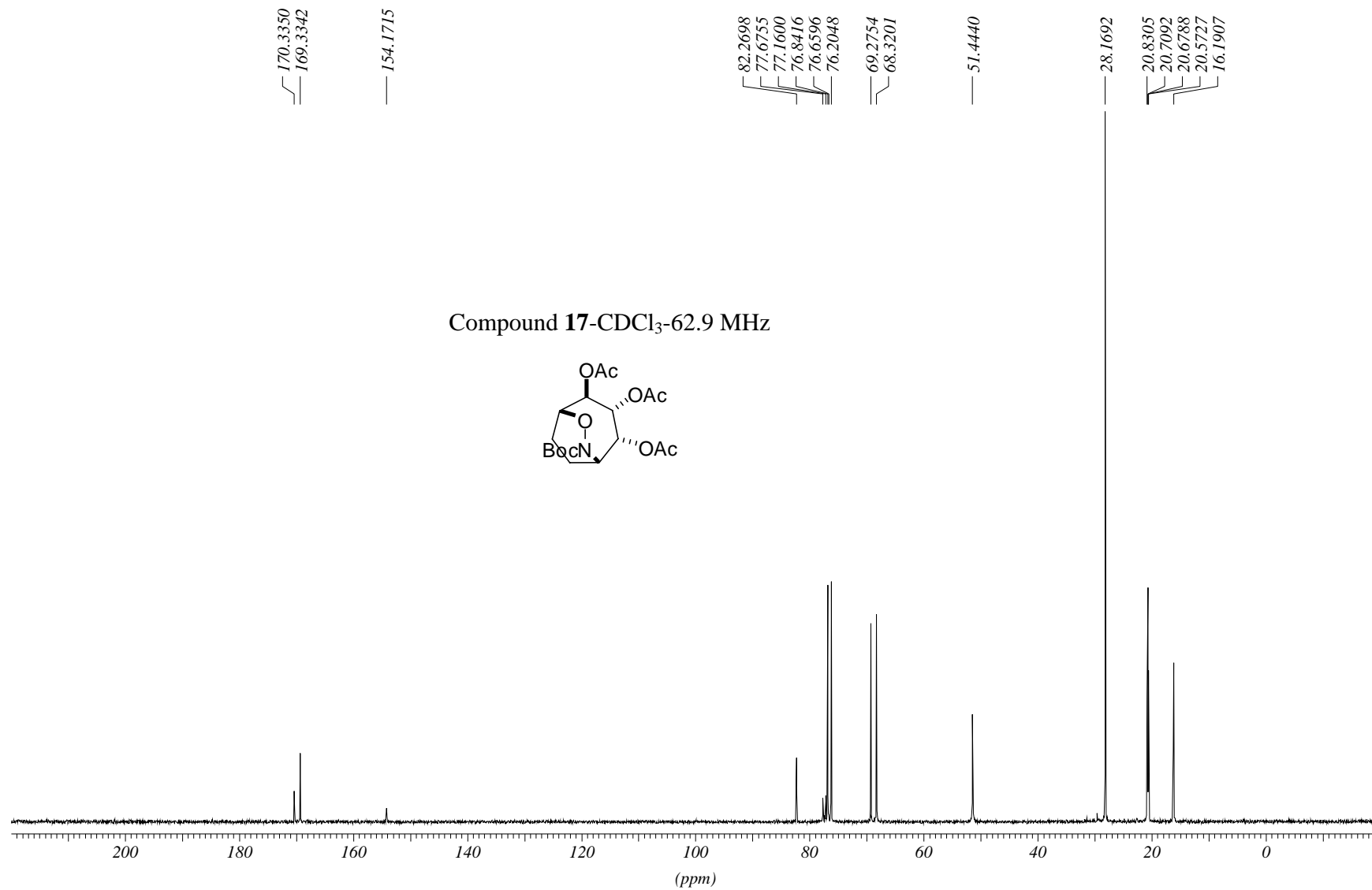


