Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information

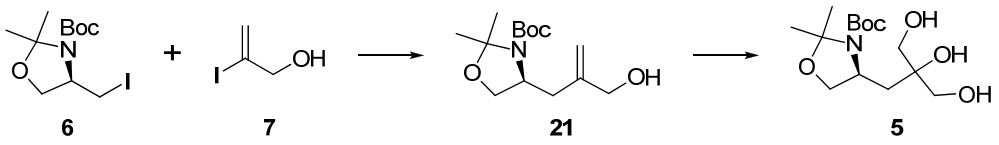
Total Synthesis of (-)-Dysiherbaine

Nelma Carurucan Celindro, Tae Woo Kim and Sung Ho Kang*

Molecular-level Interface Research Center (MIRC)
Department of Chemistry, KAIST,
Daejeon 305-701, Korea.

General Information. NMR spectra were obtained on Bruker DPX400 spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) and measured in $CDCl_3$. Chemical shifts were recorded in ppm relative to internal standard $CDCl_3$ and coupling constants were reported in Hz. The high resolution mass spectra were recorded on VG Autospec Ultima and JMS-700 spectrometers. The enantioselectivities were determined by HPLC. HPLC measurements were done on a DIONEX model equipped with P580G pump, UV 525 detector (Thermo Science, Waltham, MA) measured at 254 nm, and chiral column DAICEL AD-H. Eluting solvent was a mixture of 2-propanol and hexane. All reactions were carried out in oven-dried glassware under a N_2 atmosphere. All solvents were distilled from the indicated drying reagents right before use: Et_2O and THF (Na, benzophenone), CH_2Cl_2 (P_2O_5), and MeCN, 1,4-dioxane and DMF (CaH_2). The normal work-up included extraction, drying over Na_2SO_4 and evaporation of volatile materials in vacuo. Purification by column chromatography was performed using Merck (Darmstadt, Germany) silica gel 60 (230~400 mesh).

∘ Synthesis of the triol **5**



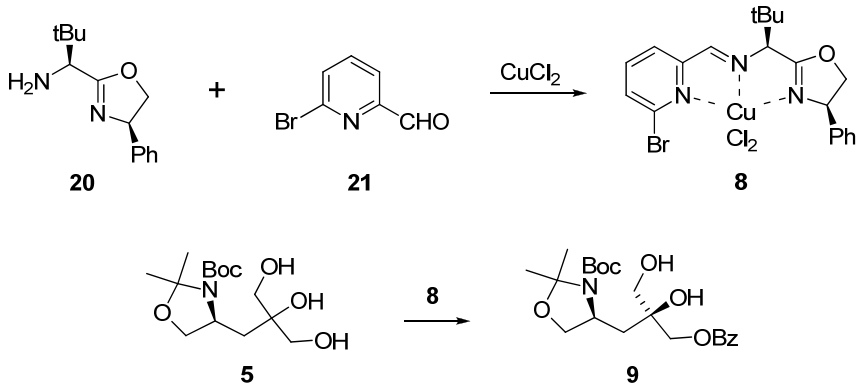
6 **7** **21** **5**

To Zn-Cu couple (959 mg, 14.68 mmol) in THF (5 mL) was added TMSCl (200 μL, 1.58 mmol) and the mixture was stirred at room temperature for 10 minutes. Then, TMEDA (880 μL, 5.87 mmol) and the iodide **6** (2.0 g, 5.86 mmol) dissolved in THF (5 mL) were injected in sequence, and the resulting solution was sonicated with 150W output power at room temperature for 4 hours. The iodide **7** (360 mg, 1.96 mmol) using THF (5 mL and 1 mL) and $Pd(PPh_3)_4$ (452 mg, 0.39 mmol) as solid were added to the sonicated mixture. The reaction mixture was sonicated again with 150W output power between room temperature to 35°C for an hour. The reaction temperature should be maintained below 35°C to minimize the side reactions. After filtering the resulting mixture through celite (5 g) with Et_2O (40 mL), saturated aqueous $NaHCO_3$ (10 mL) was added to the filtrate. Work-up with Et_2O (15mL x 4) and chromatographic purification (EtOAc/hexane = 1/1) gave the alcohol **21** (460 mg, 87 % based on **7**). To **21** (2.2 g, 8.11 mmol) dissolved in a 4 : 1 mixture of acetone and water (20 mL) were added OsO_4 (4 mg, 0.016 mmol) and NMO (1.42 g, 12.16 mmol), and the mixture was stirred at 0°C for 5 hours. After quenching the reaction with saturated aqueous $Na_2S_2O_3$ (20 mL), work-up with EtOAc (20 mL x 7) followed by chromatographic separation (EtOAc/hexane = 4/1) afforded **5** (2.47 g, 99.7 %).

For **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (1H, br s), 3.98 (1H, t, J = 8.6 Hz), 3.84 (1H, d, J = 8.7 Hz), 3.58 (2H, dd, J = 11.8, 2.6 Hz), 3.47 (2H, t, J = 9.1 Hz), 3.34 (2H, br s),

1.85–1.76 (2H, m), 1.51 (3H, s), 1.45 (9H, s), 1.42 s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 93.2, 81.2, 73.8, 69.5, 66.6, 65.0, 53.3, 38.2, 28.4, 27.3, 24.3; HRMS (ESI) calcd for $C_{14}H_{27}NO_6$ [$(M + Na)^+$]: 328.1730, found: 328.1776; $[\alpha]_D^{28}$ +30.5° (c 1.9, MeOH).

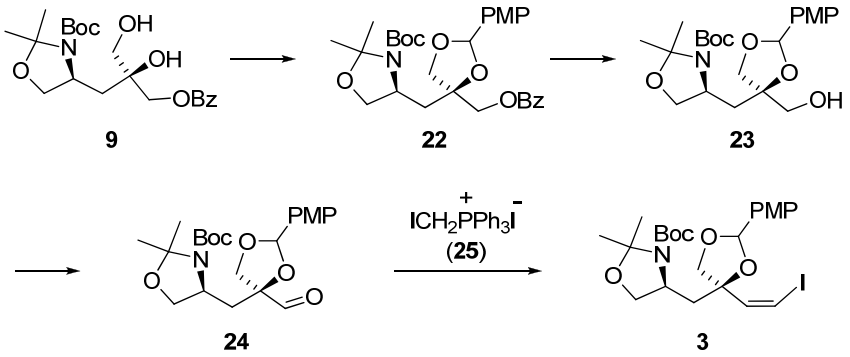
∘ Synthesis of the monobenzoate **9**



Phenyloxazolineamine **20** (376 mg, 1.618 mmol) in CH_2Cl_2 (5 mL) was stirred with bromopyridinecarboxaldehyde **21** (301 mg, 1.618 mmol) in the presence of $MgSO_4$ (974 mg, 8.09 mmol) at room temperature for an hour. Then, $CuCl_2$ (218 mg, 1.618 mmol) was added and stirred at that temperature for 4 hours. The mixture was filtered through celite (1 g) with CH_2Cl_2 (15 mL) and evaporated in vacuo to generate the catalyst **8**. To **5** (2.47 g, 8.09 mmol) in THF (130 mL) were injected the residue **8** in THF (5 mL), Et_3N (1.35 mL, 9.71 mmol) and benzoyl chloride (1.13 mL, 9.71 mmol) sequentially. After stirring the reaction solution at room temperature for 10 minutes, it was quenched with saturated aqueous NH_4Cl (50 mL), worked up with EtOAc (30 mL x 4) and purified by column chromatography (EtOAc/hexane = 1/2) to produce the desired **9** (3.25 g, 98 %) along with its diastereomer (16 mg, 0.5 %).

For **9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (2H, d, J = 7.2 Hz), 7.54 (1H, t, J = 7.3 Hz), 7.41 (2H, t, J = 7.6 Hz), 4.42 (1H, br s), 4.28–4.21 (2H, m, two overlap signals), 4.17 (1H, app. d, J = 5.0 Hz), 3.99 (1H, t, J = 8.5 Hz), 3.79 (1H, d, J = 8.8 Hz), 3.55 (2H, d, J = 6.7 Hz), 2.96 (1H, t, J = 6.5Hz), 2.06 (1H, dd, J = 14.7, 4.3 Hz), 1.91 (1H, dd, J = 14.6, 6.3 Hz), 1.49 (3H, s), 1.48 (9H, s), 1.44 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 153.2, 133.2, 129.7, 128.4, 93.5, 81.3, 72.5, 69.4, 66.6, 65.9, 53.3, 39.3, 28.4, 27.4, 24.4; HRMS (ESI) calcd for $C_{21}H_{31}NO_7$ [$(M + Na)^+$]: 432.1993, found: 432.2062; $[\alpha]_D^{28}$ +18.7^{o} (c 1.1, MeOH).

∘ Synthesis of the vinyl iodide **3**



To **9** (3.25 g, 7.94 mmol) in benzene (30 mL) were added PPTS (599 mg, 2.38 mmol) and 4-methoxybenzaldehyde dimethyl acetal (2.7 mL, 15.88 mmol). The mixture was stirred at room temperature for 30 minutes, quenched with saturated aqueous $NaHCO_3$ (30 mL) and worked up with Et_2O (20 mL x 4). The residue was purified by column chromatography (EtOAc/hexane = 1/2) to furnish a 1.5 : 1 mixture of the corresponding benzylidenes **22** (4.06 g, 97 %) along with the recovered **9** (81 mg, 2.5 %). $LiAlH_4$ (438 mg, 11.55 mmol) was added to **22** (4.06 mg, 7.7 mmol) in Et_2O (20 mL) at 0^{o}C and they

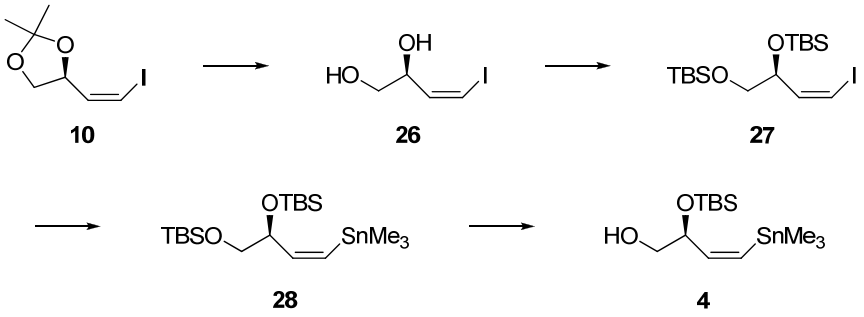
were stirred at that temperature for 40 minutes. After quenching the reaction with H_2O (438 μL), 15% aqueous NaOH (438 μL) and H_2O (1.3 mL) at 0°C sequentially, celite (2 g) was added. The mixture was stirred at room temperature for an hour, filtered through a sintered glass funnel and the filter cake was washed with EtOAc (100 mL). After evaporation of the filtrate in vacuo, the residue was purified chromatographically (EtOAc/hexane = 1/3) to provide a mixture of the corresponding alcohols **23** (3.18 g, 97.5 %; 1.9 g for the less polar alcohol, 1.28 g for the more polar alcohol). Dess Martin periodinane (1.5 g, 3.54 mmol) was added to **23** (500 mg, 1.18 mmol) in CH_2Cl_2 (10 mL) and pyridine (1 mL). The oxidation reaction proceeded at 0°C for 8 hours and quenched with saturated aqueous $NaHCO_3$ (10 mL). After work-up with EtOAc (10 mL x 4), the residue was filtered through celite (1 g) with Et_2O (30 mL) and evaporation of the filtrate yielded the crude aldehyde **24**. To the phosphonium salt **25** (1.25 g, 2.36 mmol) dissolved in THF (11.5 mL) was added NaHMDS (1.0 M in THF, 2.36 mL, 2.36 mmol) dropwise at room temperature. The generated ylide was cooled down to –78°C, and HMPA (1.6 mL) and the crude aldehyde **24** using THF (5 mL) were injected into the ylide. After stirring them at –78°C for 30 minutes, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) at 0°C, worked up with EtOAc (10 mL x 4) and separated by column chromatography (EtOAc/hexane = 1:3) to give rise to the *cis*-vinyl iodides (522 mg, 81 %).

For **3** (less polar iodide): ^{1}H NMR (400 MHz, $CDCl_3$, 55°C) δ 7.39–7.35 (2H, m), 6.88–6.85 (3H, m), 6.46 (1H, d, J = 8.8 Hz), 5.90 (1H, s), 4.13 (1H, d, J = 8.9 Hz), 4.04 (2H, d, J = 8.3 Hz), 3.93 (1H, ddd, J = 8.8, 5.3, 0.9 Hz), 3.78 (3H, s), 2.40 (1H, br s), 2.10 (1H, dd, J = 13.6, 10.6 Hz), 1.58 (3H, s), 1.47 (9H, s), 1.46 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 55°C) δ 160.6, 151.8, 143.2, 130.0, 128.1, 113.8, 103.1, 93.1, 84.1, 80.0,

78.7, 75.2, 68.2, 55.3, 54.9, 39.5, 28.6, 27.5; HRMS (ESI) calcd for $C_{23}H_{32}INO_6$ [(M + Na)$^+$]: 568.1166, found: 568.1293.

For **3** (more polar iodide): ^{1}H NMR (400 MHz, $CDCl_3$, 55^{o}C) δ 7.43–7.40 (2H, m), 6.91–6.88 (2H, m), 6.81 (1H, d, J = 8.7 Hz), 6.54 (1H, d, J = 8.7 Hz), 5.90 (1H, s), 5.84 (1H, s), 4.12–4.06 (3H, m), 4.00–3.97 (1H, br m), 3.86 (1H, dd, J = 8.5, 5.5 Hz), 3.79 (3H, s), 2.35 (1H, br s), 2.02 (1H, t, J = 11.0 Hz), 1.54 (3H, s), 1.46 (9H, s), 1.44 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 55^{o}C) δ 160.7, 151.8, 142.0, 129.5, 128.1, 114.0, 104.3, 93.1, 83.5, 79.9, 78.4, 75.9, 68.2, 55.3, 54.9, 41.4, 28.6, 27.4; HRMS (ESI) calcd for $C_{23}H_{32}INO_6$ [(M + Na)$^+$]: 568.1166, found: 568.1293.

∘ Synthesis of the vinyltin **4**

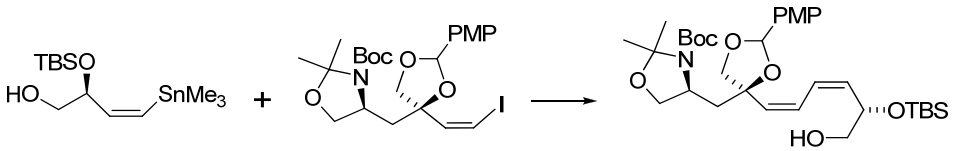


To the acetonide **10** (2.0g, 7.87 mmol) in MeOH (10 mL) was added 6M aqueous HCl (100 μL) and the mixture was stirred at room temperature for 24 hours. After evaporation of all the volatile materials in vacuo, the residue was separated by column chromatography (EtOAc/hexane = 1/1) to render the diol **26** (1.6 g, 95 %). Et_3N (3.13 mL, 22.43 mmol), TBSCl (4.5 g, 29.92 mmol) and DMAP (457 mg, 3.74 mmol) were added sequentially to **26** (1.6 g, 7.48 mmol) in CH_2Cl_2 (30 mL). The reaction mixture

was stirred at room temperature for 12 hours, quenched with saturated aqueous NH_4Cl (30 mL), worked up with Et_2O (20 mL x 3), and the residue was purified chromatographically (Et_2O/hexane = 1/50) to procure the disilyl ether **27** (3.045 g, 92 %). To **27** (3.045 g, 6.88 mmol) in THF (15 mL) were injected $(Me_3Sn)_2$ (2.85 mL, 13.76 mmol) and $Pd(PPh_3)_2Cl_2$ (48 mg, 0.069 mmol) dissolved in DMF (3 mL). After stirring the mixture at room temperature for 24 hours, it was evaporated and purified by column chromatography (petroleum ether) to form the vinyltin **28** (2.67 g, 81 %) along with the starting **27** (304 mg, 10 %). **28** (1.0 g, 2.08 mmol) was stirred in MeOH (10 mL) in the presence of PPTS (52 mg, 0.208 mmol) at 0°C for 48 hours. After evaporation of all the volatile materials in vacuo, the residue was separated chromatographically (Et_2O/hexane = 1/6) to give **4** (570 mg, 75 %) along with the recovered **28** (150 mg, 15 %).

For **4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (1H, dd, J = 13.2, 8.0 Hz), 5.99 (1H, dd, J = 13.1, 1.0 Hz), 4.09–4.04 (1H, m), 3.46–3.56 (2H, m), 1.98 (1H, dd, J = 8.1, 5.0 Hz), 0.87 (9H, s), 0.18 (9H, s), 0.05 (6H, d, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 131.8, 76.9, 67.0, 25.8, 18.1, –3.9, –4.6, –8.4; HRMS (ESI) calcd for $C_{13}H_{30}O_2SiSn$ [$(M + Na)^+$]: 389.0929, found: 389.0992.

∘ Synthesis of the dienes **2**



4 **3** **2**

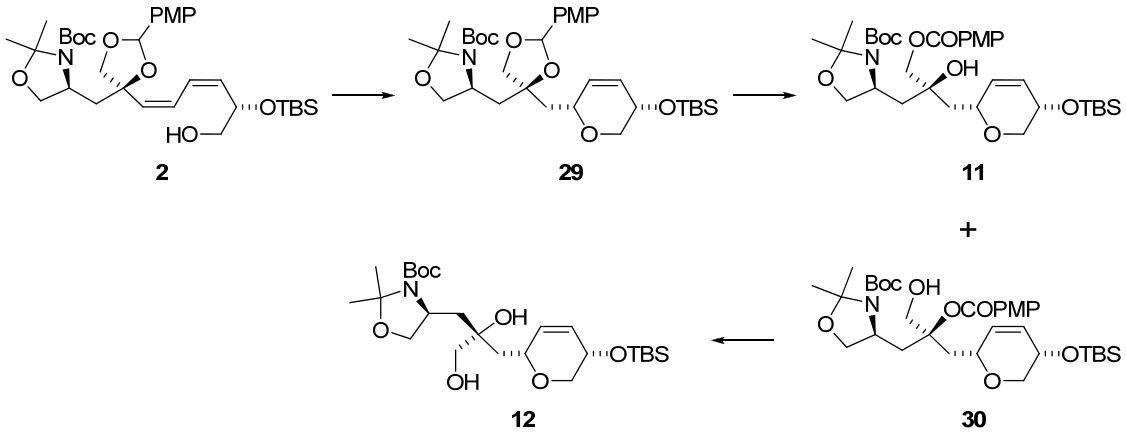
To **4** (803 mg, 2.20 mmol) in DMF (5 mL) were added $Pd(PPh_3)_4$ (211 mg, 0.183

mmol), CsF (556 mg, 3.66 mmol), CuI (70 mg, 0.37 mmol) and **3** (1.0 g, 1.83 mmol) using DMF (10 mL) consecutively. After stirring the mixture at room temperature for 4 hours, it was quenched with H_2O (15 mL), worked up with Et_2O (15 mL x 4) and purified by column chromatography (Et_2O/hexane = 1/2) to afford the dienes **2** (964 mg, 85 %).

For **2** (less polar diene): ^{1}H NMR (400 MHz, $CDCl_3$, 55^{o}C) δ 7.36–7.33 (2H, m), 6.88–6.84 (2H, m), 6.36 (2H, app. t, J = 11.6 Hz), 5.89 (1H, s), 5.67 (1H, br s), 5.36 (1H, t, J = 7.7 Hz), 4.66 (1H, app. q, J = 5.8 Hz), 4.13–4.08 (2H, m, two overlap signals), 4.02 (1H, br s), 3.93-3.87 (2H, m, two overlap signals), 3.78 (3H, s), 3.50–3.40 (2H, m, two overlap signals), 2.13–2.07 (2H, m, two overlap signals), 1.55 (3H, s), 1.45 (9H, s), 1.44 (3H, s), 0.88 (9H, s), 0.06 (6H, d, J = 10.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 55^{o}C) δ 160.6, 151.8, 133.6, 130.0, 128.1, 125.9, 124.8, 113.9, 103.5, 93.0, 83.9, 80.1, 77.1, 69.7, 68.0, 66.8, 55.3, 40.6, 28.6, 27.4, 25.9, 18.2, –4.3, –4.7; HRMS (ESI) calcd for $C_{33}H_{53}NO_8Si$ [$(M + Na)^+$]: 642.3432, found: 642.3588.

For **2** (more polar diene): ^{1}H NMR (400 MHz, $CDCl_3$, 55^{o}C) δ 7.39–7.37 (2H, m), 6.90–6.88 (2H, m), 6.56 (1H, br s), 6.41 (1H, t, J = 11.7 Hz), 5.74 (1H, s), 5.58 (1H, br s), 5.44 (1H, ddd, J = 9.9, 8.4, 1.2 Hz), 4.70 (1H, q, J = 6.0 Hz), 4.11 (1H, dd, J = 8.9, 1.4 Hz), 3.98 (3H, q, J = 7.7 Hz), 3.82 (1H, dd, J = 8.9, 5.5 Hz), 3.79 (3H, s), 3.49–3.46 (2H, m), 2.25 (1H, br s), 2.02 (1H, t, J = 11.1 Hz), 1.53 (3H, s), 1.44 (9H, s), 1.42 (3H, s), 0.89 (9H, s), 0.07 (6H, d, J = 9.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 55^{o}C) δ 160.7, 151.8, 134.3, 133.7, 129.6, 128.1, 125.4, 125.1, 114.0, 104.0, 92.9, 84.0, 79.9, 77.1, 69.7, 67.8, 66.8, 55.3, 42.3, 28.5, 27.3, 25.8, 18.1, –4.3, –4.7; HRMS (ESI) calcd for $C_{33}H_{53}NO_8Si$ [$(M + Na)^+$]: 642.3432, found: 642.3588.