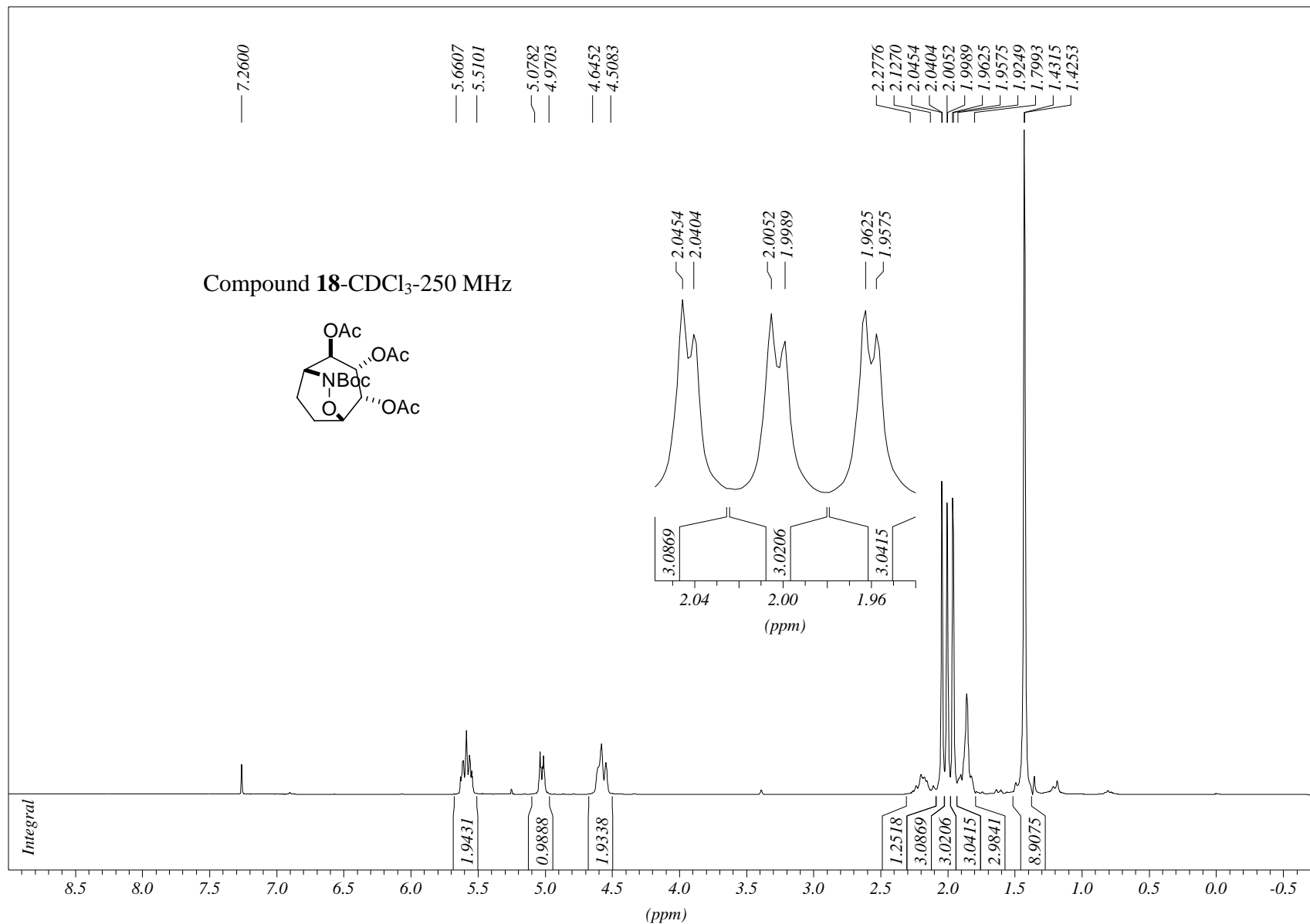


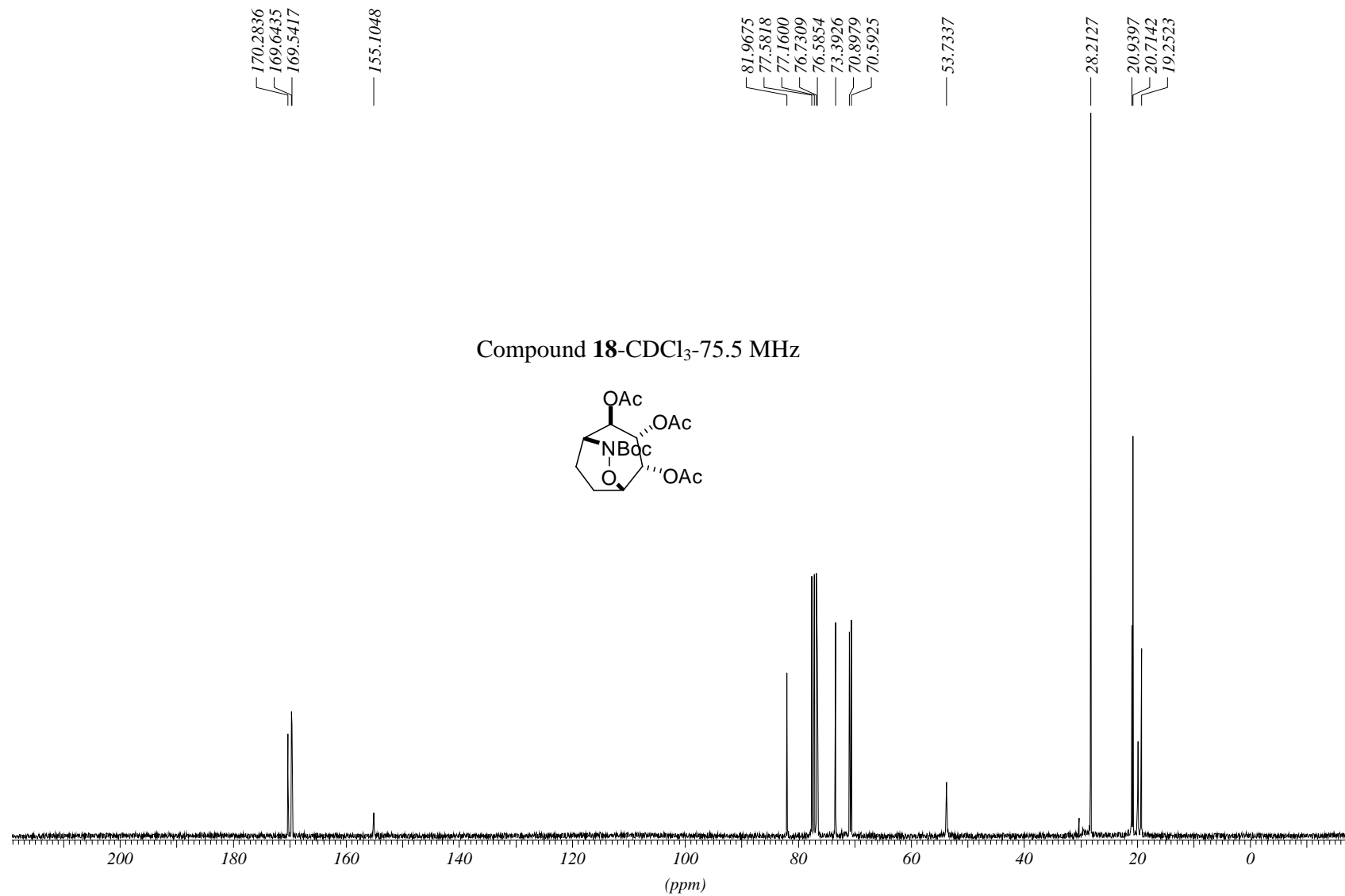