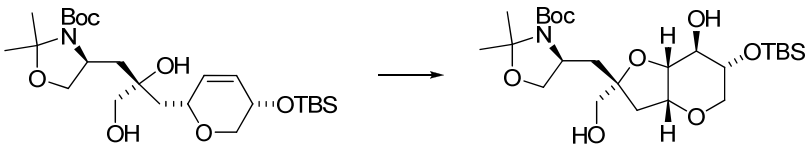
∘ Synthesis of the diol **12**



To the dienes **2** (150 mg, 0.24 mmol) dissolved in toluene (3 mL) were added $Hg(CF_3CO_2)_2$ (124 mg, 0.29 mmol) and K_2CO_3 (66 mg, 0.48 mmol) at –30°C in sequence, and the mixture was stirred at that temperature for 3 hours. After cooling down the resulting solution to –78°C, THF (3 mL), Et_3B (0.24 mL, 0.24 mmol) and $LiBH_4$ (2.0M in THF, 0.13 mL, 0.26 mmol) were injected into the solution, and the mixture was stirred at –78°C for 15 minutes. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) at 0°C. Work-up with EtOAc (5 mL x 3) and chromatographic separation (EtOAc/hexane = 1/4) furnished the dihydropyran **29** (84 mg, 70%). To **29** (150 mg, 0.24 mmol) in benzene (4 mL) were added 4Å molecular sieve (30 mg) and DDQ (71 mg, 0.31 mmol) at room temperature, and the mixture was stirred at that temperature for 18 hours. After addition of 15% aqueous NaOH (2 mL), work-up with EtOAc (3 mL x 3) gave the crude benzoate **11** and **30**. All the crude benzoates were dissolved in methanol (3 mL), K_2CO_3 (66mg, 0.48 mmol) was added, and the solution was stirred at room temperature for 2 hours. After removal of methanol in vacuo, the

residue was dissolved in H_2O (5 mL), worked up with EtOAc (3 mL x 4) and purified by column chromatography (EtOAc/hexane = 1/2) to deliver the diol **12** (115 mg, 95%). For **12**: ^{1}H NMR (400 MHz, $CDCl_3$, 55°C) δ 5.79 (1H, dddd, J = 10.3, 3.9, 2.1, 0.8 Hz), 5.73 (1H, app. d, J = 10.4 Hz), 4.32 (1H, dt, J = 9.8, 2.3 Hz), 4.03 (2H, tdd, J = 4.3, 2.2, 1.0 Hz), 3.99 (1H, br s), 3.96 (1H, dd, J = 8.8, 5.6 Hz), 3.75 (1H, dd, J = 11.6, 3.2 Hz), 3.65 (1H, dd, J = 11.6, 3.6 Hz), 3.58–3.44 (3H, m), 2.04–1.81 (2H, m), 1.72 (1H, dd, J = 15.0, 2.8 Hz), 1.53 (3H, s), 1.47 (9H, s), 1.46 (3H, s), 0.89 (9H, s), 0.07 (6H, d, J = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 55°C) δ 152.4, 132.3, 127.6, 93.1, 80.2, 77.2, 73.5, 71.2, 69.3, 69.2, 63.2, 54.1, 41.6, 40.5, 28.6, 27.3, 25.9, 18.2, –4.3, –4.4; HRMS (ESI) calcd for $C_{25}H_{47}NO_7Si$ $[(M + Na)^+]$: 524.3014, found: 524.3057; $[\alpha]_D^{23}$ +40.6° (c 1.0, MeOH).

∘ Synthesis of the bicyclic alcohol **14**



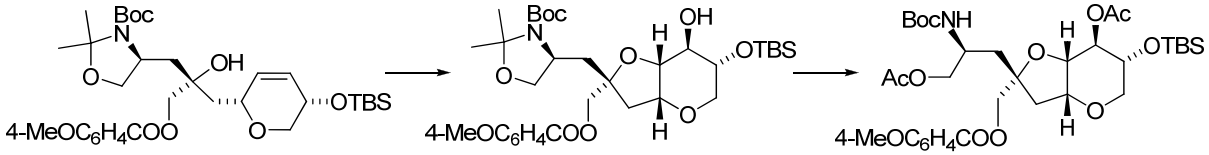
12 **14**

To the diol **12** (115 mg, 0.23 mmol) in MeCN (6 mL) were added aqueous Na_2EDTA solution (4 x 10^{-4} M in H_2O, 2 mL), CF_3COCH_3 (0.69 mL, 7.7 mmol), $NaHCO_3$ (580 mg, 6.9 mmol) and OXONE® (1.41 g, 2.3 mmol) at 0°C successively. After stirring the mixture at 0°C for 40 minutes, aqueous work-up was carried out using EtOAc (3 mL x 4). The crude product was dissolved in $CDCl_3$ (1 mL) and stirred at room temperature

for an hour. Evaporation of $CDCl_3$ in vacuo followed by chromatographic purification (EtOAc/hexane = 1/2) offered the bicyclic alcohol **14** (103 mg, 87%)

For **14**: ^{1}H NMR (400 MHz, $CDCl_3$, 55°C) δ 4.21–4.13 (1H, m), 3.95 (3H, br s), 3.88 (1H, br s), 3.73 (1H, dd, J = 11.9, 2.2 Hz), 3.67–3.54 (3H, m), 3.47 (1H, dd, J = 11.2, 3.4 Hz), 3.41 (1H, dd, J = 11.3, 8.3 Hz), 3.16 (1H, br s), 2.27 (1H, br s), 2.19 (1H, app. d, J = 14.0 Hz), 2.04 (1H, br s), 1.83 (2H, d, J = 9.2 Hz), 1.52 (3H, s), 1.46 (9H, s), 1.45 (3H, s), 0.90 (9H, s), 0.09 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 55°C) δ 151.9, 93.2, 85.3, 81.1, 80.1, 75.6, 69.4, 68.7, 68.6, 66.7, 54.0, 40.7, 39.0, 28.6, 27.3, 25.8, 18.3, –4.9; HRMS (ESI) calcd for $C_{25}H_{47}NO_8Si$ [(M + Na)$^+$]: 540.2963, found: 540.3004; $[\alpha]_D^{24}$ –11.3° (c 1.0, MeOH).

∘ Synthesis of the diacetate **15**

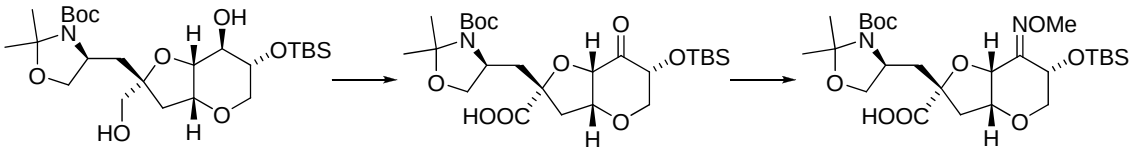


To the purified benzoate **11** (10 mg, 0.016 mmol) in MeCN (0.6 mL) were added aqueous Na_2EDTA solution (4 x 10^{-4} M in H_2O, 0.2 mL), CF_3COCH_3 (0.05 mL, 0.56 mmol), $NaHCO_3$ (40 mg, 0.48 mmol) and OXONE® (90 mg, 0.15 mmol) at 0°C successively. After stirring the mixture at 0°C for 30 minutes, aqueous work-up was carried out using EtOAc (2 mL x 4). The crude product was dissolved in $CDCl_3$ (0.3 mL) and stirred at 0 to 10 °C for 15 minutes. Evaporation of $CDCl_3$ in vacuo followed by chromatographic purification (EtOAc/hexane = 1/3) offered the bicyclic alcohol **13**

(8 mg, 75%). To **13** (8 mg, 0.012 mmol) dissolved in undried MeCN (0.04 mL) was added $InCl_3$ (5 mg, 0.018 mmol) at room temperature. After stirring the mixture at room temperature for 3 hours, the reaction was quenched with H_2O (1 mL). Work-up with EtOAc (1 mL x 4) and chromatographic separation rendered the diol (7 mg, 95%). Ac_2O (0.003 mL, 0.033 mmol) and DMAP (0.7 mg, 0.006 mmol) were added in sequence to the prepared diol (7 mg, 0.011 mmol) dissolved in CH_2Cl_2 (0.05 mL) and Et_3N (0.005 mL). The resulting mixture was stirred at room temperature for 30 minutes. After quenching the reaction with saturated aqueous NaCl (0.5 mL), workup with EtOAc (1 mL x 3) and chromatographic purification (EtOAc/hexane = 1/2) produced the diacetate **15** (7.7 mg, 100%).

For **15**: ^{1}H NMR (400 MHz, C_6D_6, RT) δ 8.19–8.16 (2H, m), 6.67–6.63 (2H, m) 5.26 (1H, br s), 4.91 (1H, d, J = 10.8 Hz), 4.75 (1H, br d, J = 6.8 Hz), 4.66 (1H, d, J = 10.8 Hz), 4.23–4.21 (2H, m), 3.98–3.94 (1H, m), 3.90–3.88 (1H, br m), 3.83 (1H, br s), 3.66 (1H, d, J = 12.0 Hz), 3.53 (1H, d, J = 2.0 Hz), 3.38 (1H, dd, J = 12.0, 1.6 Hz), 3.14 (3H, s), 2.30 (1H, d, J = 14.4 Hz), 2.02 (1H, dd, J = 14.4, 4.8 Hz), 1.77 (1H, dd, J = 14.8, 4.8 Hz), 1.67 (1H, app. dd, J_b = 6 Hz, overlap with OAc), 1.62 (6H, s), 1.44 (9H, s), 1.01 (9H, s), 0.19 (6H, d, J = 28.0 Hz); HRMS (ESI) calcd for $C_{34}H_{53}NO_{12}Si$ $[(M + Na)^+]$: 718.3229, found: 718.3254.

∘ Synthesis of the oxime **17**



14 **16** **17**

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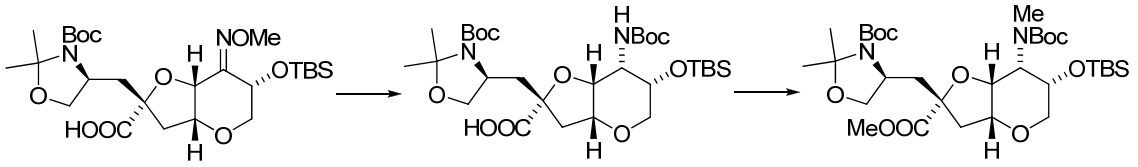
To the diol **14** (103 mg, 0.2 mmol) dissolved in a mixture of MeCN (3 mL) and phosphate buffer solution (pH 6.2, 2 mL) were added AZADO (3 mg, 0.02 mmol), $PhI(OAc)_2$ (193 mg, 0.6 mmol) and $NaClO_2$ at room temperature. $NaClO_2$ (24 mg) was added three times and its total amount was 72 mg (0.8 mmol). After each addition, the mixture was stirred at room temperature for 15 minutes. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (0.3 mL) and H_2O (3 mL). Work-up with EtOAc (4 mL x 6) gave rise to the crude keto carboxylic acid **16**. To the crude **16** were added pyridine (3 mL) and $MeONH_2 \cdot HCl$ (50 mg) in an ice bath. The mixture was stirred at that temperature for an hour and then at room temperature for 8 hours. After addition of saturated aqueous NH_4Cl (4 mL), work-up with EtOAc (3 mL x 5) and column chromatography (EtOAc/hexane = 1/1) provided the oxime **17** (98 mg, 88%). **17** better be purified as quickly as possible due to its stability problem.

∘ Synthesis of the ester **18**

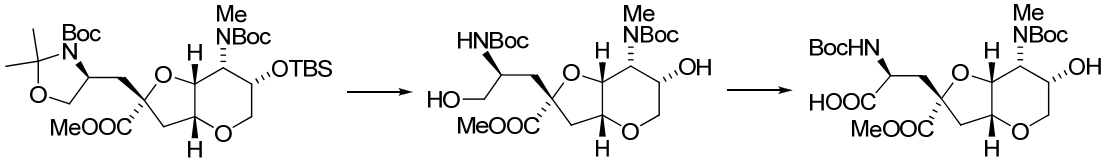


To the oxime **17** (70 mg, 0.12 mmol) dissolved in MeOH (4 mL) were added Raney Ni (Raney® 2800, slurry in H_2O, 0.1 mL), $NaHCO_3$ (32 mg, 0.36 mmol) and di-tert-butyl dicarbonate (57 μL, 0.24 mmol) at room temperature. After charging the reaction flask with hydrogen gas in a balloon, the mixture was stirred at room temperature for 6 hours. $MgSO_4$ (150 mg) was added to the reaction mixture and then the mixture was filtered through celite (1 g) using EtOAc (8 mL). Evaporation of the volatile materials in vacuo produced the crude carbamate carboxylic acid **31**. To the crude **31** in DMF (2 mL) were added NaH (60% oil dispersion, 15 mg, 0.36 mmol) and MeI (30 μL, 0.48 mmol) in an ice bath, and then the mixture was stirred at that temperature for 3 hours. After quenching the reaction with saturated aqueous NH_4Cl (2 mL), the resulting mixture was worked up with EtOAc (2 mL x 4) and purified chromatographically (EtOAc/hexane = 1/1) to yield the ester **18** (64 mg, 81%).

For **18**: ^{1}H NMR (400 MHz, $CDCl_3$, 55°C) δ 4.32 (1H, br s), 4.02–3.83 (6H, m), 3.80 (1H, d, J = 12.8 Hz), 3.68 (3H, s), 3.48–3.44 (1H, m), 3.19 (3H, s), 2.75 (1H, d, J = 14.2 Hz), 2.22 (1H, br s), 2.07 (2H, br s), 1.50 (3H, s), 1.46 (9H, s), 1.45 (9H, s), 1.44 (3H, s), 0.90 (9H, s), 0.03 (6H, d, J = 9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 55°C) δ 173.4, 156.7, 151.7, 93.2 85.5, 80.4, 80.1, 79.7, 79.2, 71.9, 68.4, 68.1, 54.1, 53.9, 52.2, 41.6,

40.5, 34.5, 28.6, 28.5, 27.2, 25.9, 18.2, –4.8, –5.0; HRMS (ESI) calcd for $C_{32}H_{58}N_2O_{10}Si$ [$(M + Na)^+$]: 681.3753, found: 681.3769.

∘ Synthesis of the carboxylic acid **19**



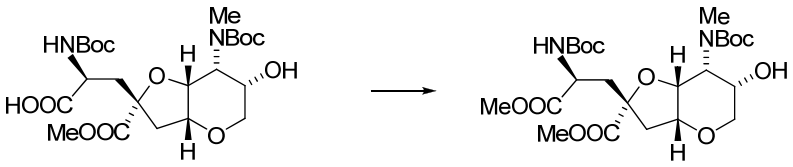
18 **32** **19**

To the ester **18** (46 mg, 0.07 mmol) dissolved in undried MeCN (2 mL) was added $InCl_3$ (62 mg, 0.21 mmol) at room temperature. After stirring the mixture at room temperature for 3 hours, the reaction was quenched with H_2O (2 mL). Work-up with EtOAc (2 mL x 4) and chromatographic separation rendered the diol **32** (34 mg, 96%). To **32** (34 mg, 0.067 mmol) dissolved in a mixture of MeCN (1.5 mL) and phosphate buffer solution (pH 5.8, 1 mL) were added AZADO (1 mg, 0.007 mmol), $PhI(OAc)_2$ (32 mg, 0.1 mmol) and $NaClO_2$ (12 mg, 0.13 mmol) at room temperature for 10 minutes and then quenched with saturated aqueous $Na_2S_2O_3$ (0.15 mL). After adding phosphate-citrate buffer solution (pH 4, 2 mL), work-up with EtOAc (2 mL x 5) provided the crude carboxylic acid **19** (35 mg, 100%), which was used directly in the next step. Chromatographic separation of the crude **19** with EtOAc afforded **19** in 85-90% yield.

For **19**: ^{1}H NMR (400 MHz, $CDCl_3$, 55^{o}C) δ 5.56 (1H, br s), 4.79 (1H, d, J = 12.6 Hz), 4.37 (1H, br s), 4.17 (2H, dt, J = 3.0, 1.5 Hz), 4.01 (1H, dd, J = 3.3, 1.5 Hz), 3.86 (1H, dd, J = 12.0, 2.2 Hz), 3.79 (3H, s), 3.83–3.73 (1H, m, overlap with COOMe), 3.54 (1H, d, J = 11.9 Hz), 3.26 (3H, s), 2.63 (1H, dd, J = 14.8, 4.8 Hz), 2.56 (1H, d, J = 13.9 Hz),

2.12 (1H, dd, J = 14.8, 8.3 Hz), 2.05 (1H, dd, J = 14.0, 3.6 Hz), 1.46 (9H, s), 1.43 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 55°C) δ 174.3, 172.8, 156.4, 85.5, 82.2, 80.7, 80.2, 77.7, 73.0, 69.0, 52.9, 51.4, 44.4, 39.3, 33.2, 29.6, 28.4, 28.2; HRMS (ESI) calcd for $C_{23}H_{38}N_2O_{11}$ [(M + Na)$^+$]: 541.2368, found: 541.2385; $[\alpha]_D^{21}$ +57.1° (c 0.75, $CHCl_3$).

∘ Synthesis of the diester **20**

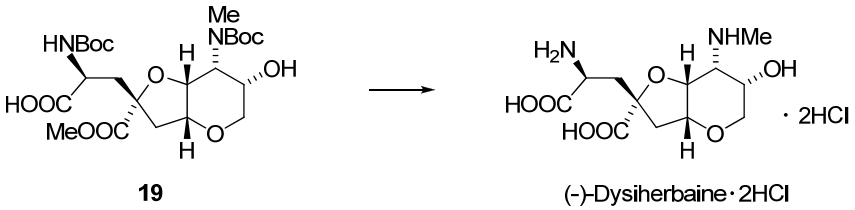


To the crude carboxylic acid **19** (9 mg, 0.017 mmol) dissolved in a 1 : 1 mixture of benzene and methanol (0.4 mL) was added $TMSCHN_2$ (2 M in Et_2O, 0.017 mL, 0.034 mmol), and then the mixture was stirred at room temperature for 15 minutes. After evaporating all the volatile materials in vacuo, the remaining crude product was purified chromatographically (EtOAc/hexane = 3/2) to furnish the diester **20** (9 mg, 100%).

For **20**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (1H, br d, J = 4.8 Hz), 4.92 (1H, d, J = 12.8 Hz), 4.44 (1H, br s), 4.22–4.20 (1H, m), 4.11 (1H, dd, J = 3.0, 1.5 Hz), 4.01 (1H, br s), 3.85 (1H, dd, J = 12.0, 2.3 Hz), 3.79 (3H, s), 3.78–3.77 (1H, m, overlap with COOMe), 3.70 (3H, s), 3.54 (1H, d, J = 12.0 Hz), 3.25 (3H, s), 2.62 (1H, dd, J = 14.4, 4.8 Hz), 2.51 (1H, d, J = 14.0 Hz), 2.06 (1H, dd, J = 14.4, 7.6 Hz), 2.00 (1H, dd, J = 14.2, 3.2 Hz), 1.45 (9H, s), 1.40 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 172.1,156.6, 155.2, 85.3, 82.4, 80.0, 77.7, 73.1, 69.0, 53.2, 52.6, 52.3, 51.3, 44.7, 39.8, 33.4, 28.4, 28.3; HRMS (ESI) calcd for $C_{24}H_{40}N_2O_{11}$ [(M + Na)$^+$]: 555.2524, found: 555.2542;

$[\alpha]_D^{21}$ –59.2° (c 0.45, $CHCl_3$).

∘ Synthesis of (-)-dysiherbaine·2HCl

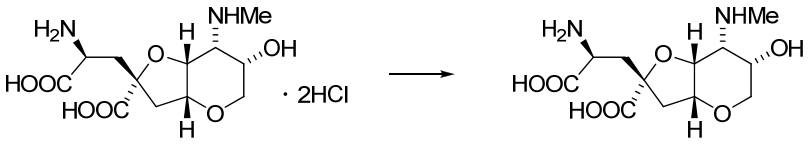


The crude carboxylic acid **19** (20 mg, 0.038 mmol) was dissolved in 6M aqueous HCl (0.8 mL) and the mixture was stirred at 80°C for 18 hours. Evaporation of all the volatile materials produced (-)-dysiherbaine·2HCl (14 mg, 100%).

For (-)-dysiherbaine·2HCl: ^{1}H NMR (400 MHz, D_2O, 0.05M, pH 2) δ 4.37 (1H, br s), 4.20 (1H, br s), 3.90 (1H, br s), 3.85 (1H, d, J = 12.8 Hz), 3.80 (1H, dd, J = 10.4, 2.8 Hz), 3.59 (1H, t, J = 3.9 Hz), 3.54 (1H, d, J = 13.0 Hz), 2.74 (1H, app. dd, J_b = 2.9 Hz, overlap with NMe), 2.71 (3H, s), 2.60 (1H, d, J = 14.4 Hz), 2.26 (1H, dd, J = 14.4, 3.4 Hz), 2.08 (1H, dd, J = 15.4, 10.6 Hz); ^{1}H NMR (400 MHz, D_2O, 0.03 M, pH 2) δ 4.38 (1H, br s), 4.20 (1H, br s), 3.91 (1H, br s), 3.85 (2H, td, J = 11.9, 10.8, 2.6 Hz), 3.61 (1H, t, J = 3.9 Hz), 3.55 (1H, d, J = 13.1 Hz), 2.76 (1H, app. dd, J_b = 2.8 Hz, overlap with NMe), 2.72 (3H, s), 2.61 (1H, d, J = 14.5 Hz), 2.28 (1H, dd, J = 14.4, 3.5 Hz), 2.10 (1H, dd, J = 15.4, 10.5 Hz); ^{1}H NMR (400 MHz, D_2O, 0.005 M, pH 4) δ 4.31 (1H, br s), 4.14 (1H, br s), 3.86–3.83 (2H, m), 3.60 (1H, dd, J = 10.8, 1.6 Hz), 3.55–3.50 (2H, m), 2.70 (3H, s), 2.63 (1H, dd, J = 15.6, 2.0 Hz), 2.56 (1H, d, J = 14.4 Hz), 2.18 (1H, dd, J = 14.4, 3.6 Hz), 1.97 (1H, dd, J = 15.2, 11.2 Hz); ^{13}C NMR (100 MHz, D_2O, 0.03 M, pH 2) δ

177.6, 171.2, 86.3, 75.9, 75.5, 68.6, 62.0, 55.8, 51.3, 44.4, 38.0, 29.5; $[\alpha]_D^{23}$ +7.0° (c 0.54, H_2O), $[\alpha]_D^{21}$ +22.7° (c 0.35, MeOH).

- Synthesis of (-)-dysiherbaine **1**



To (-)-dysiherbaine·2HCl (14.5 mg, 0.038 mmol) was added aqueous NaOH (10 M, 0.3 mL) and the mixture was stirred at room temperature for 10 minutes. After all the volatile materials were evaporated in vacuo, the residue was purified using Amberlite, weakly acidic cation exchanger, hydrogen form, wet mesh 100-200 (Fluka). The resin (0.45 g) was washed with water until the eluted water became neutral, and then the residue was loaded and eluted with water. The ninhydrin-positive fraction (about 1.2 mL) was collected and then evaporated in vauo to give (-)-dysiherbaine **1** (11 mg, 95%). For (-)-dysiherbaine **1**: ^{1}H NMR (400 MHz, D_2O, 0.05M, neutral) δ 4.27 (1H, br s), 4.12 (1H, br s), 3.84 (1H, app. dd, J_b = 2.0 Hz, two overlap signals), 3.81 (1H, br s, two overlap signals), 3.52–3.48 (2H, m), 3.45 (1H, dd, J = 11.6, 2.0 Hz), 2.71 (3H, s), 2.56 (1H, dd, J = 15.2, 2.0 Hz), 2.54 (1H, d, J = 14.0Hz), 2.11 (1H, dd, J = 14.0, 3.2 Hz), 1.88 (1H, dd, J = 15.2, 12.0 Hz); ^{13}C NMR (100 MHz, D_2O) δ 180.0, 173.6, 88.4, 76.0, 74.7, 68.5, 62.0, 56.3, 53.4, 44.2, 39.0, 29.4; HRMS (ESI) calcd for $C_{12}H_{20}N_2O_7$ [(M + Na)$^+$]: 327.1163, found: 327.1166; $[\alpha]_D^{24}$ –7.3° (c 0.38, H_2O).

Figure 1. ^{1}H NMR Spectrum of the triol **5** (RT)

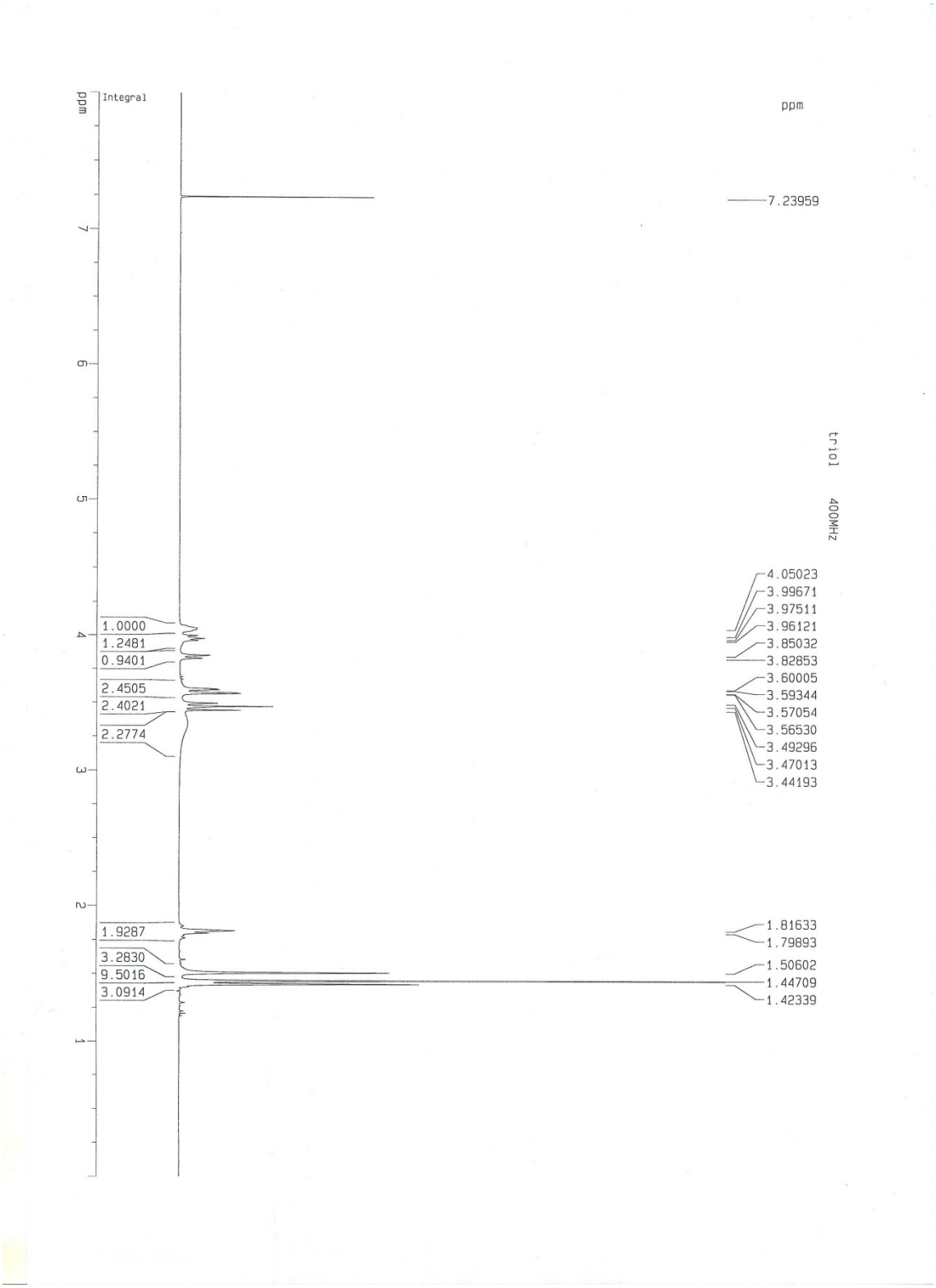


Figure 2. ^{13}C NMR Spectrum of the triol **5** (RT)

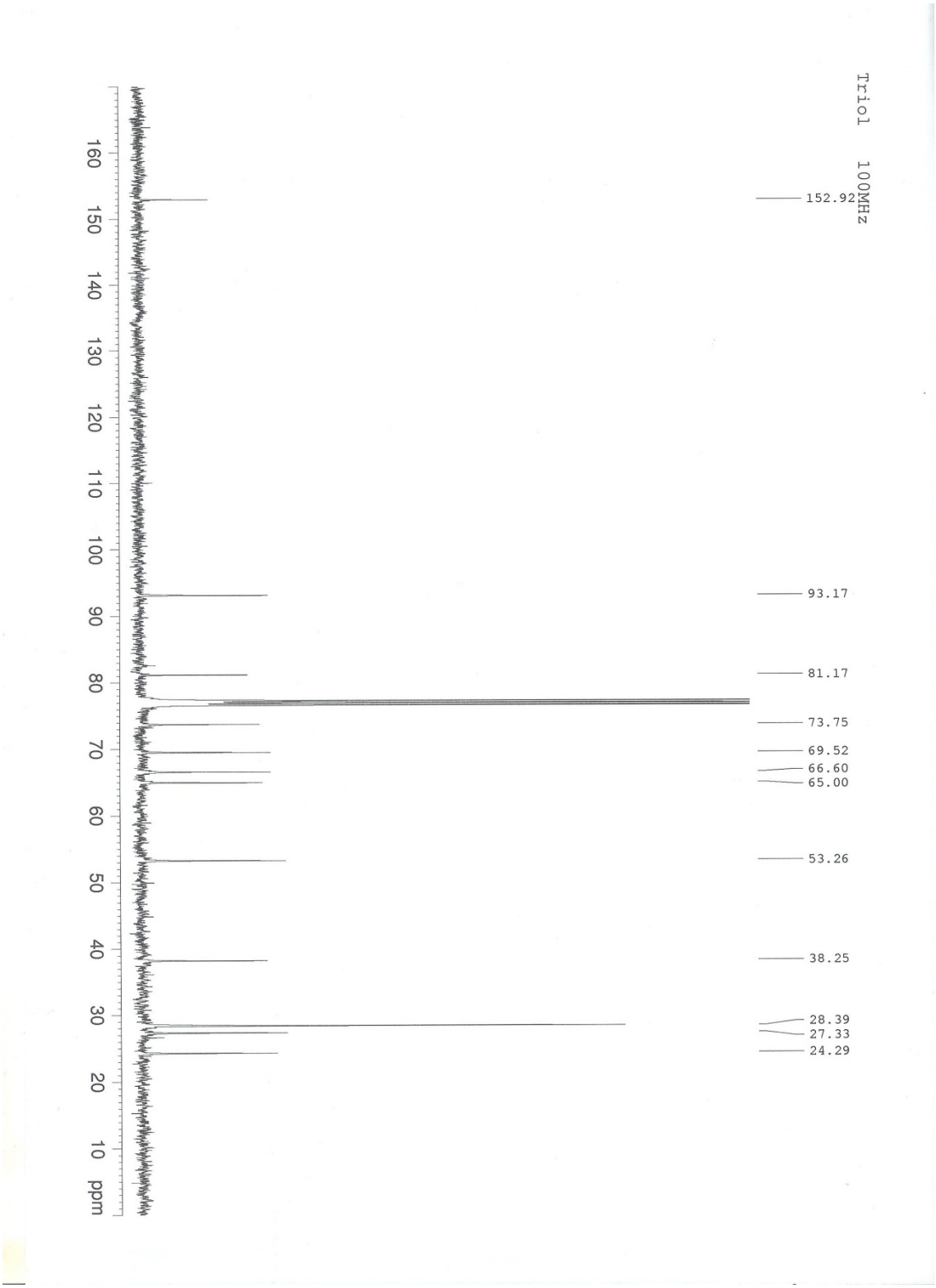


Figure 3. ^{1}H NMR Spectrum of the monobenzoate **9** (RT)

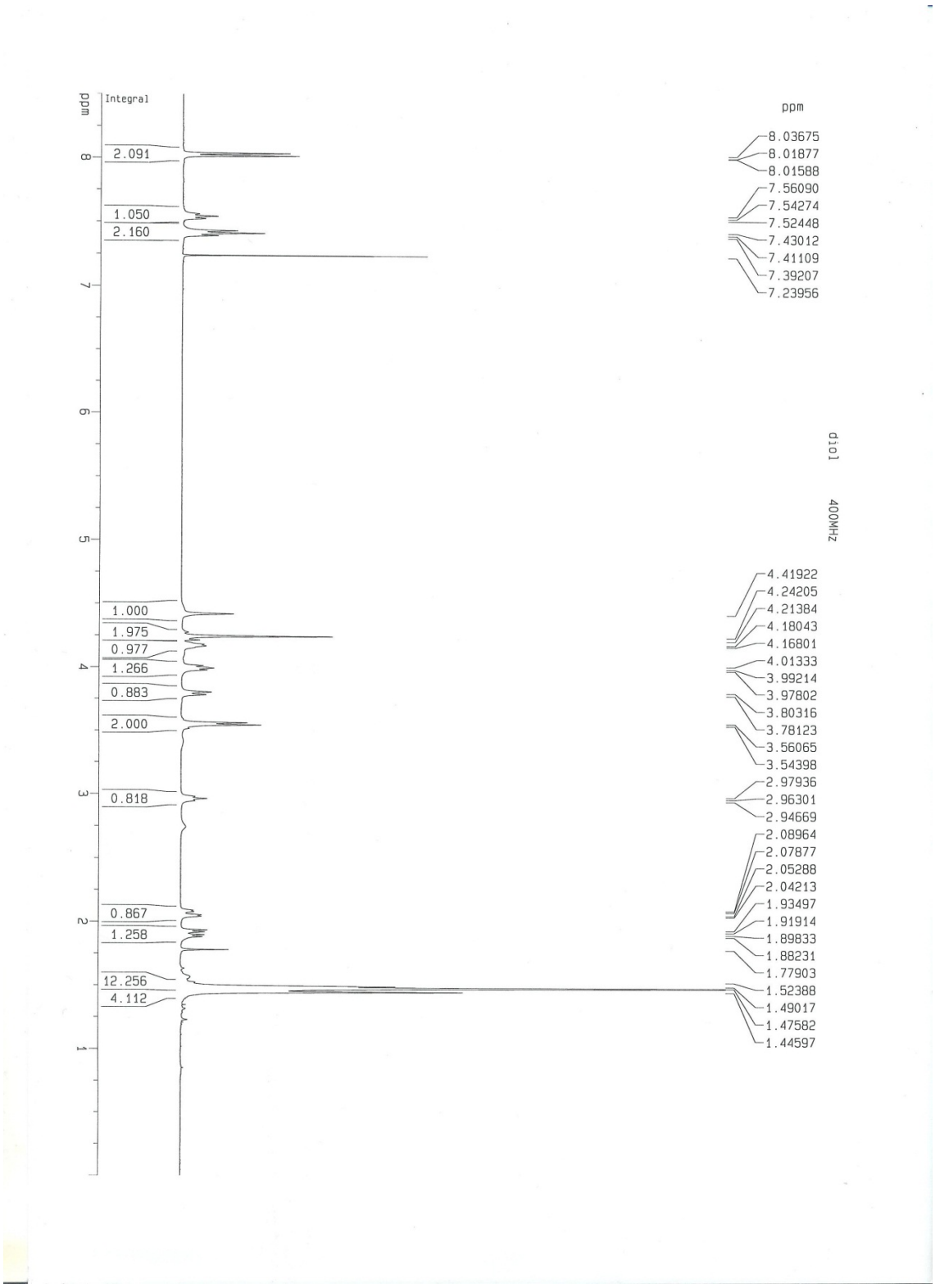


Figure 4. ^{13}C NMR Spectrum of the monobenzoate **9** (RT)

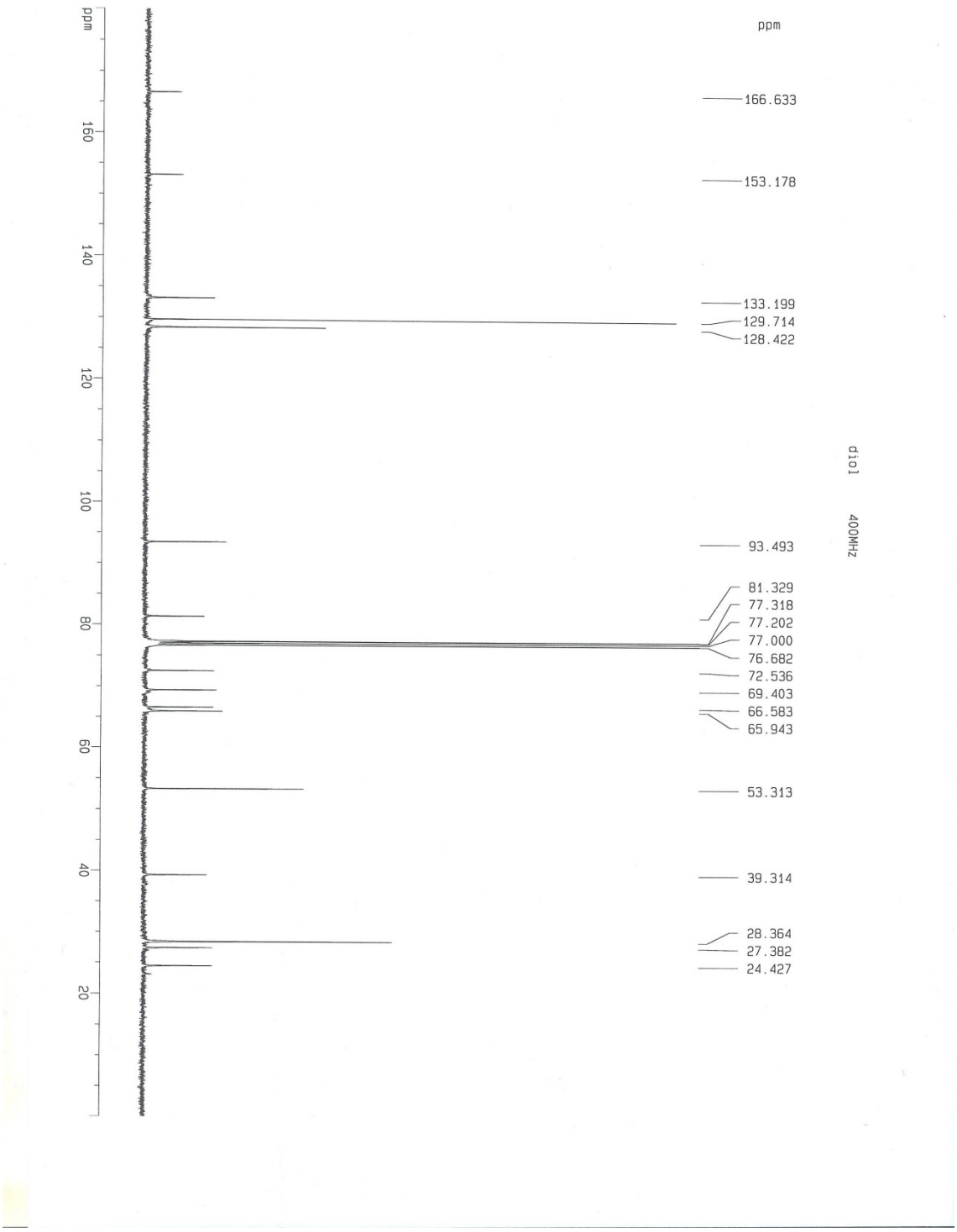


Figure 5. ^{1}H NMR Spectrum of the vinyl iodide **3** (less polar, RT)

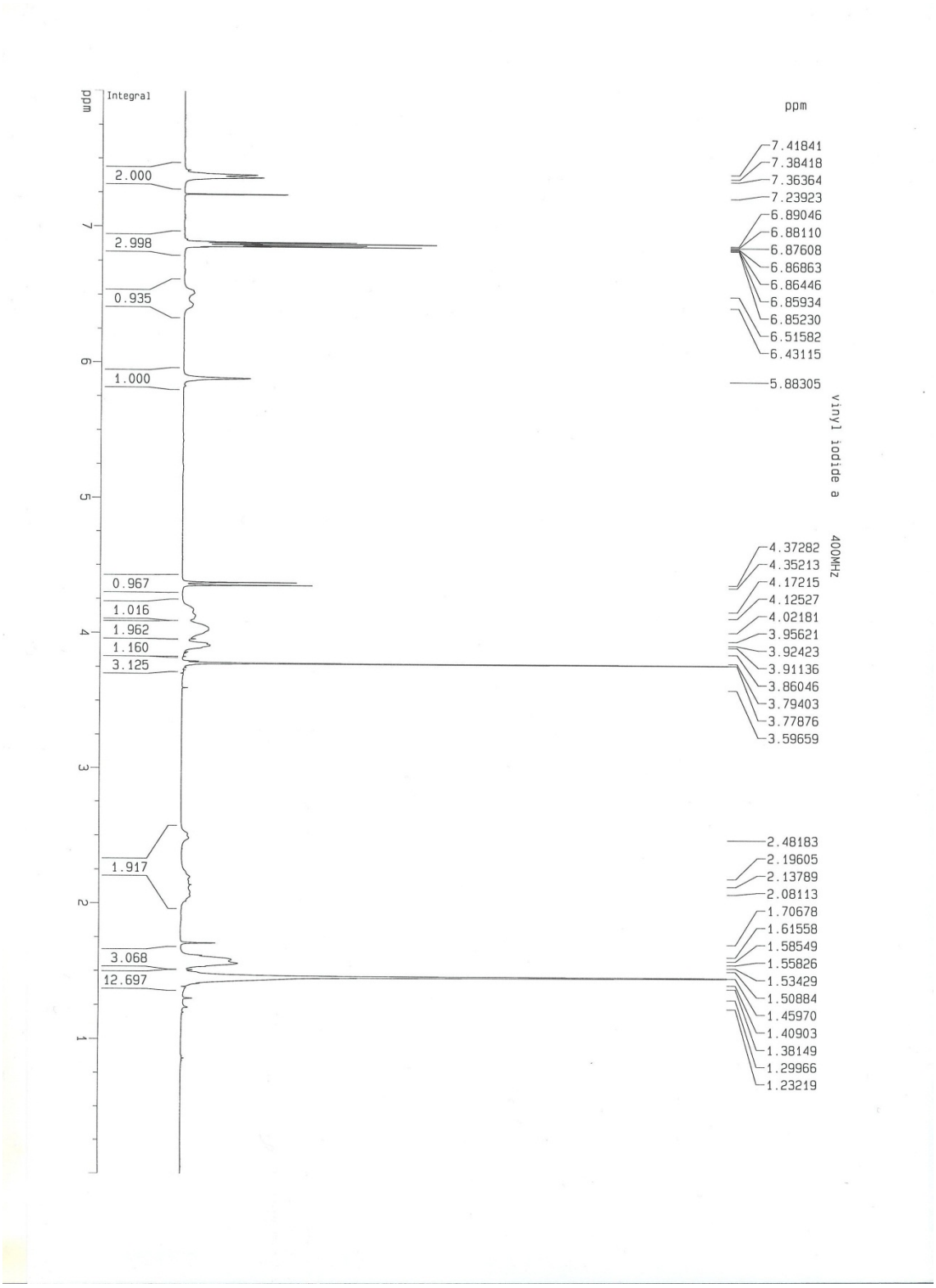


Figure 6. ^{1}H NMR Spectrum of the vinyl iodide **3** (less polar, 55^{o}C)