Compound **16**-CDCl₃-75.5 MHz

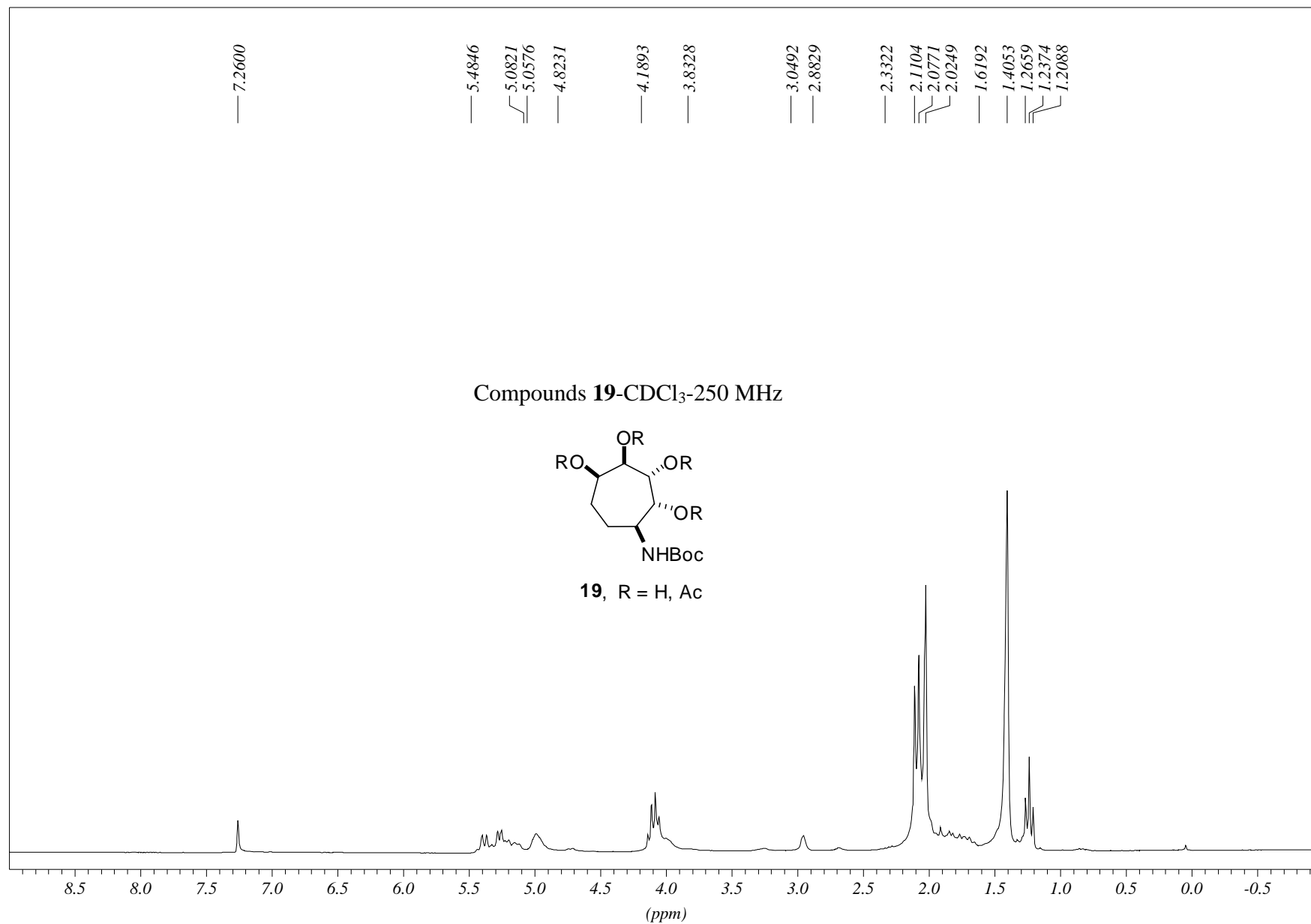