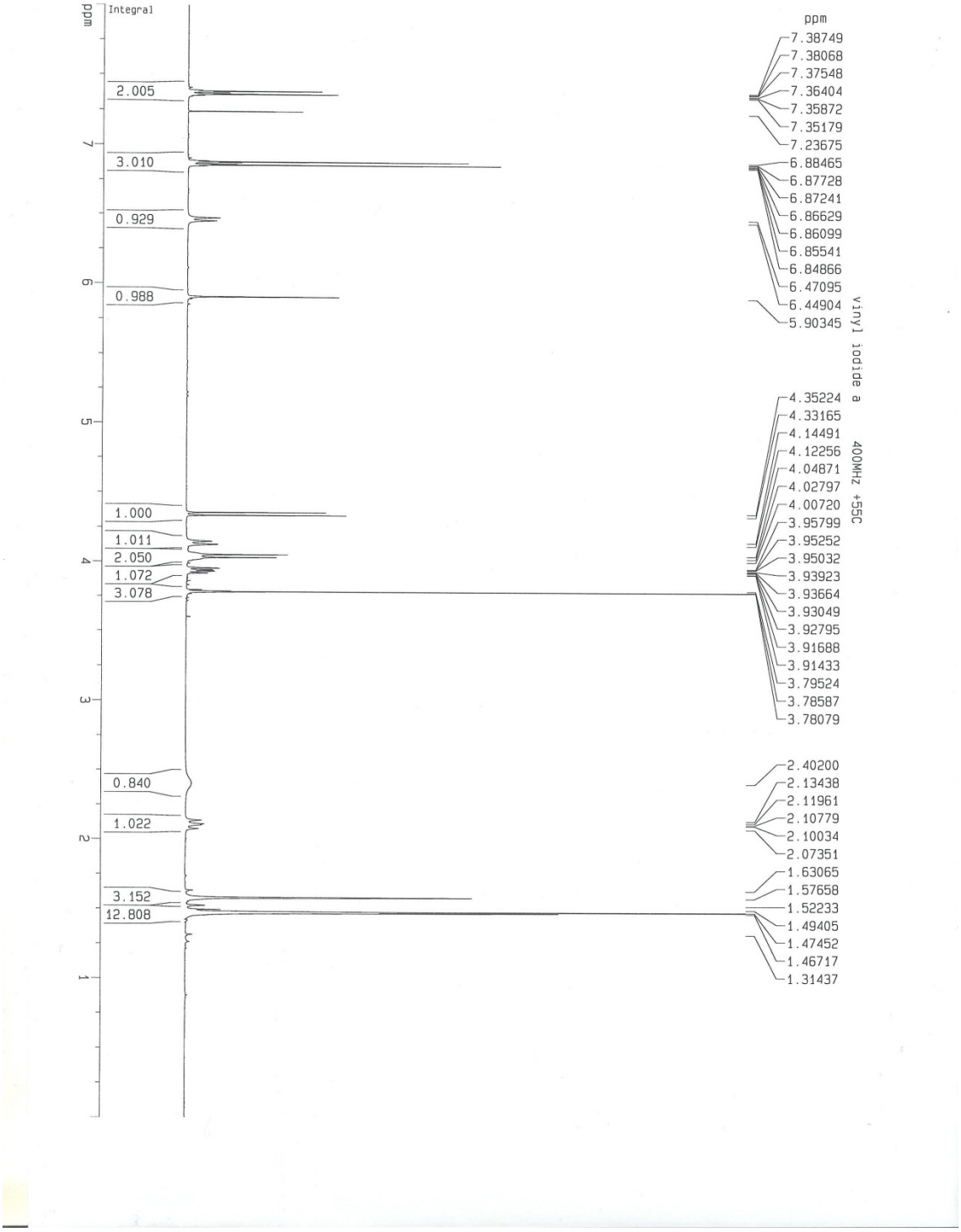


Figure 7. ^{1}H NMR Spectrum of the vinyl iodide **3** (more polar, RT)

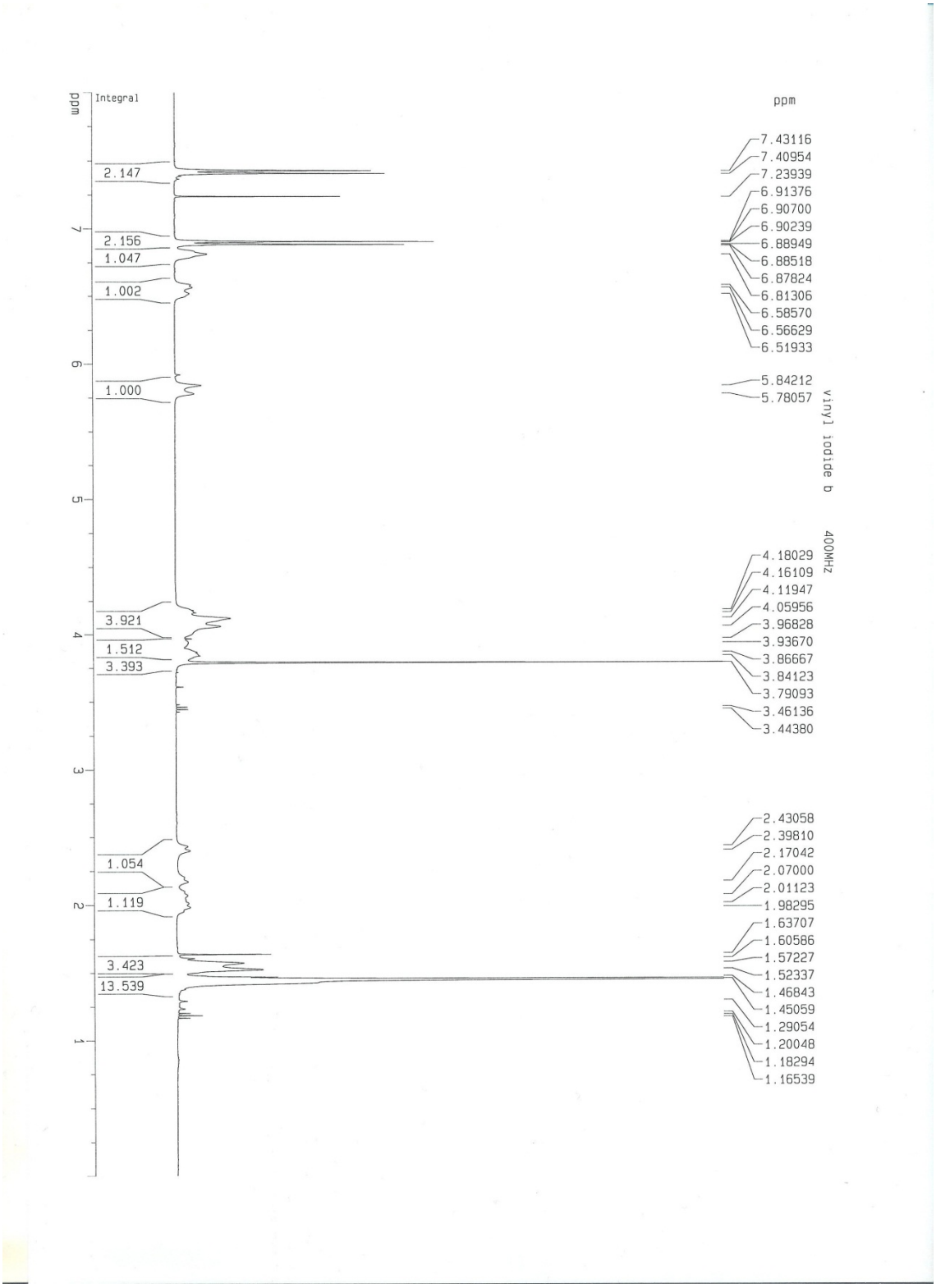


Figure 8. ^{1}H NMR Spectrum of the vinyl iodide **3** (more polar, 55^{o}C)

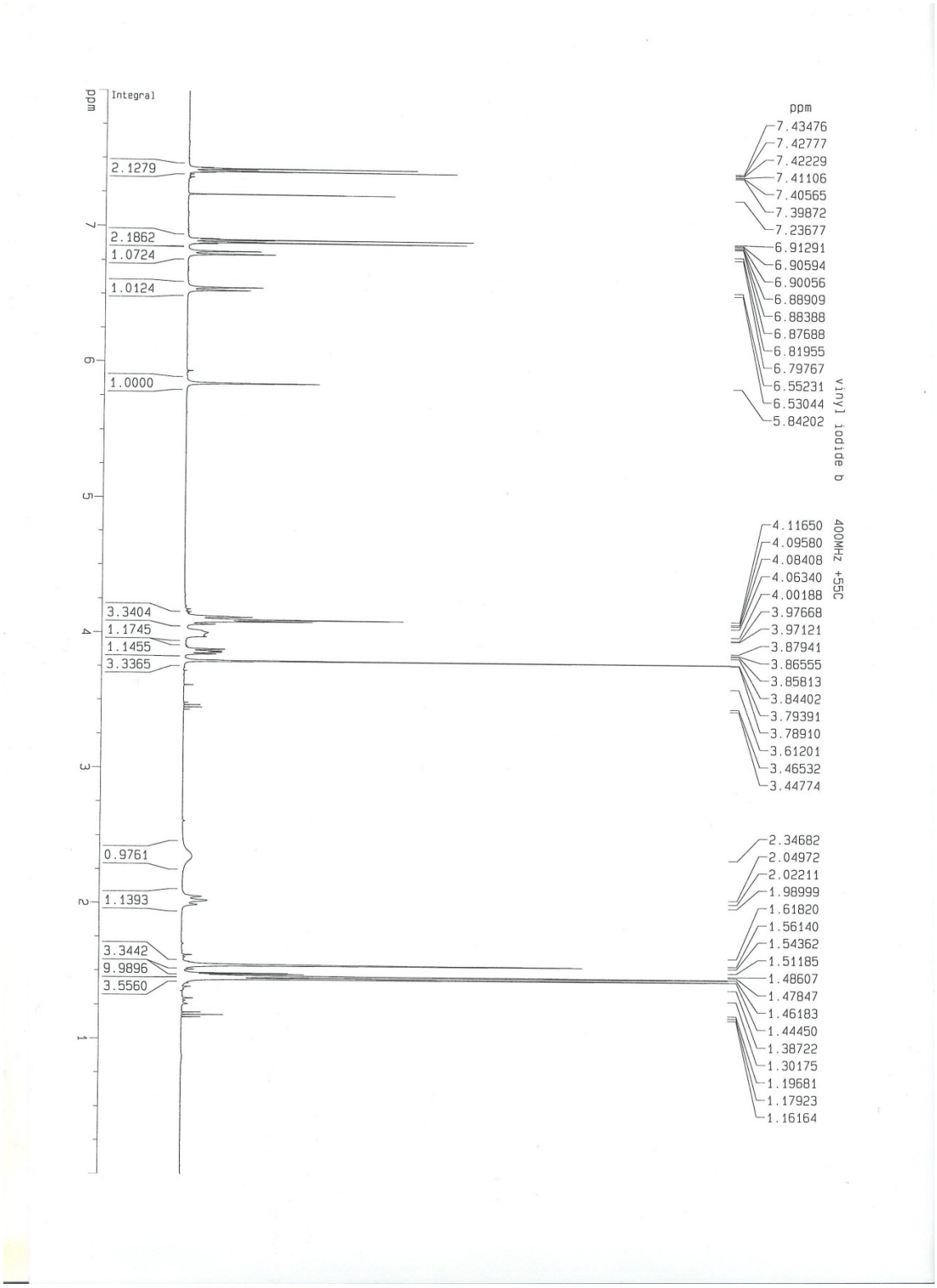


Figure 9. ^{13}C NMR Spectrum of the vinyl iodide **3** (less polar, 55°C)

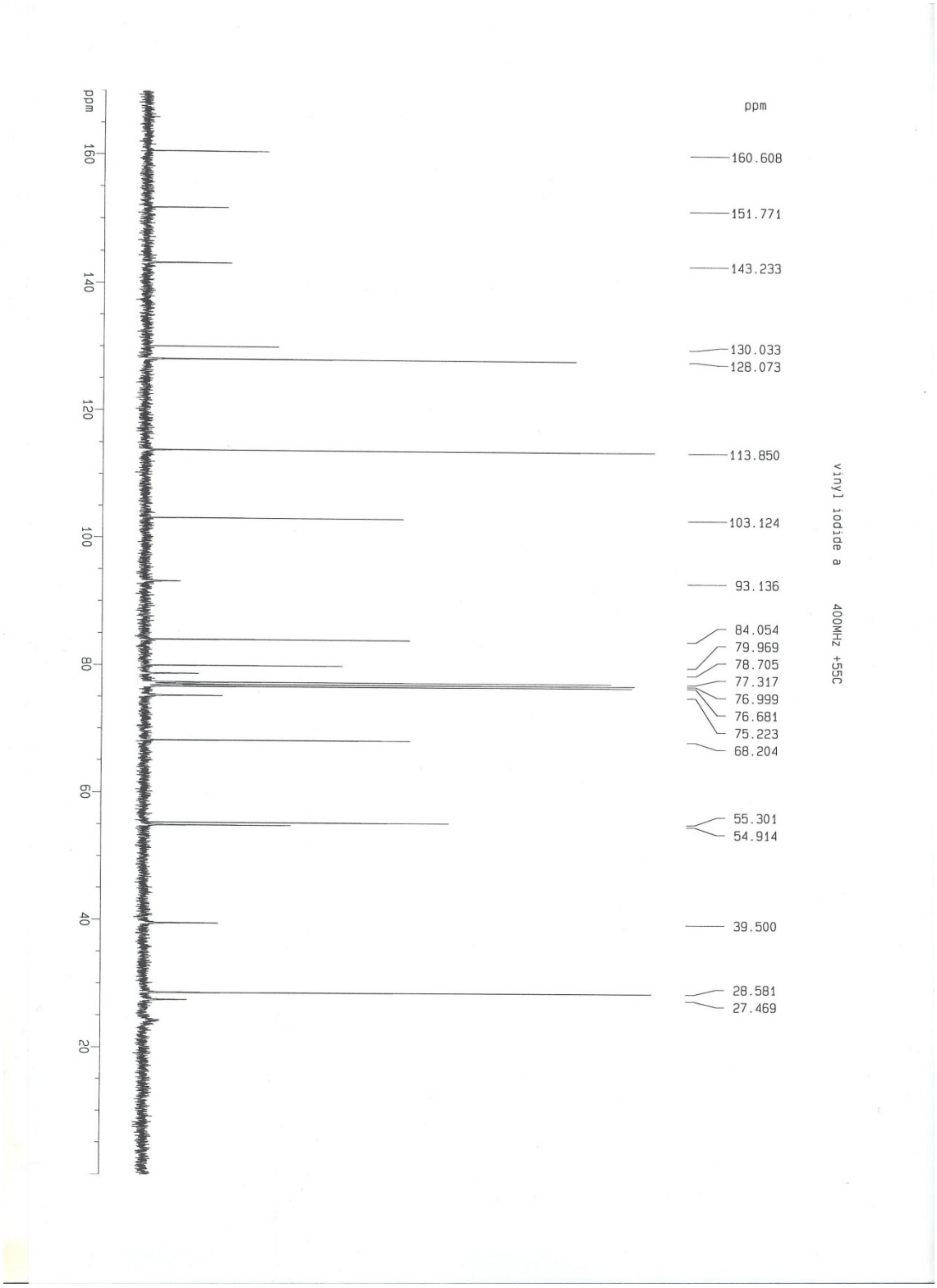


Figure 10. ^{13}C NMR Spectrum of the vinyl iodide **3** (more polar, 55°C)

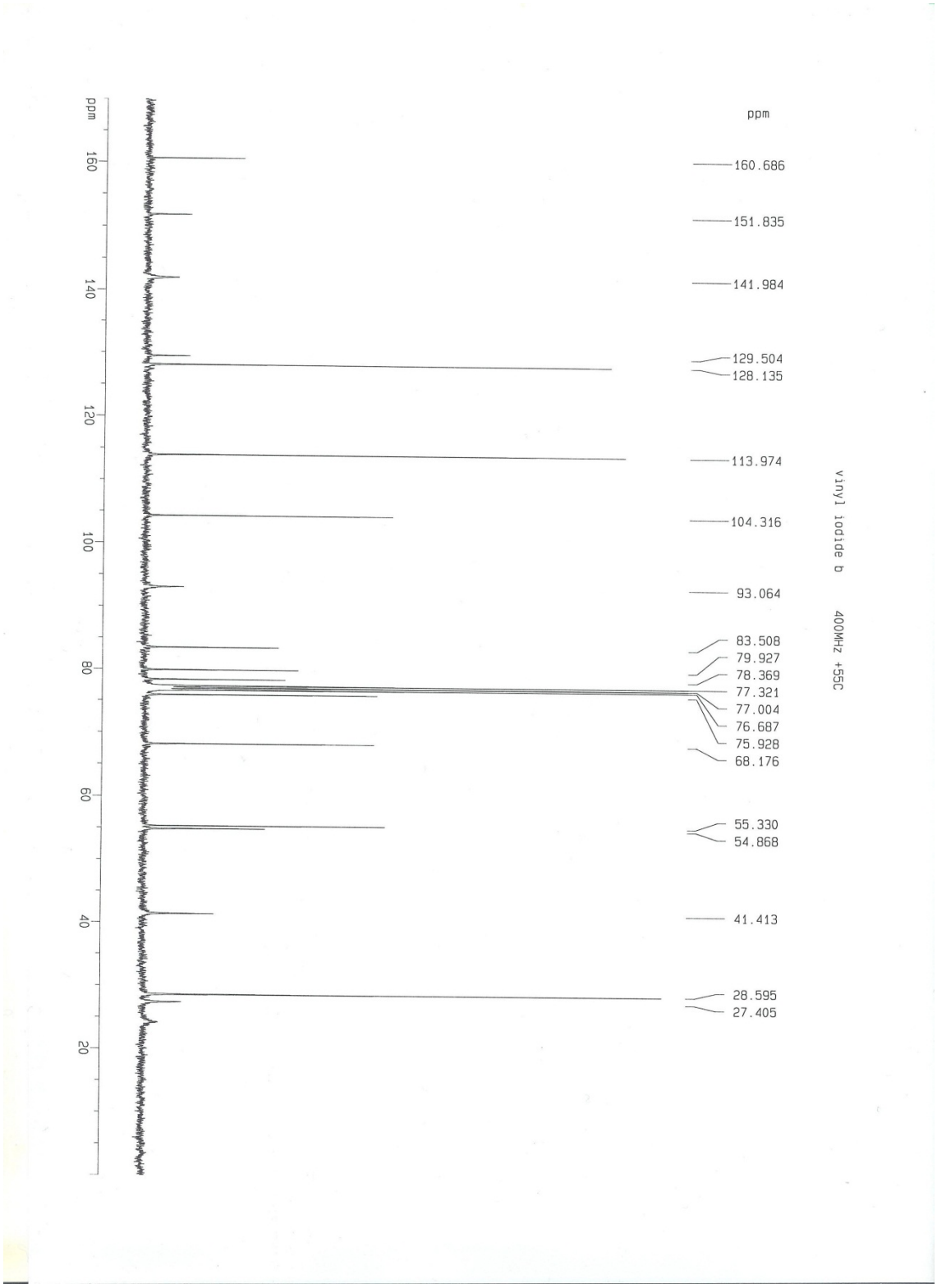


Figure 11. ^{1}H NMR Spectrum of the vinyltin **4** (RT)

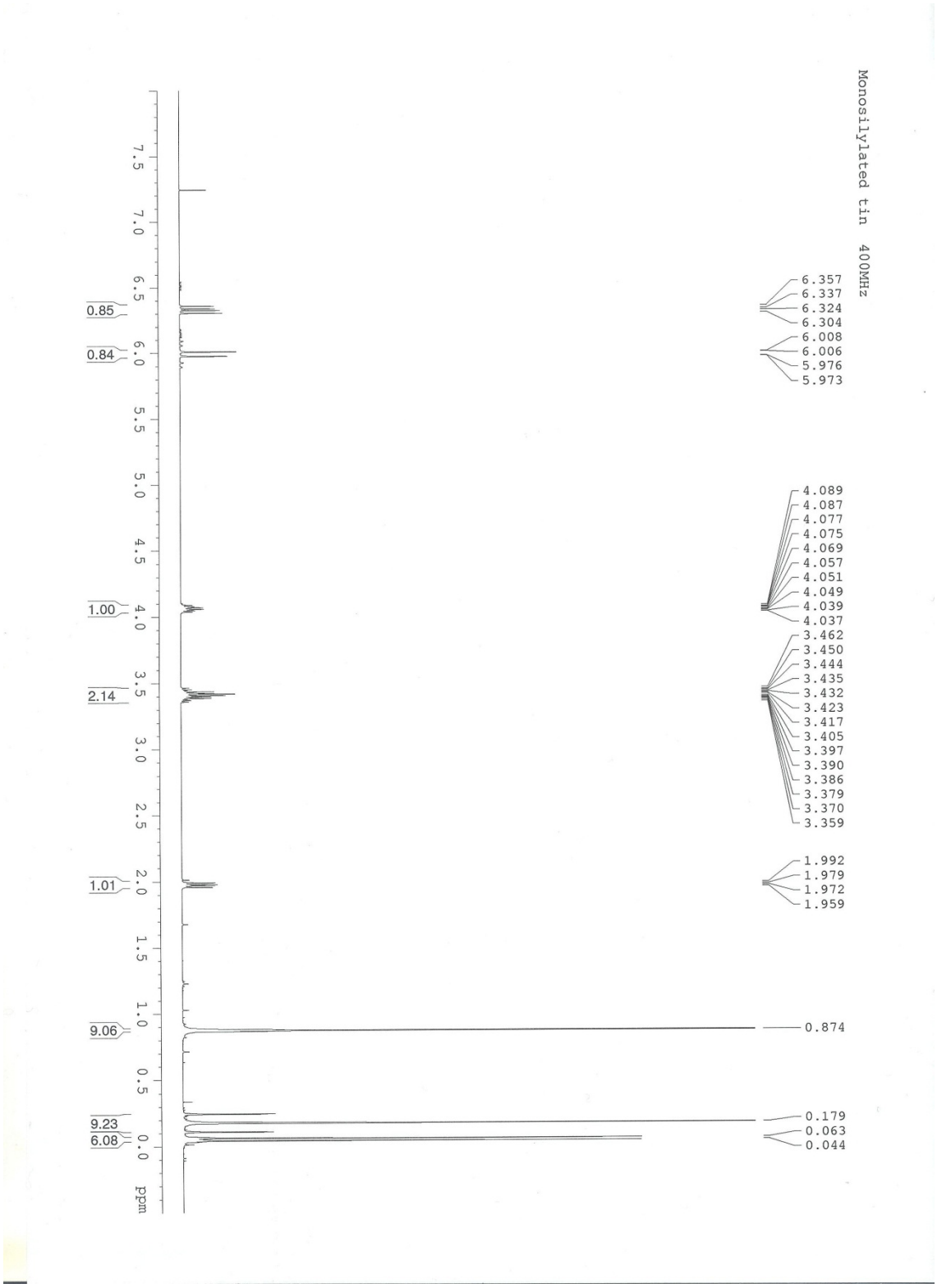


Figure 12. ^{13}C NMR Spectrum of the vinyltin **4** (RT)

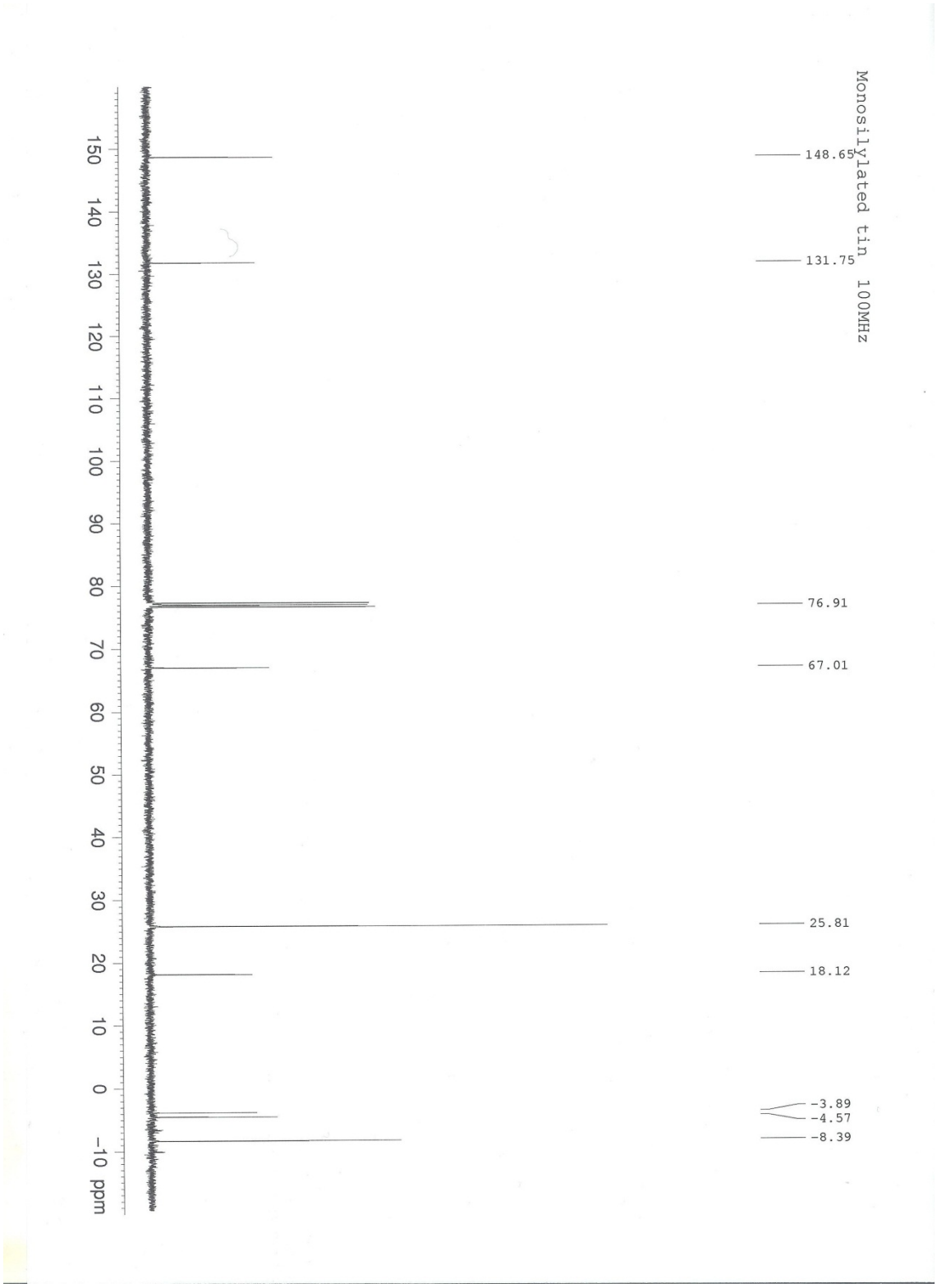


Figure 13. ^{1}H NMR Spectrum of the diol **12**

(RT)

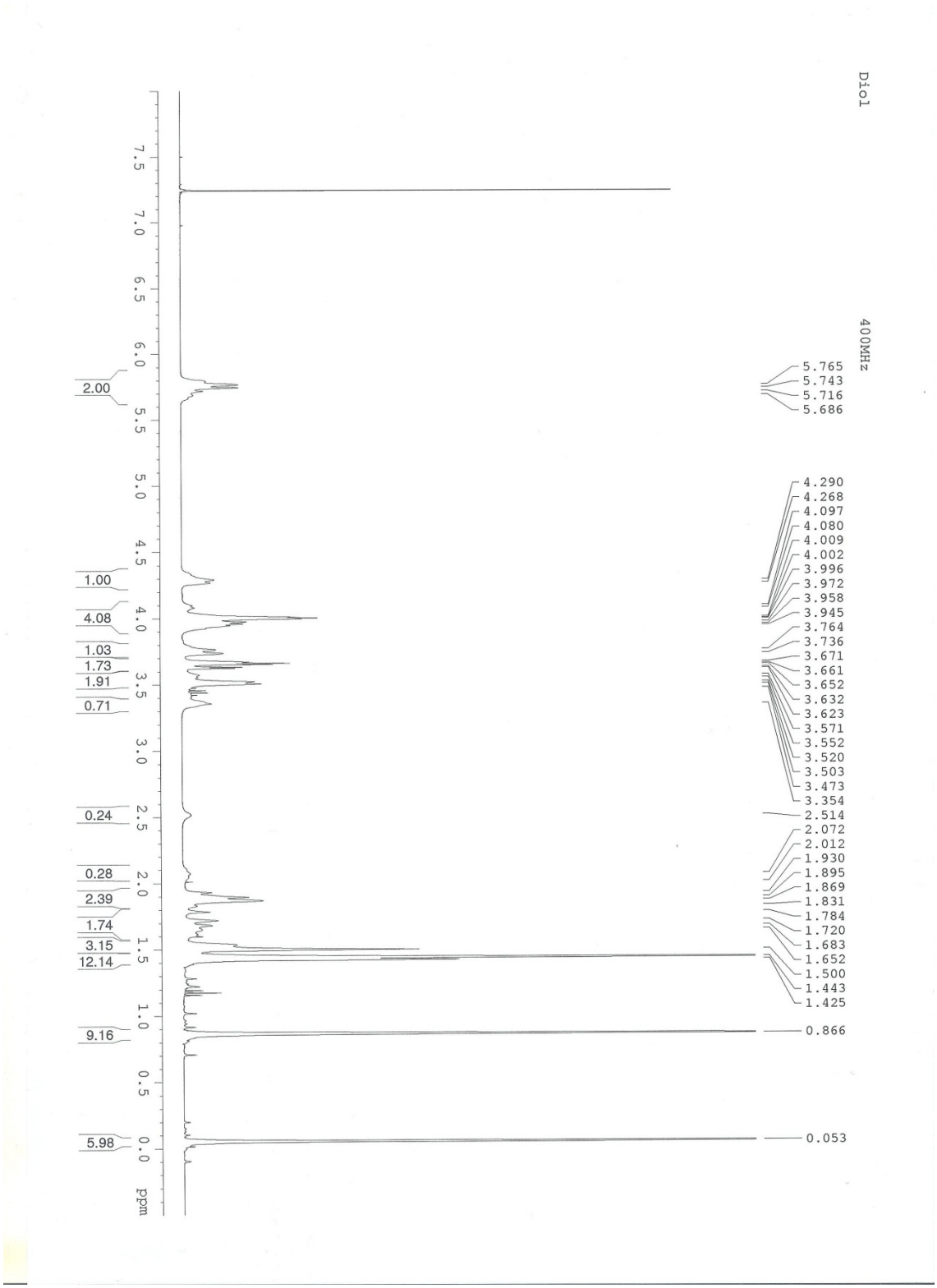


Figure 14. ^{1}H NMR Spectrum of the diol **12** (55^{o}C)

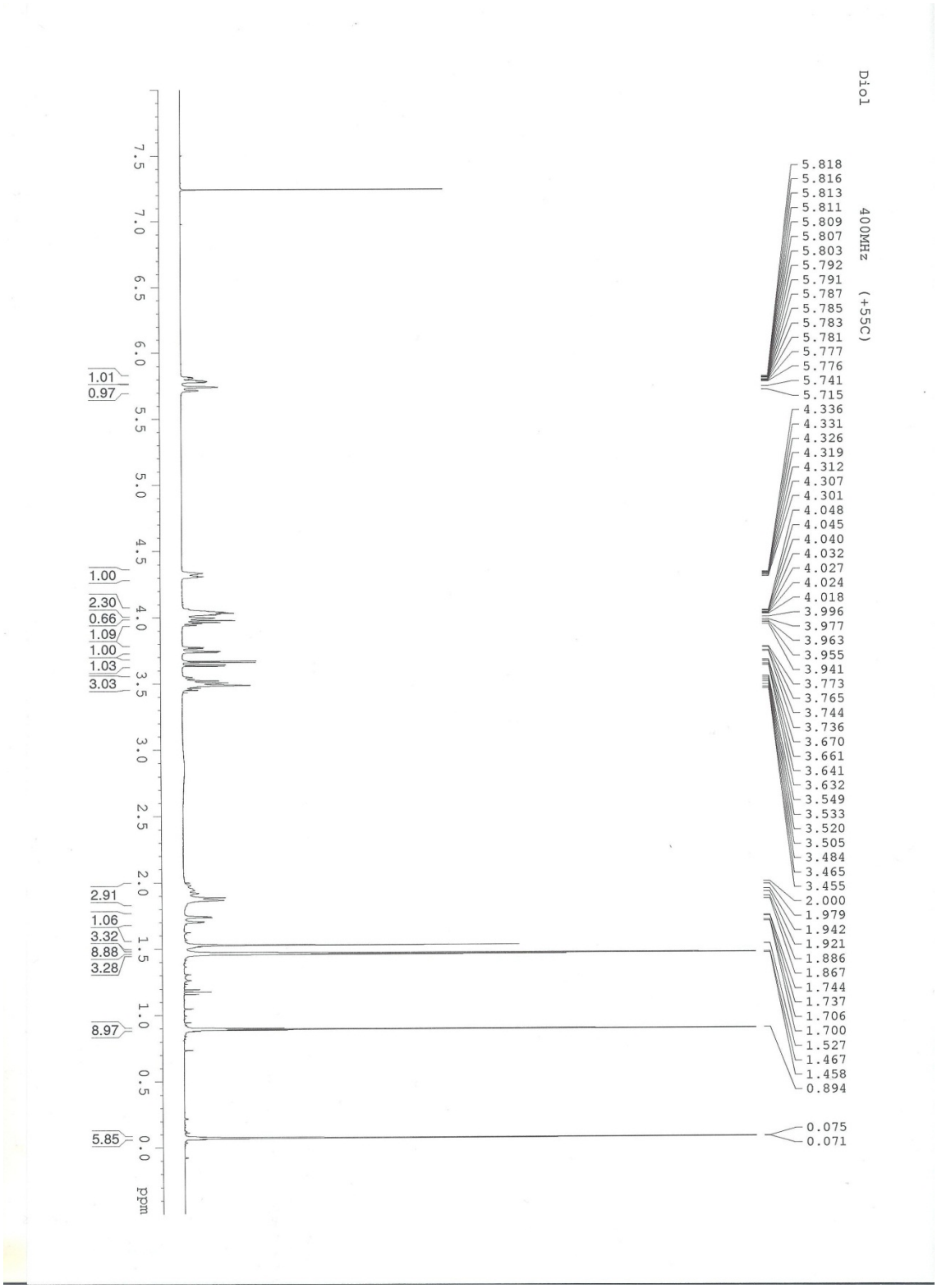


Figure 15. ^{13}C NMR Spectrum of the diol **12** (RT)

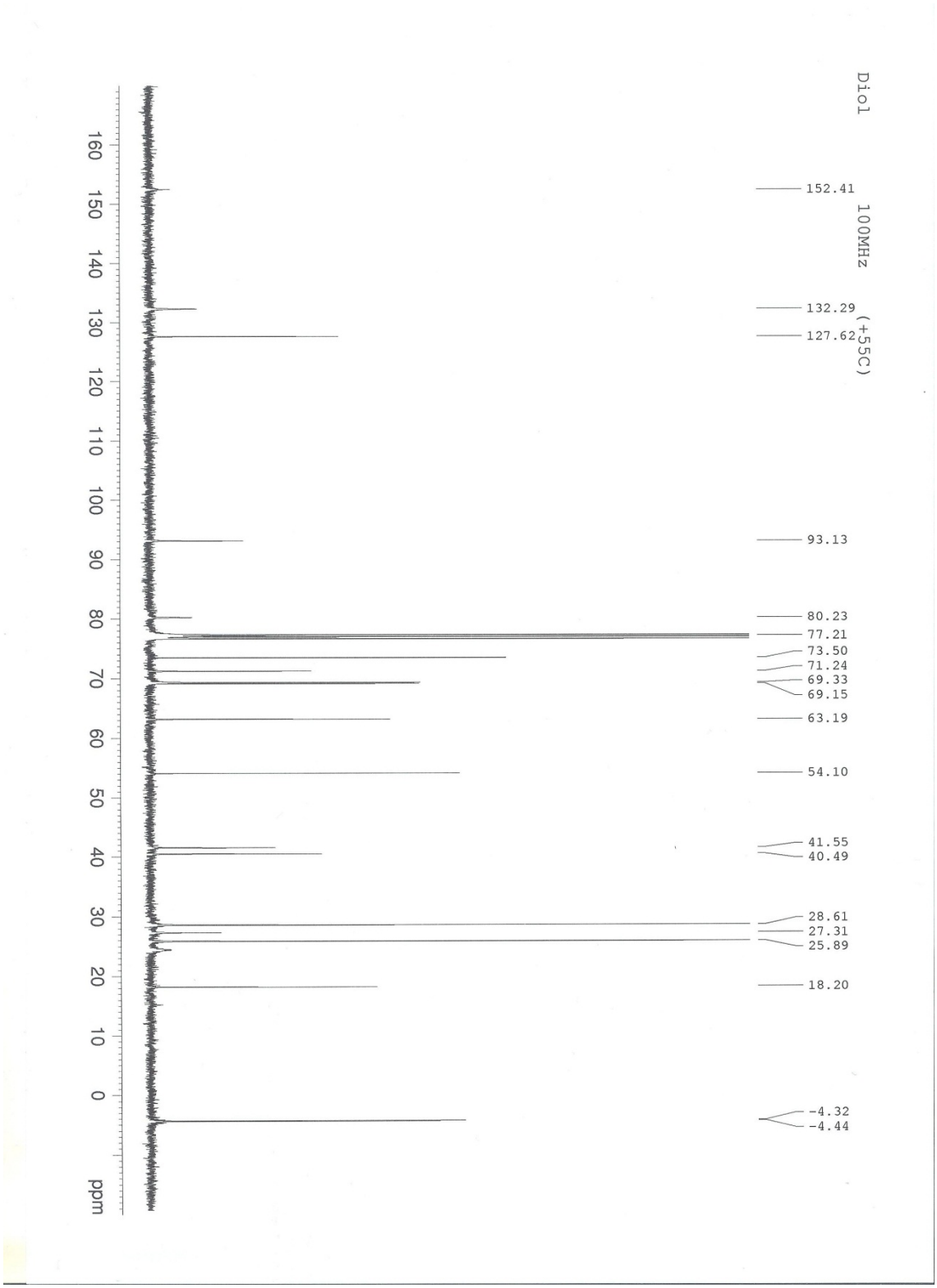


Figure 16. ^{1}H NMR Spectrum of the bicyclic alcohol **14** (RT)

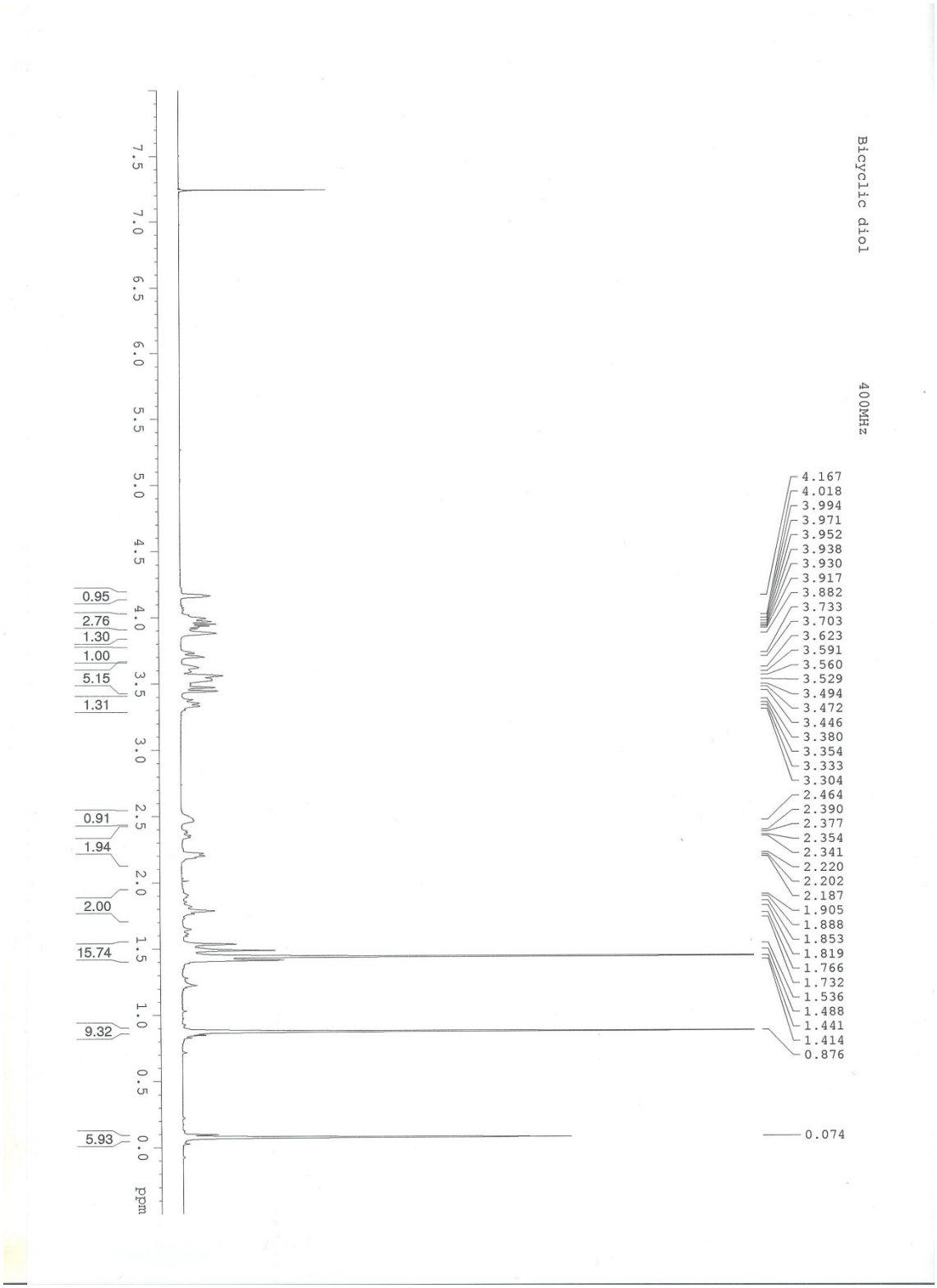


Figure 17. ^{1}H NMR Spectrum of the bicyclic alcohol **14** (55^{o}C)