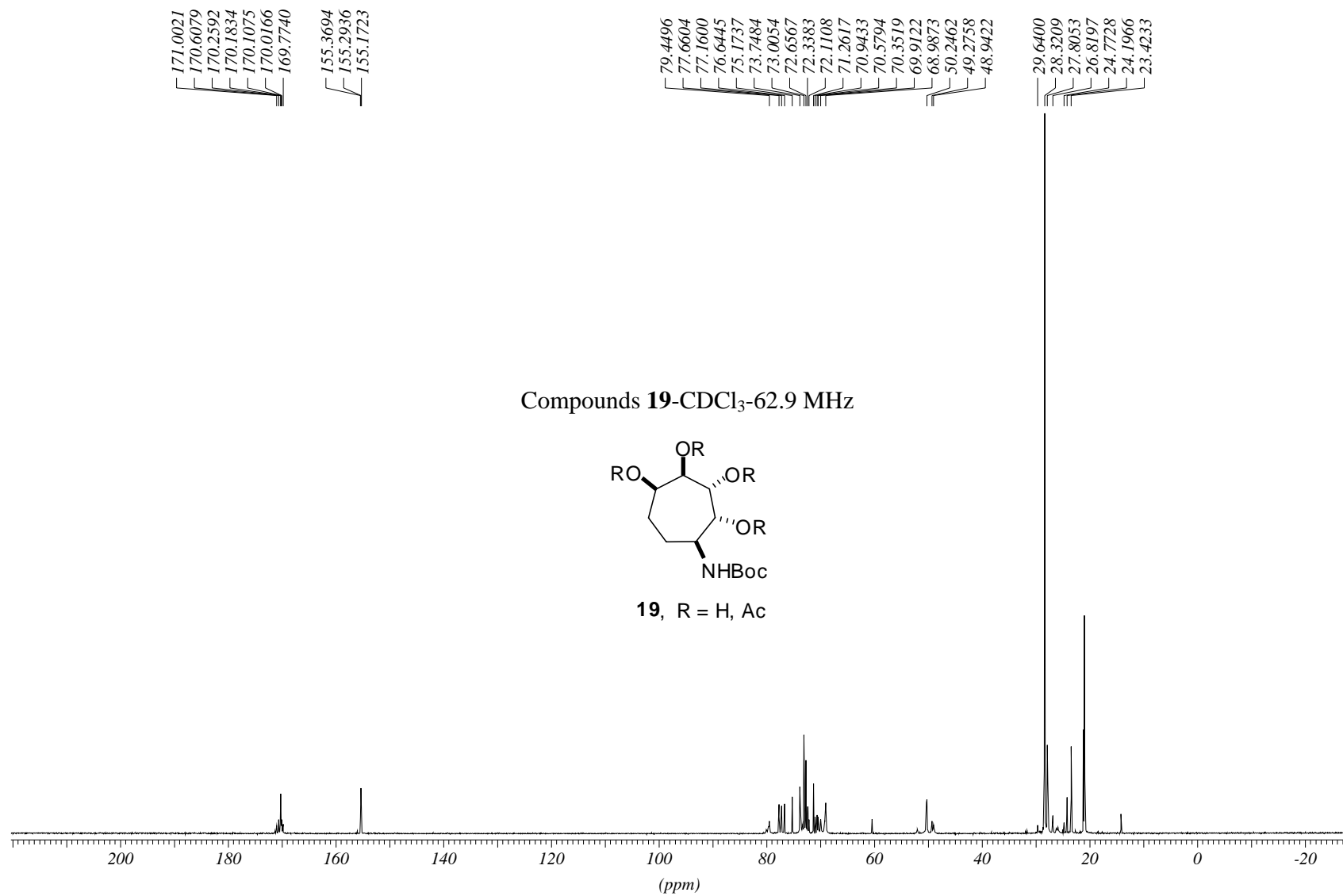