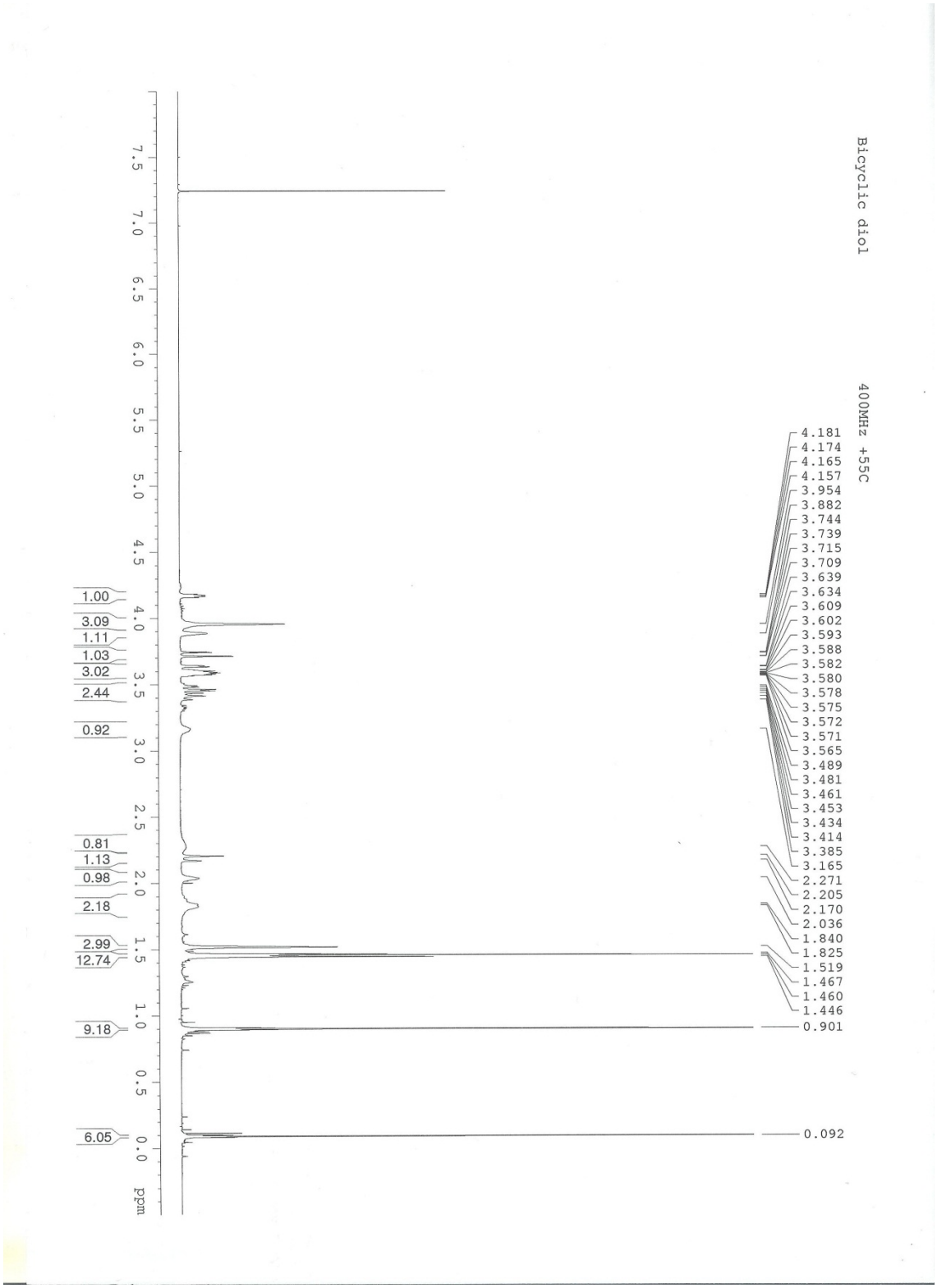


Figure 18. ^{13}C NMR Spectrum of the bicyclic alcohol **14** (RT)

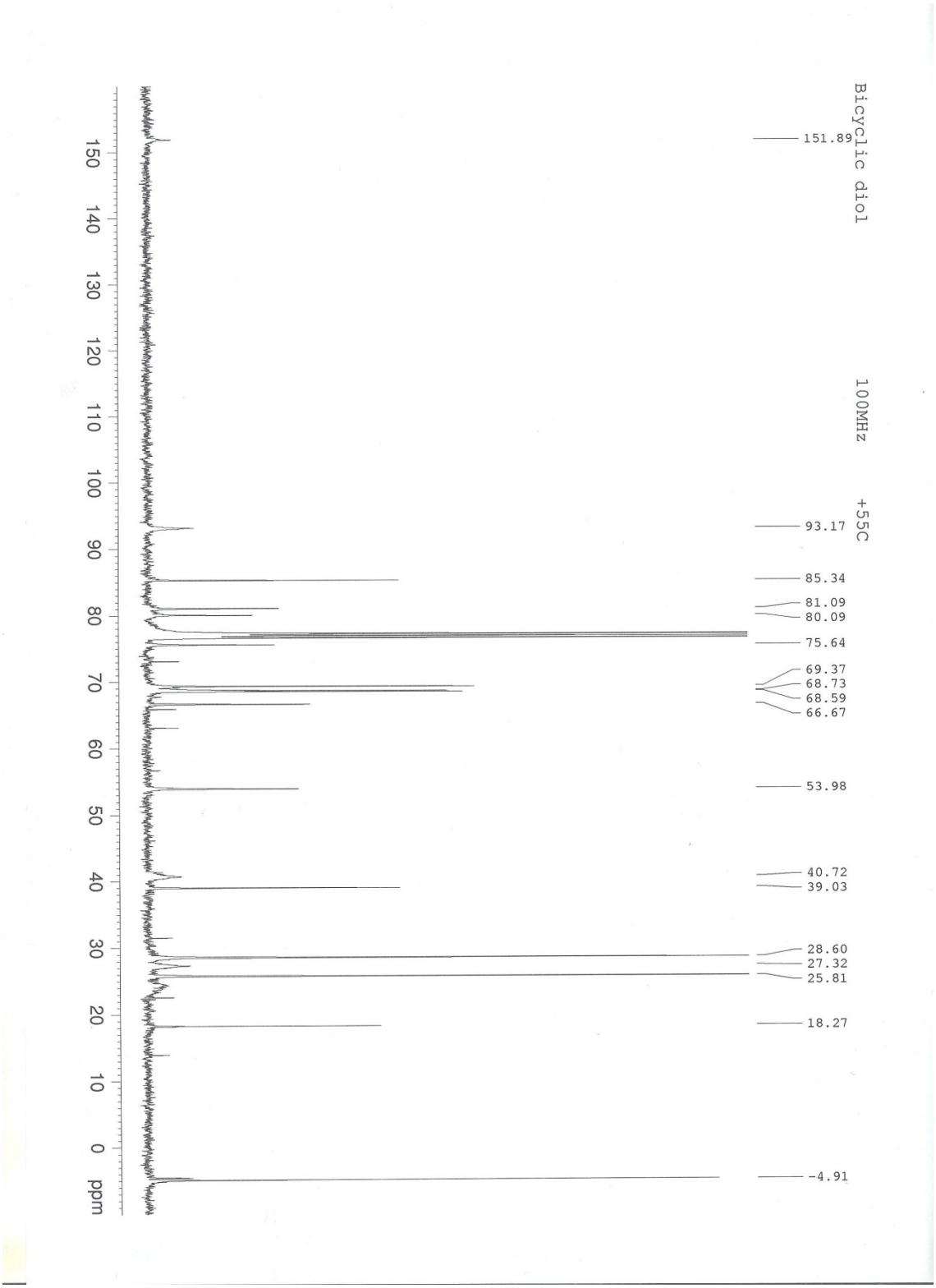


Figure 19. ^{1}H NMR Spectrum of the diacetate **15** (RT)

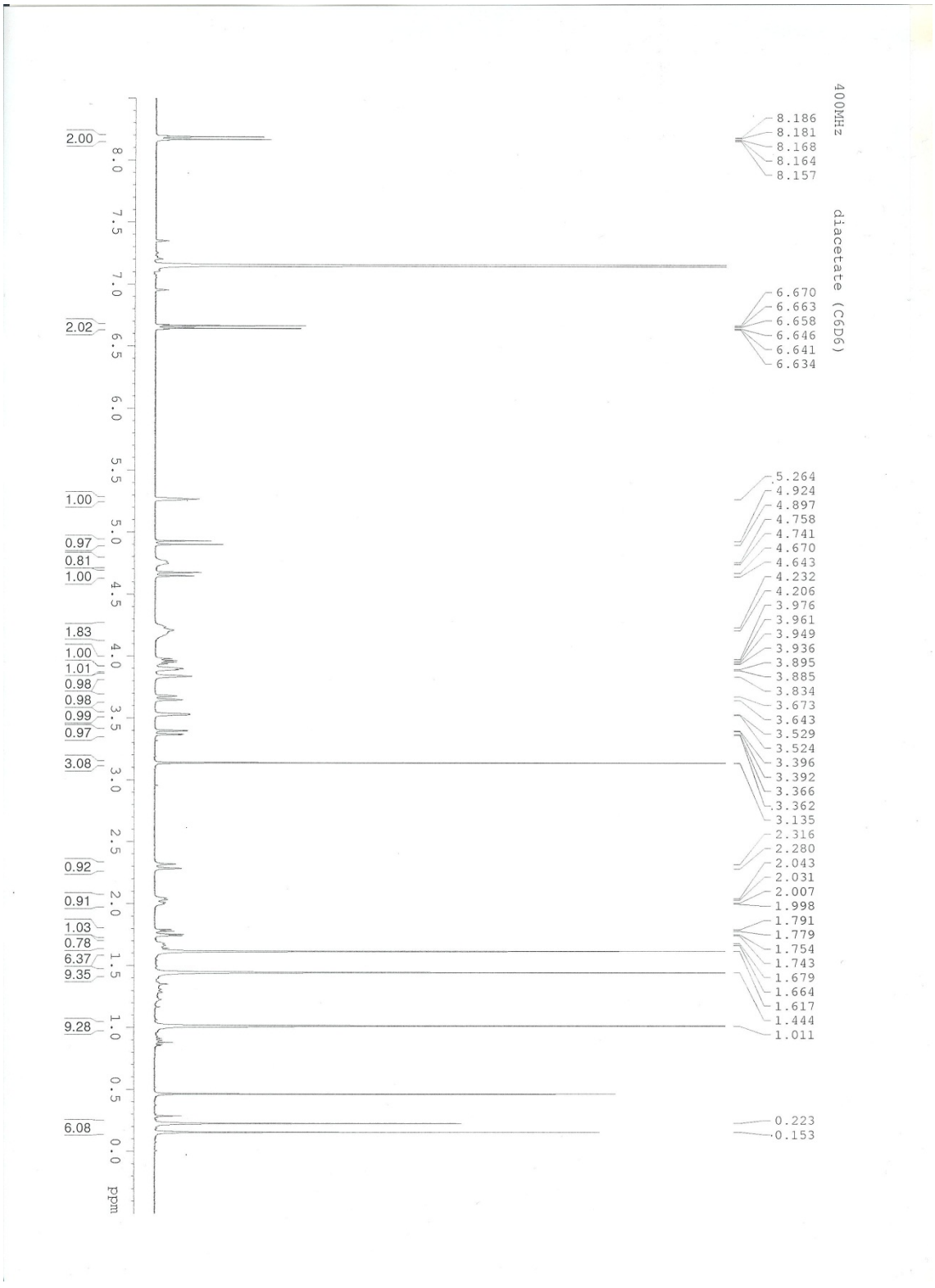


Figure 20. ^{1}H NMR Spectrum of the ester **18**

(RT)

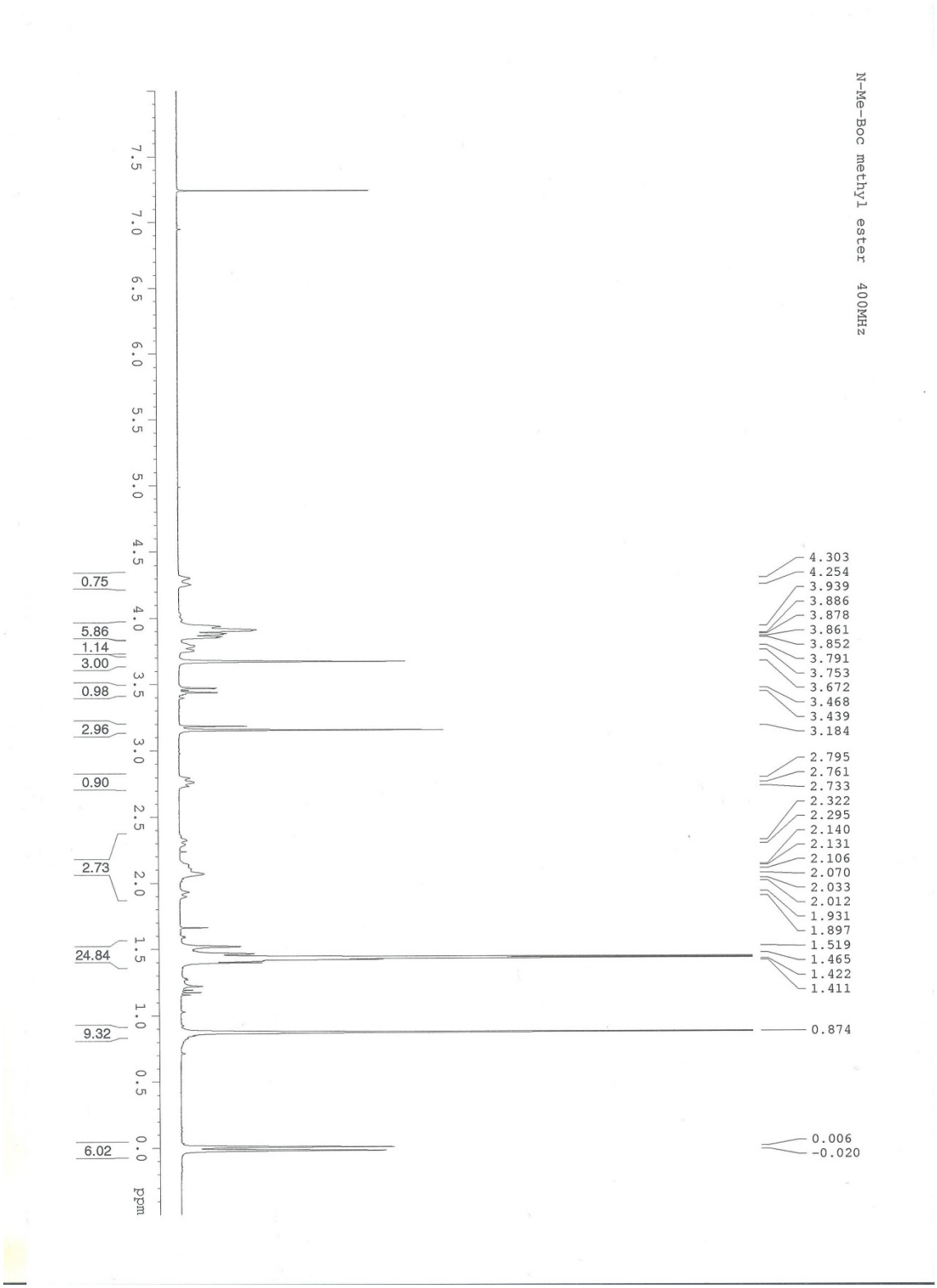


Figure 21. ^{1}H NMR Spectrum of the ester **18** (55^{o}C)

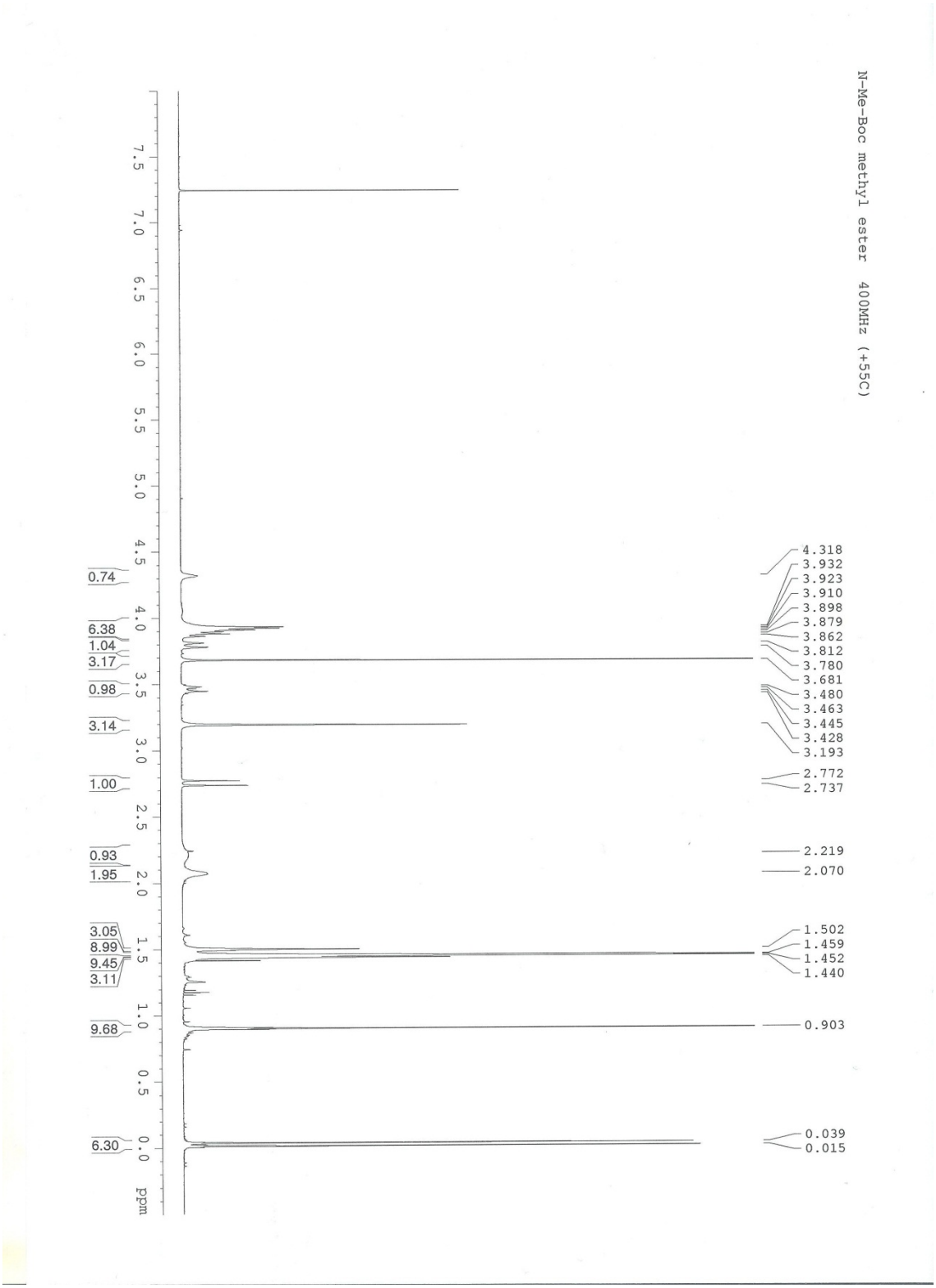


Figure 22. ^{13}C NMR Spectrum of the ester **18** (RT)