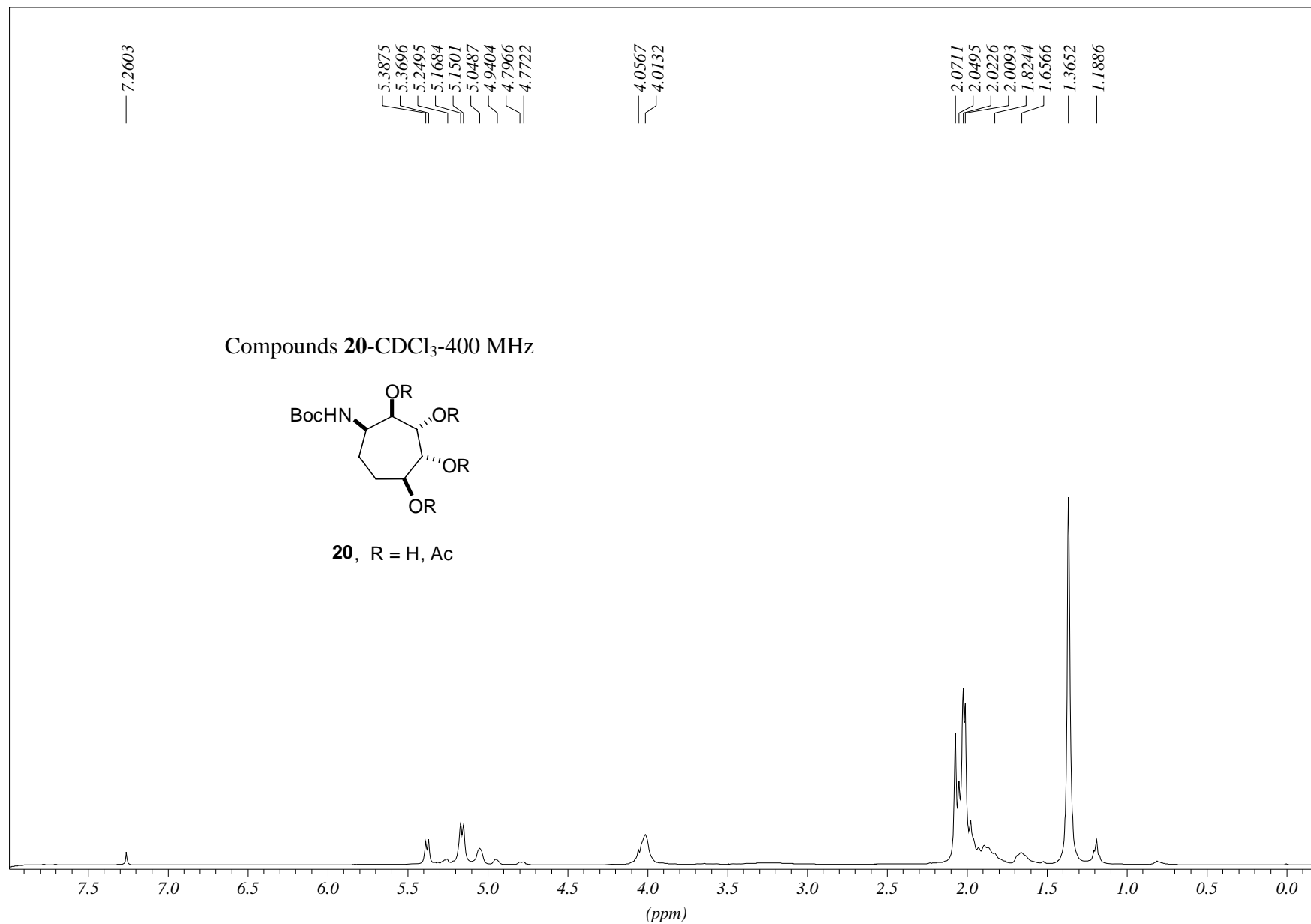


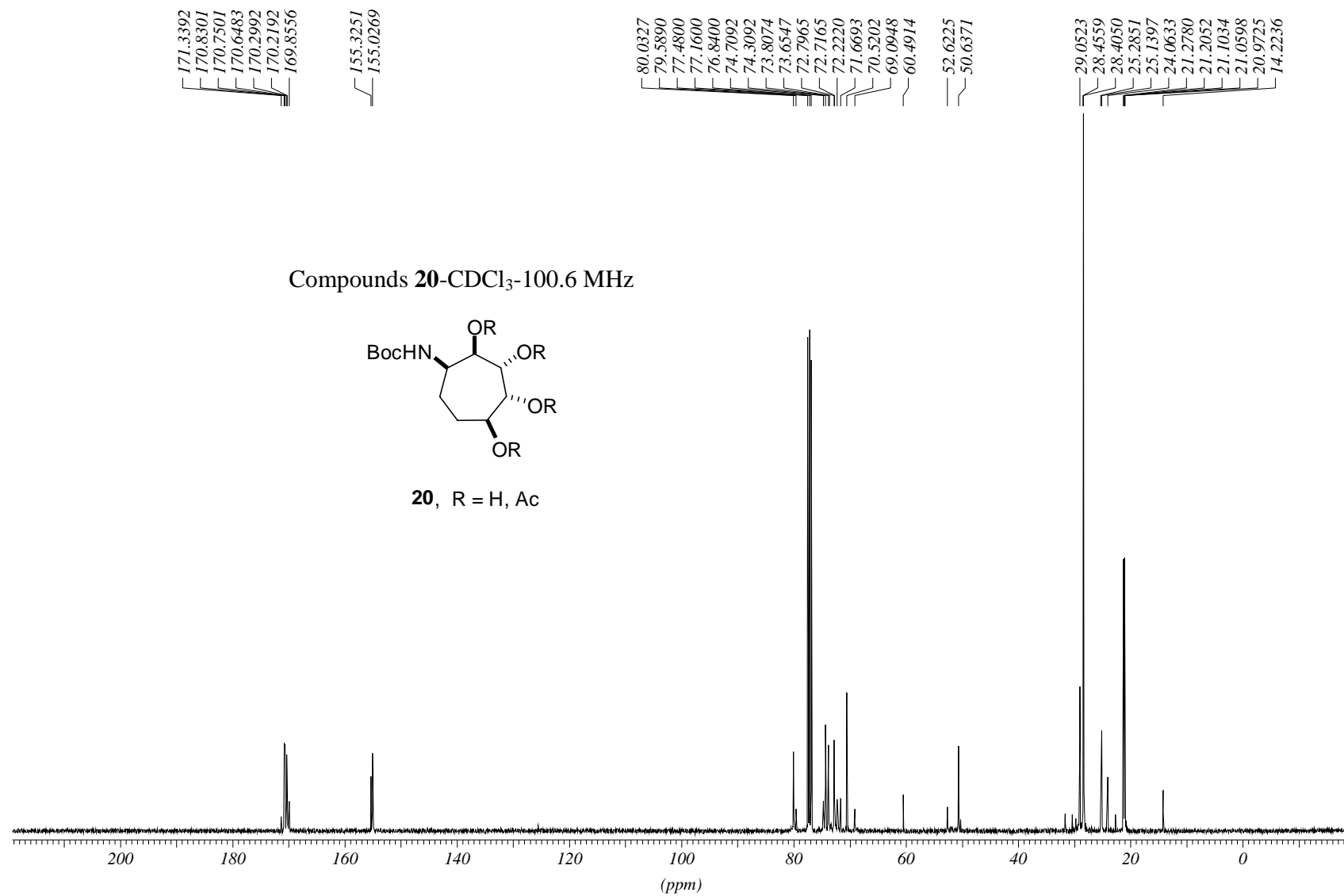