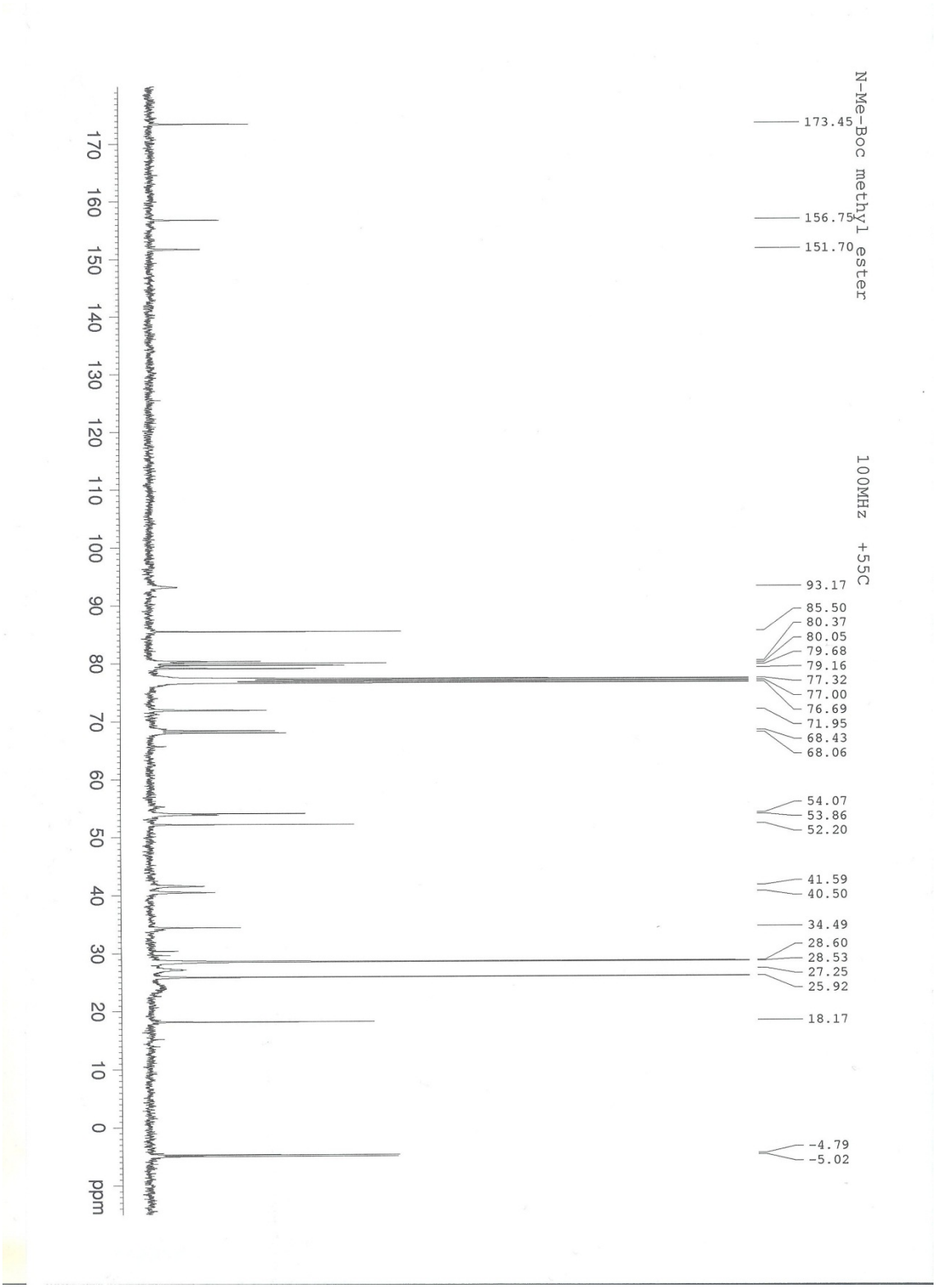


Figure 23. ^{1}H NMR Spectrum of the carboxylic acid **19** (RT)

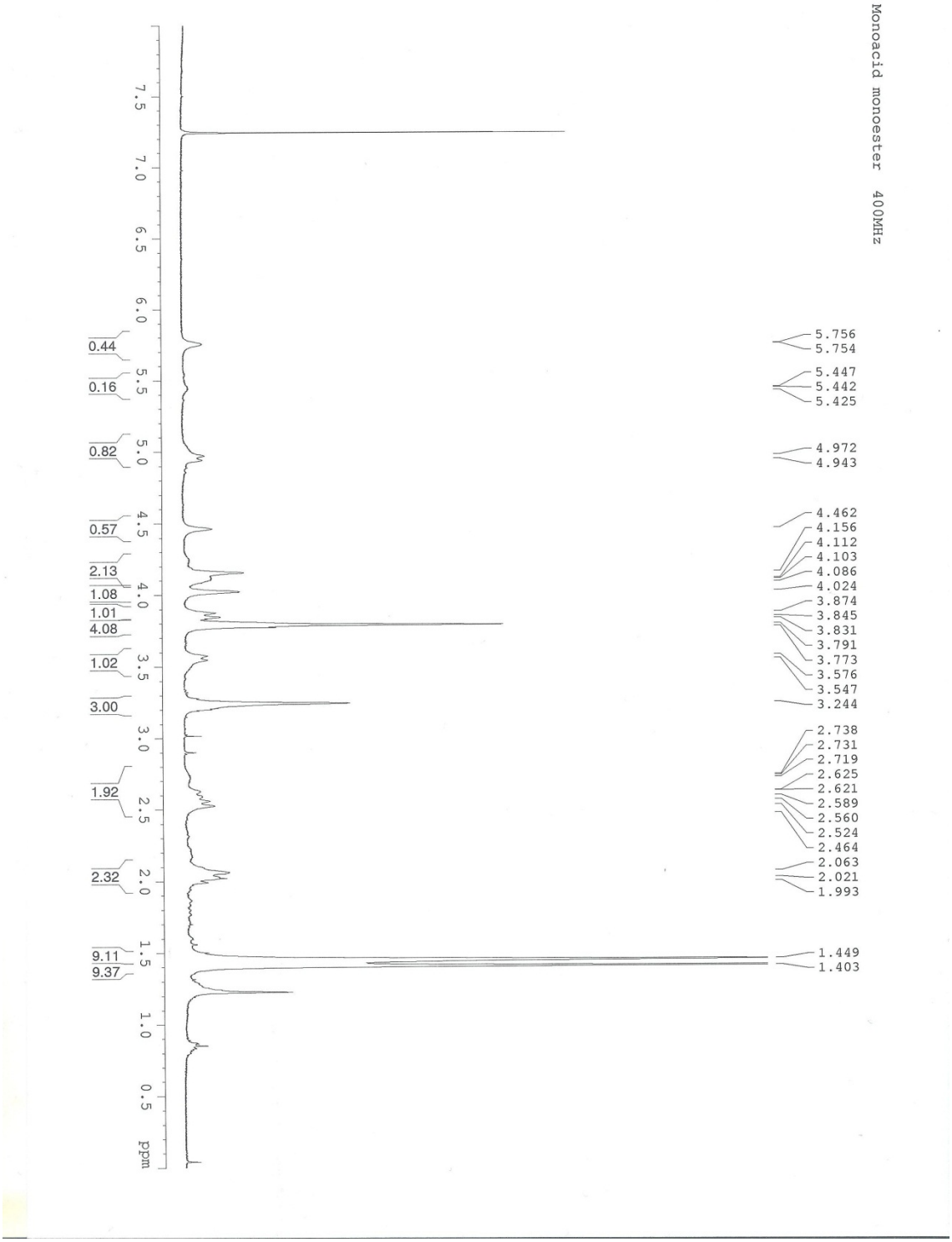


Figure 24. ^{1}H NMR Spectrum of the carboxylic acid **19** (55^{o}C)

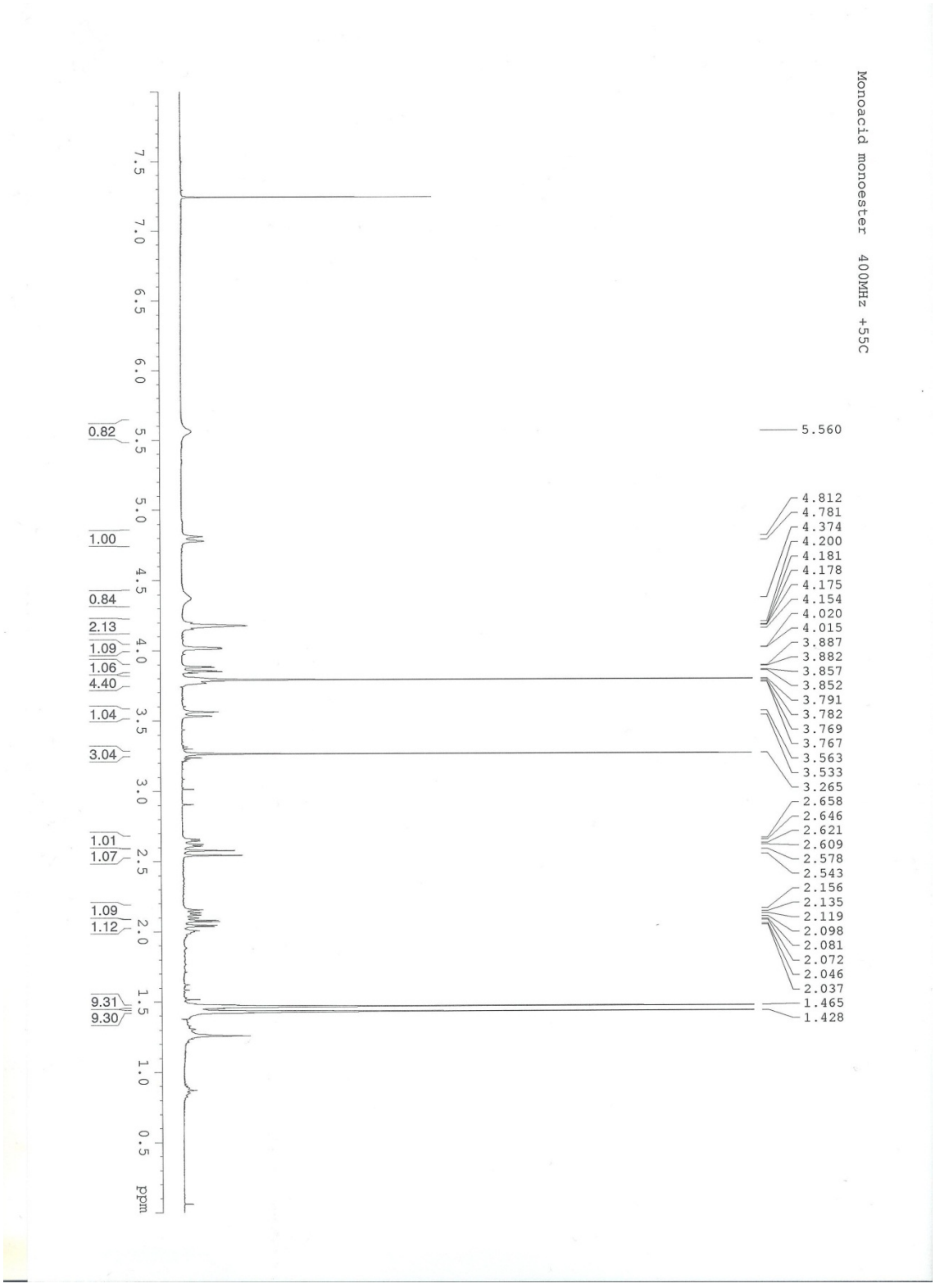


Figure 25. ^{13}C NMR Spectrum of the carboxylic acid **19** (RT)

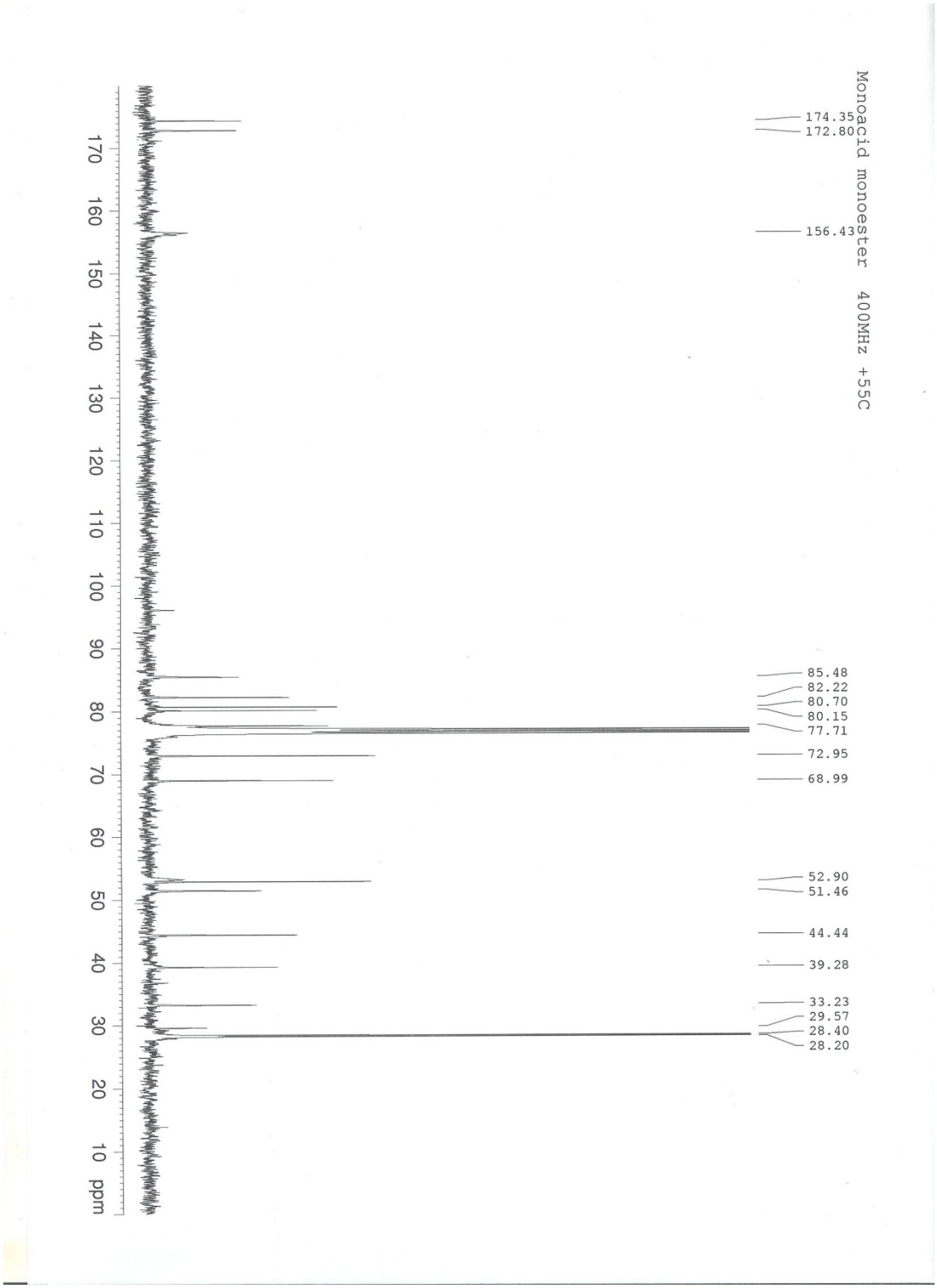


Figure 26. ^{1}H NMR Spectrum of the diester **20**

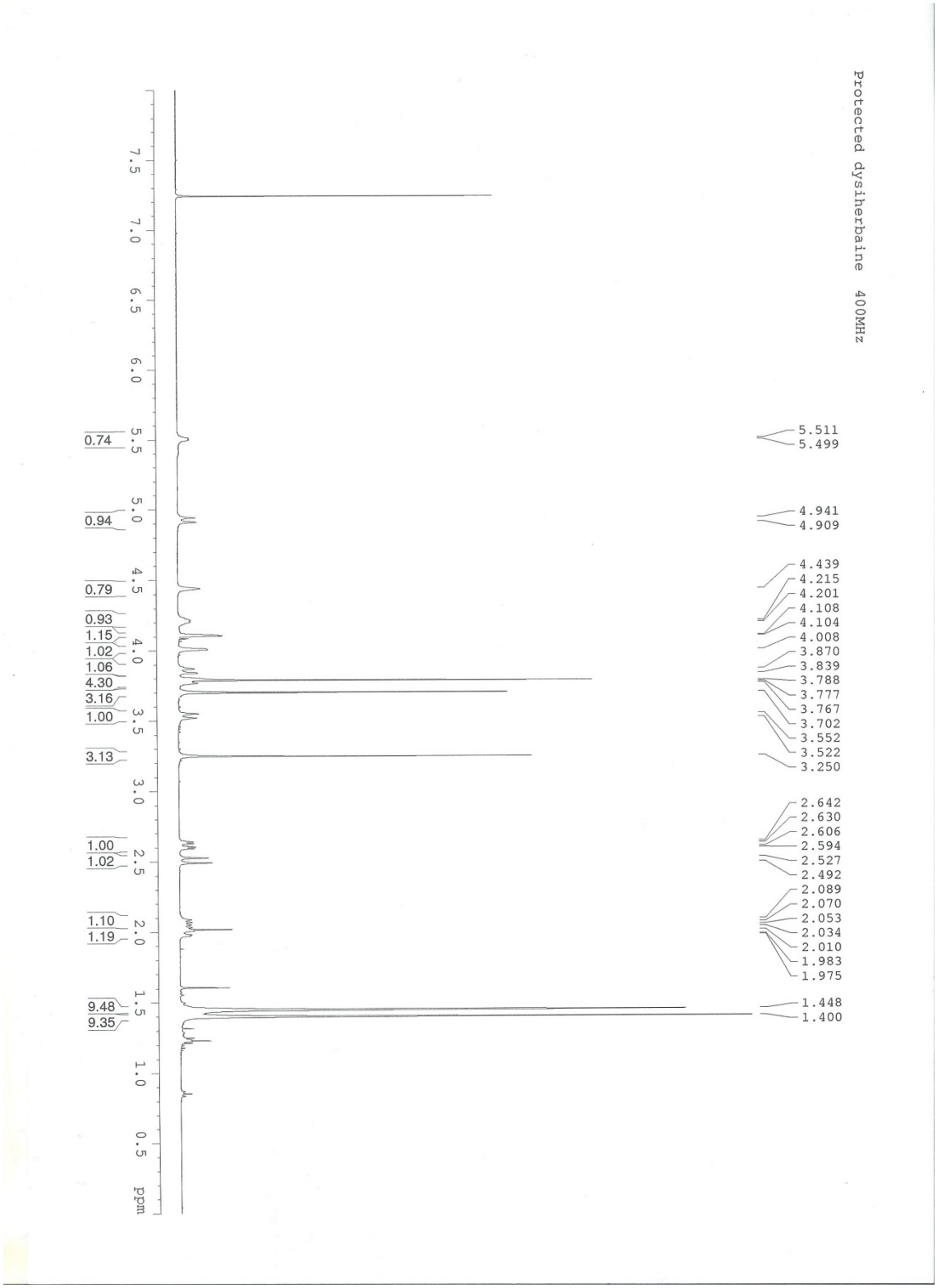


Figure 27. ^{13}C NMR Spectrum of the diester **20**

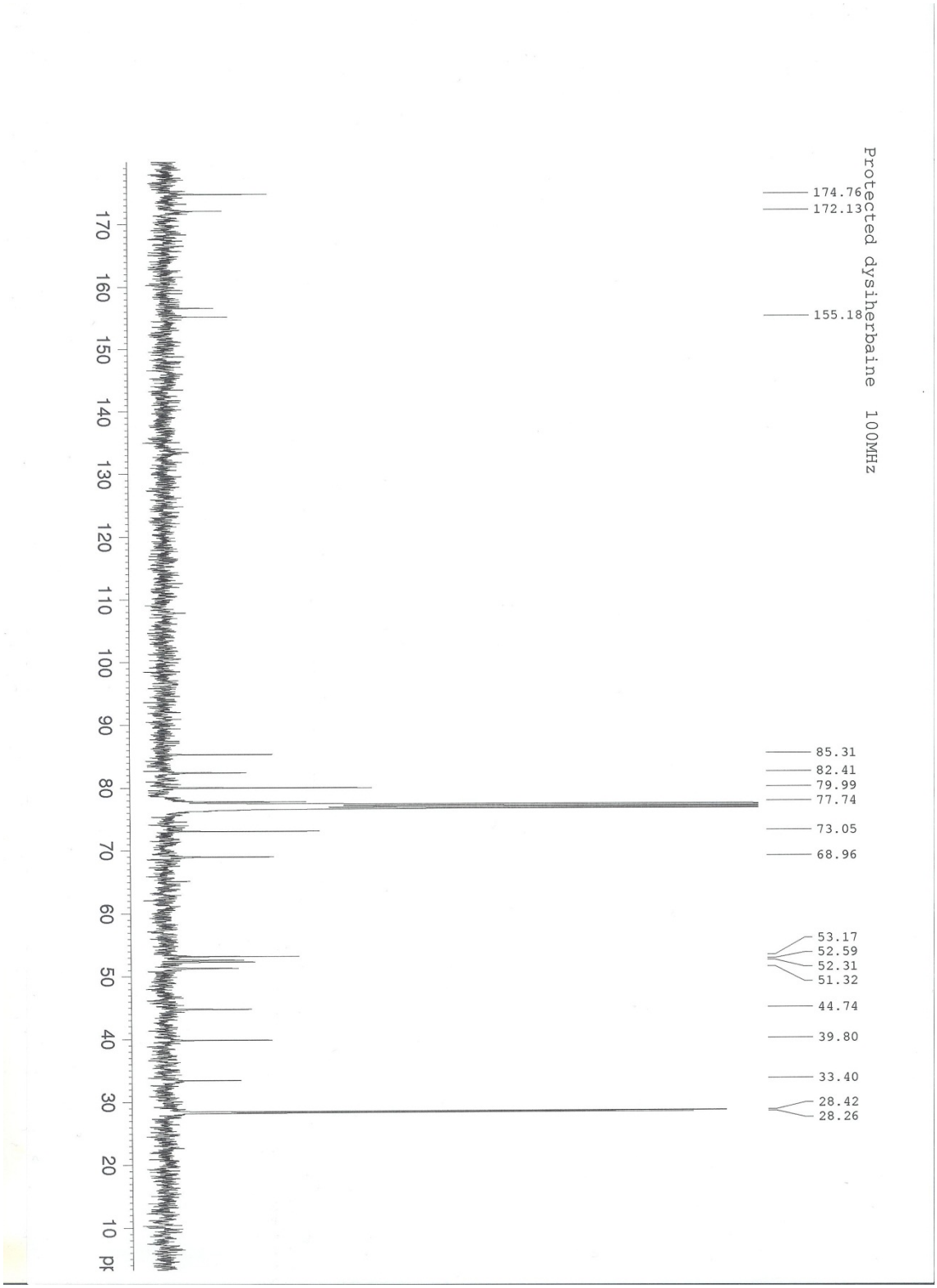


Figure 28 ^{1}H NMR Spectrum of (-)-dysiherbaine·2HCl (0.05 M, RT)

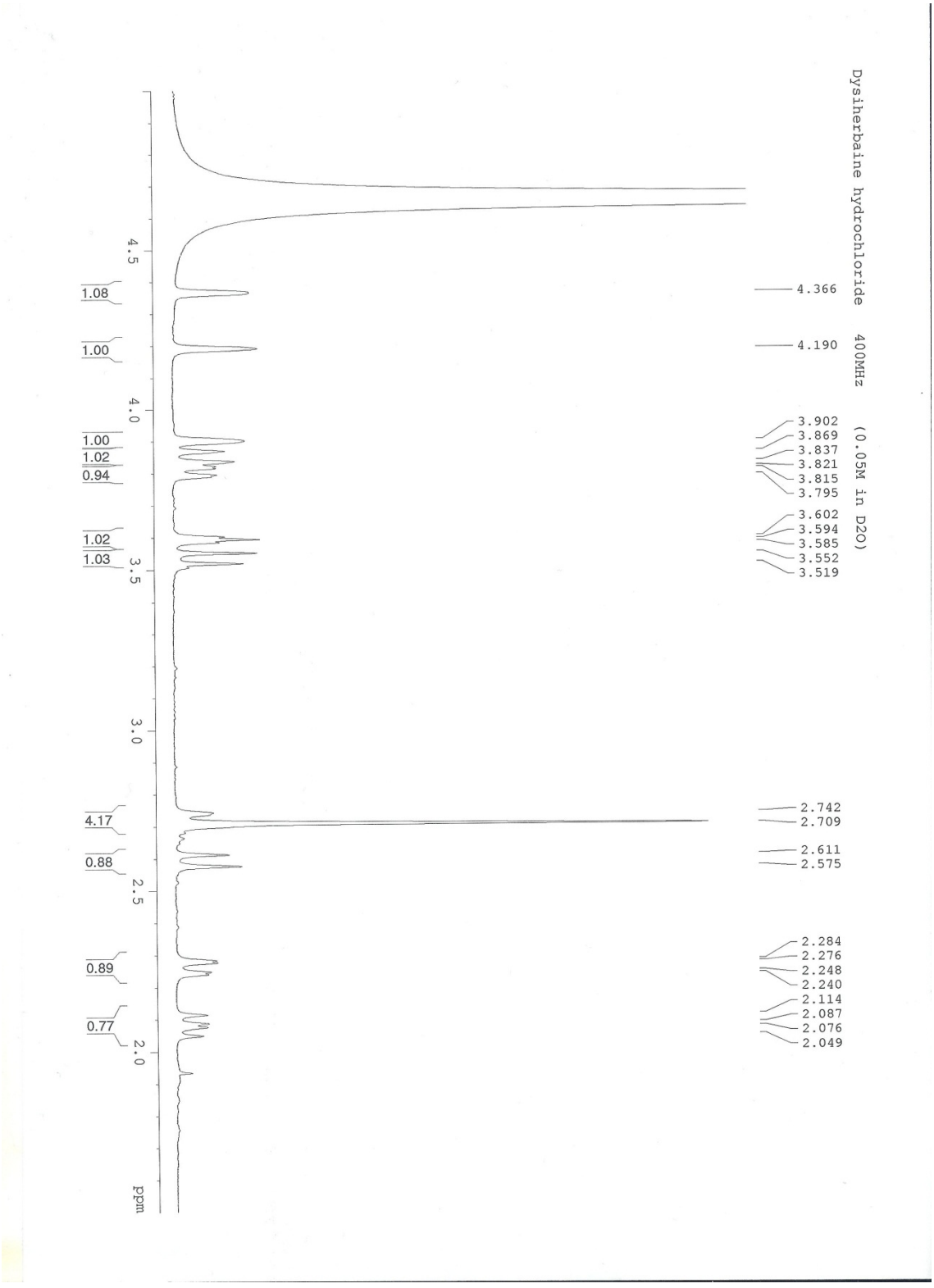


Figure 29 ^{1}H NMR Spectrum of (-)-dysiherbaine·2HCl (0.03 M, RT)

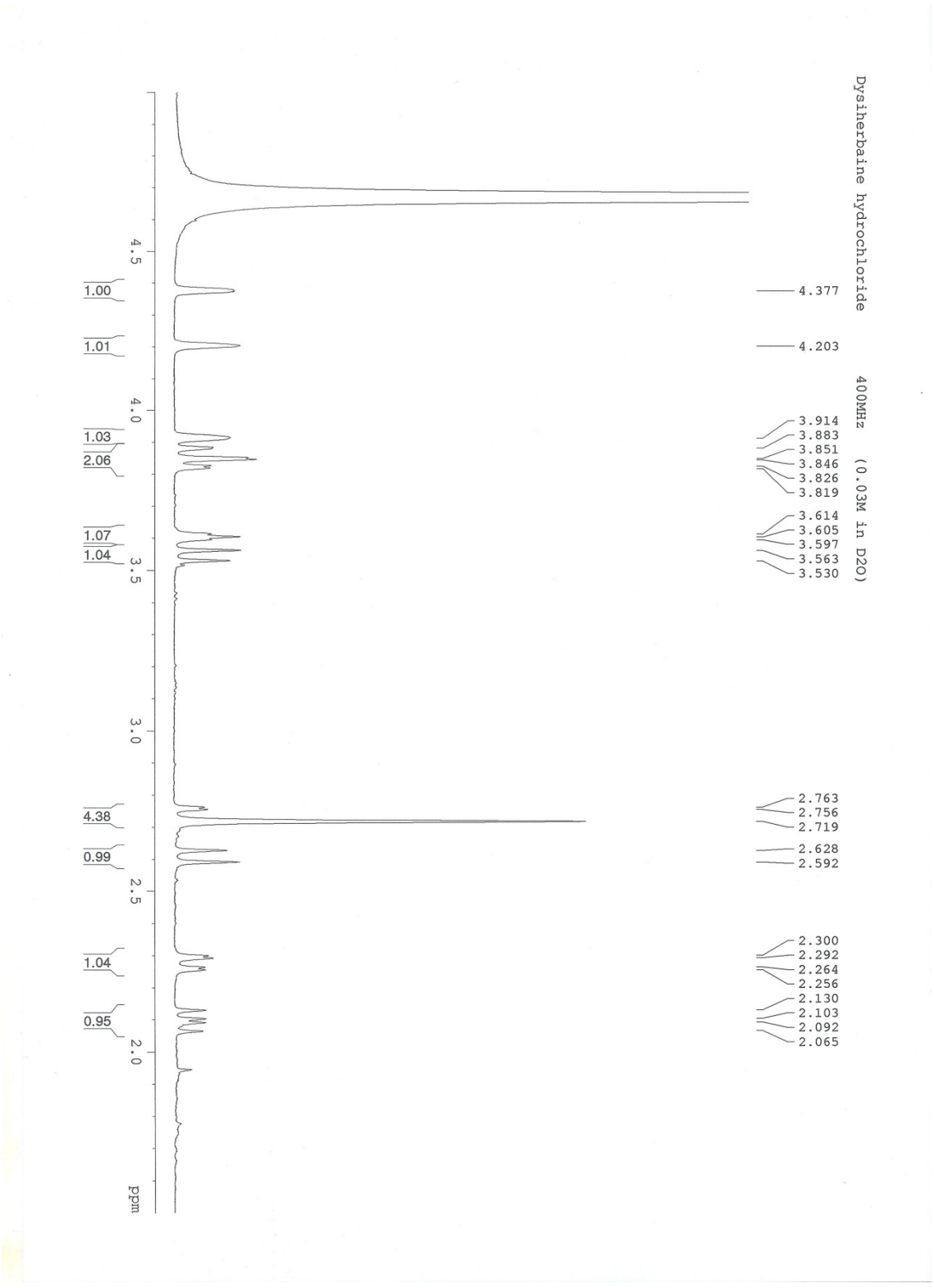


Figure 30 ^{1}H NMR Spectrum of (-)-dysiherbaine·2HCl (0.005 M, RT)

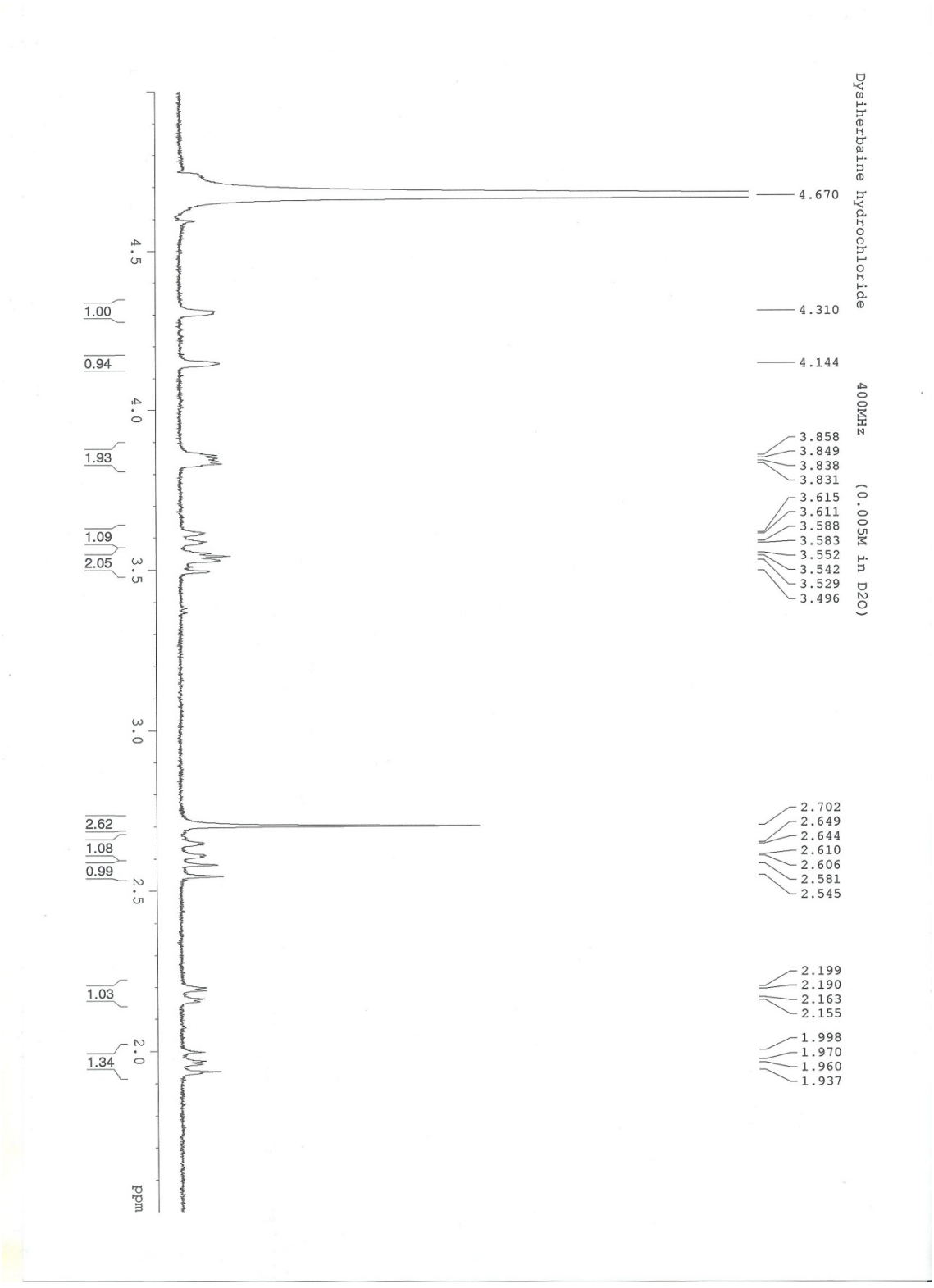


Figure 31 ^{13}C NMR Spectrum of (-)-dysiherbaine·2HCl (0.05 M, RT)

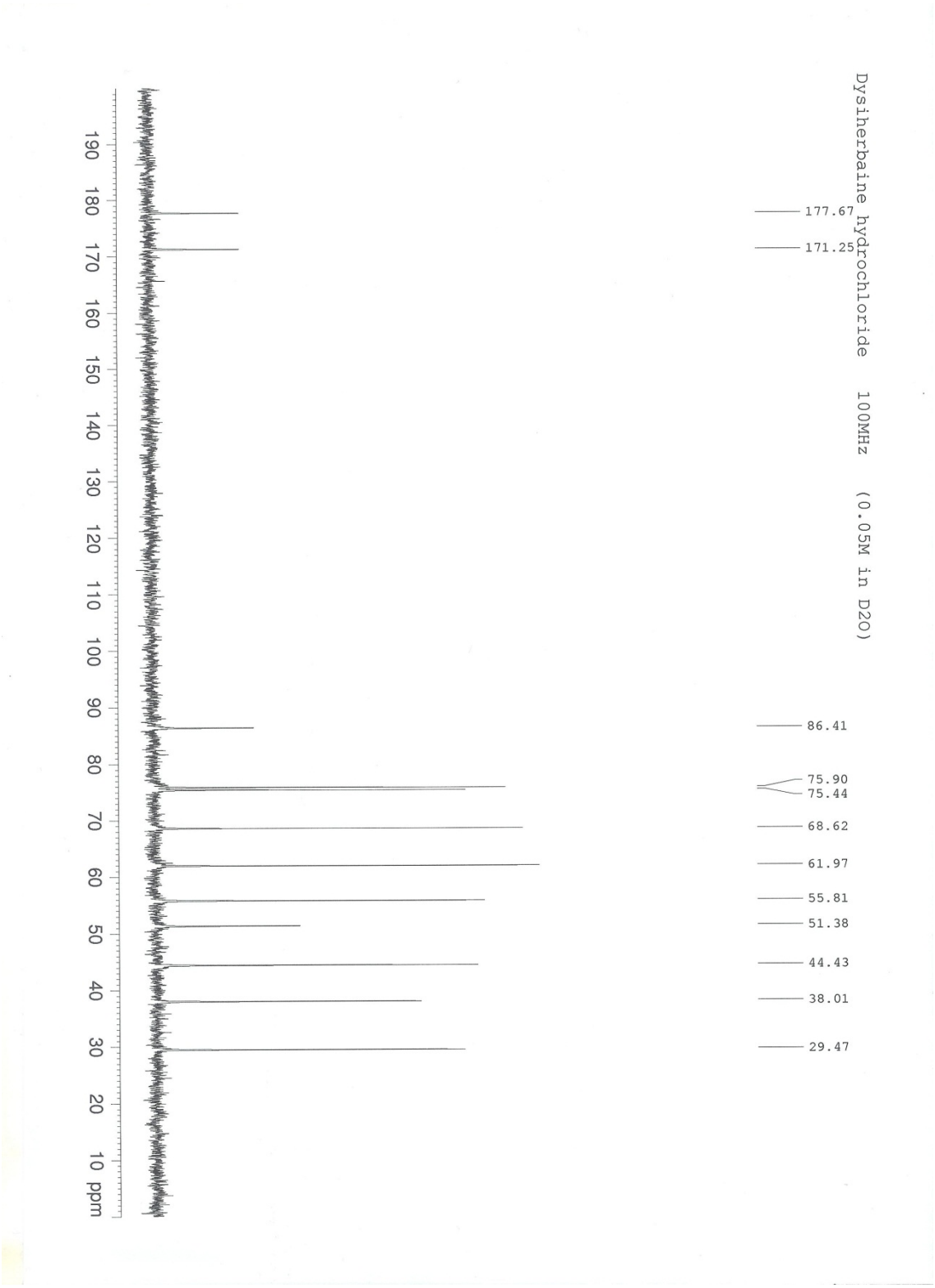


Figure 32. ^{1}H NMR Spectrum of (-)-dysiherbaine (**1**) (0.05 M, RT)

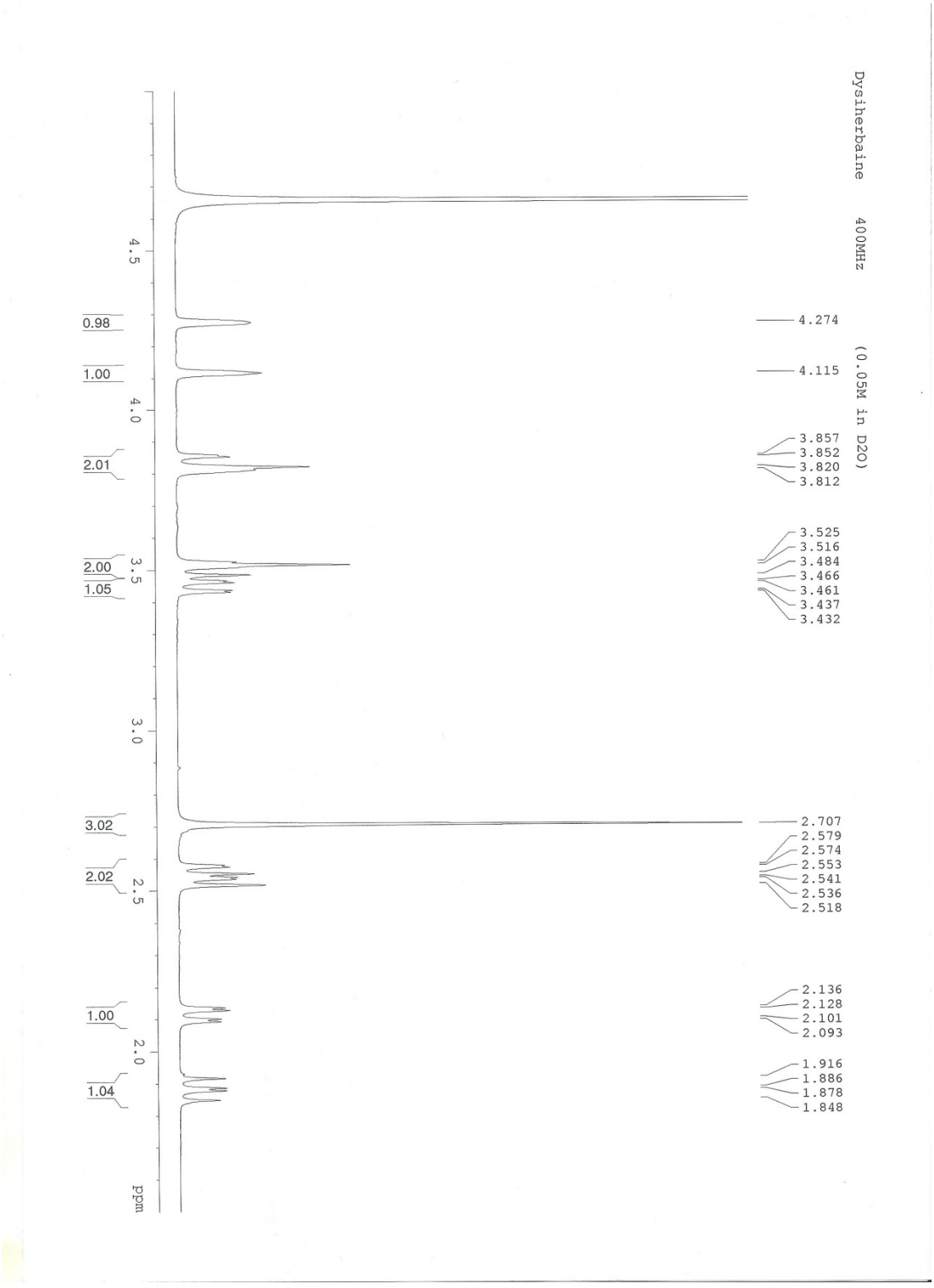


Figure 33. ^{13}C NMR Spectrum of (-)-dysiherbaine (**1**) (0.05 M, RT)