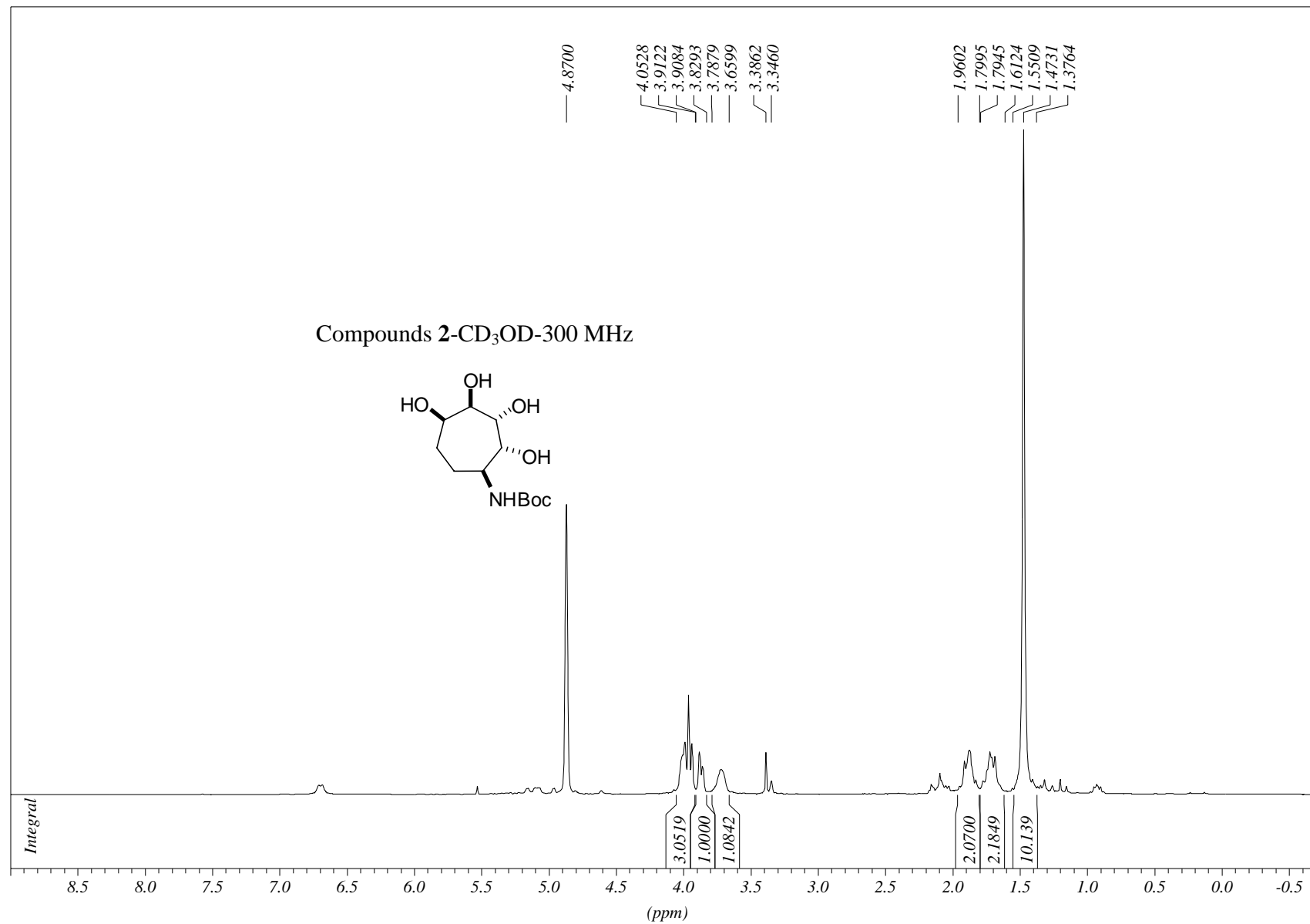


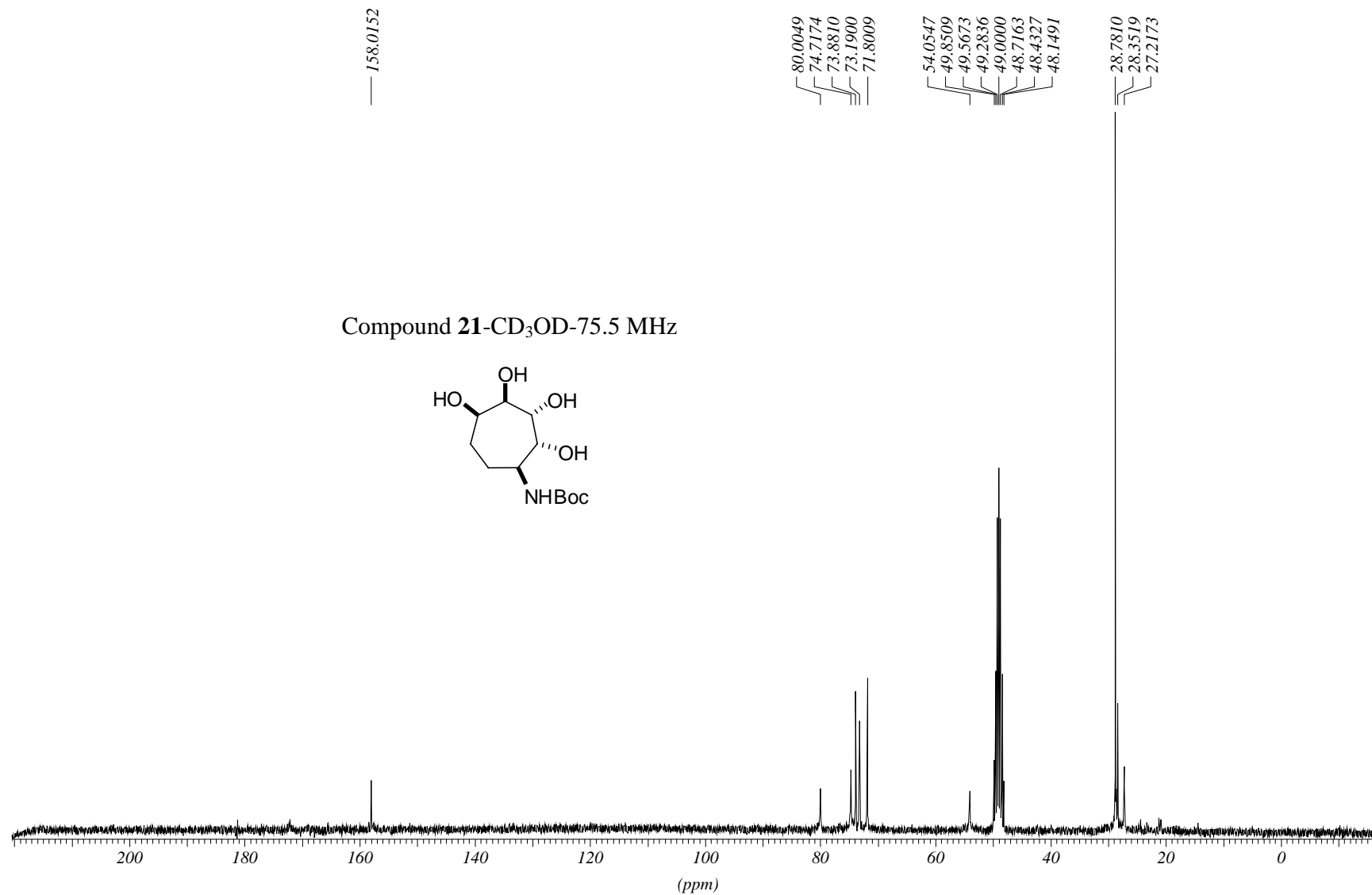


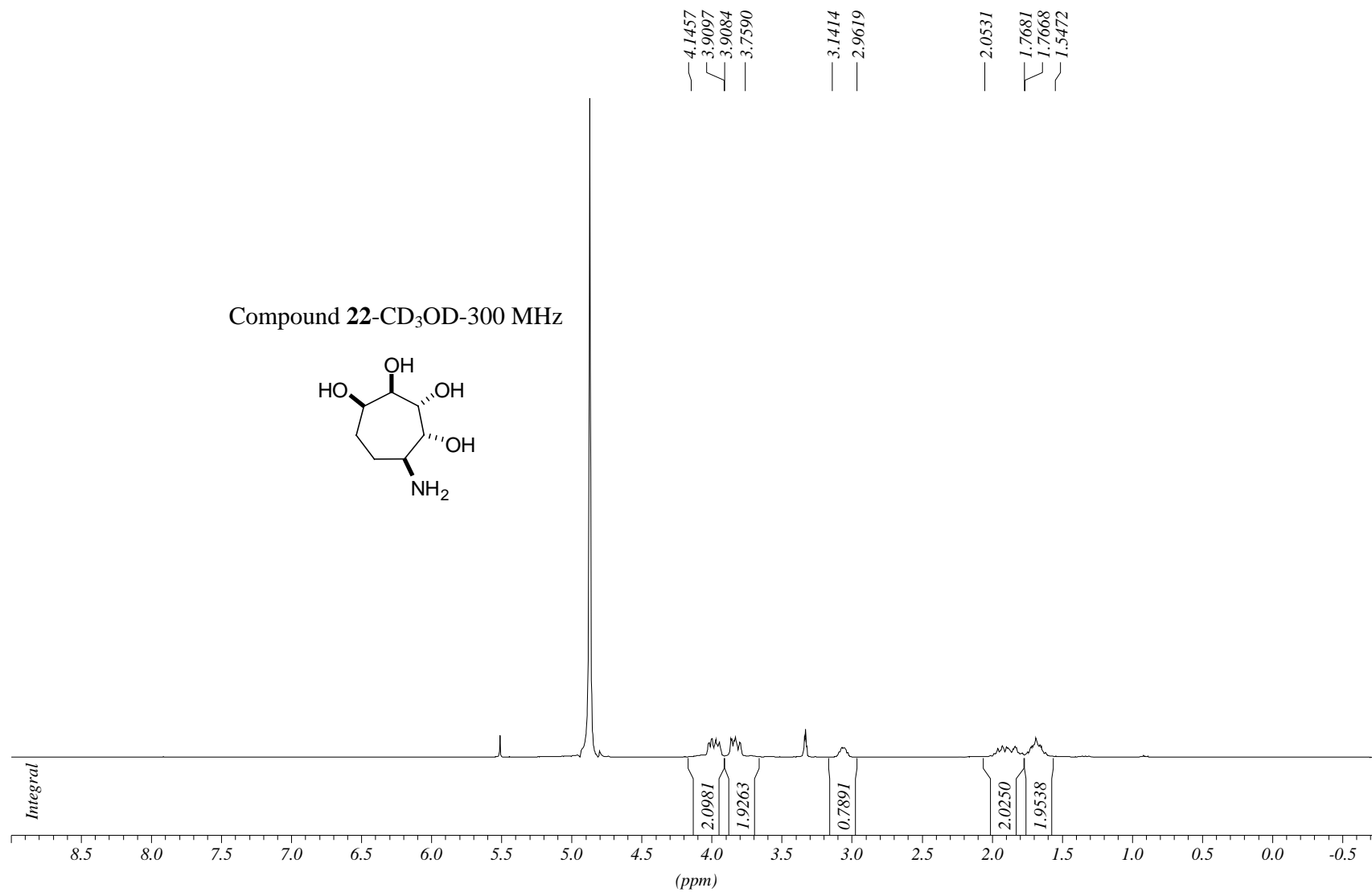












Compound **22**-CD₃OD-75.5 MHz

