

50.0	3.1	100	77	9
200	13	100	79	7

Table S-5. The Br/Li exchange reaction of 2,6-dibromopyridine with *n*-BuLi (1.0 eq) followed by reaction with iodomethane in flow microreactor systems.

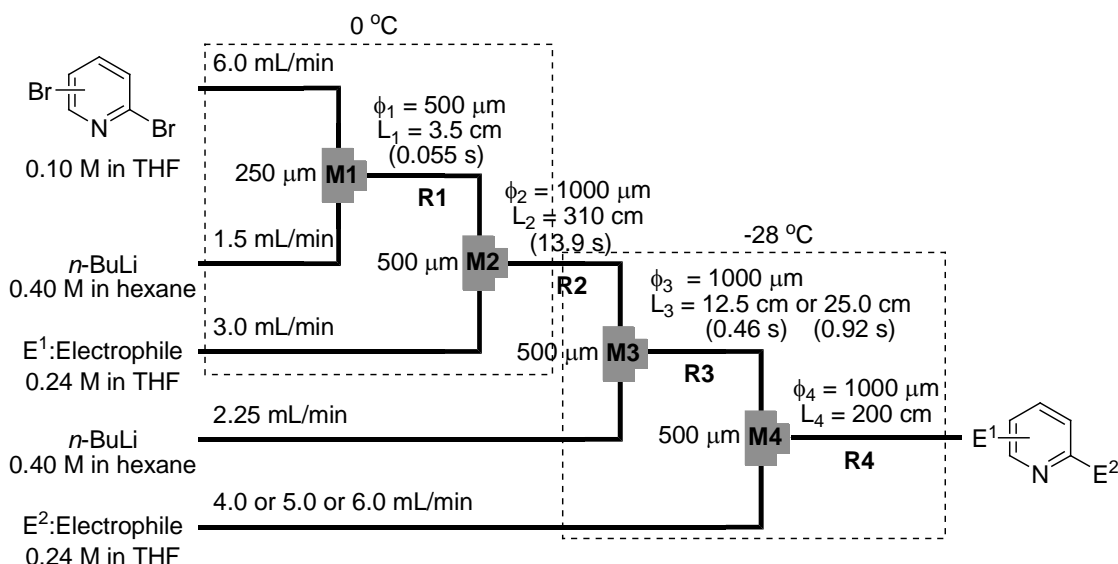
L ₁ (cm)	ϕ_1 (μm)	t^{R1} (s)	T ($^{\circ}\text{C}$)	conversion (%)		yield (%)	
				2,6-dibromopyridine	2-bromo-6-methylpyridine	2-bromopyridine	
3.50	250	0.014	25	100	92	3	
3.50	500	0.055		100	94	3	
3.50	1000	0.22		100	89	4	
12.5		0.79		100	88	3	
50.0		3.1		94	69	6	
200		13		100	69	3	
3.50	250	0.014	0	100	82	6	
3.50	500	0.055		100	90	4	
3.50	1000	0.22		98	90	4	
12.5		0.79		99	91	4	
50.0		3.1		99	90	4	
200		13		95	80	6	
3.50	250	0.014	-28	100	85	2	
3.50	500	0.055		100	93	2	
3.50	1000	0.22		100	92	2	
12.5		0.79		100	89	2	
50.0		3.1		100	89	3	
200		13		100	82	5	
3.50	250	0.014	-48	89	81	3	
3.50	500	0.055		95	85	3	
3.50	1000	0.22		99	92	4	
12.5		0.79		100	91	4	
50.0		3.1		95	86	5	
200		13		100	87	5	
3.50	250	0.014	-78	85	78	4	
3.50	500	0.055		93	89	3	
3.50	1000	0.22		92	86	3	
12.5		0.79		95	89	4	
50.0		3.1		97	91	3	
200		13		99	90	3	

In all cases of 2,3-dibromopyridine, 2,5-dibromopyridine, and 2,6-dibromopyridine, $T = 0\text{ }^{\circ}\text{C}$ was selected as a bath temperature under the $t^{\text{R1}} = 0.055\text{ s}$.

The spectral data of 2-bromo-3-trimethylsilylpyridine, 2-bromo-3-(α -hydroxybenzyl)pyridine, 2-bromo-5-(α -hydroxybenzyl)pyridine, 2-bromo-6-trimethylsilylpyridine, 2-bromo-6-(α -hydroxybenzyl)pyridine were identical to those reported in the literature.¹

The analytical data for 2-bromo-5-trimethylsilylpyridine were identical to those reported in the literature.²

Typical Procedure for Sequential Introduction of Two Electrophiles into Dibromopyridines



A flow microreactor system consisting of four T-shaped micromixers (**M1**, **M2**, **M3** and **M4**), four microtube reactors (**R1**, **R2**, **R3** and **R4**) and six tube pre-cooling units (**P1** (inner diameter $\phi = 1000 \mu\text{m}$, length $L = 100 \text{ cm}$), **P2** ($\phi = 1000 \mu\text{m}$, $L = 50 \text{ cm}$) and **P3** ($\phi = 1000 \mu\text{m}$, $L = 100 \text{ cm}$), **P4** ($\phi = 1000 \mu\text{m}$, $L = 50 \text{ cm}$), **P5** ($\phi = 1000 \mu\text{m}$, $L = 100 \text{ cm}$)) was used. The flow microreactor system consisting of **M1**, **M2**, **R1**, **R2**, **P1**, **P2** and **P3** was dipped in a cooling bath at 0°C . The flow microreactor system consisting of **M3**, **M4**, **R2**, **R3**, **R4**, **P4** and **P5** was dipped in a bath cooled at -28°C . A solution of dibromopyridines (0.10 M in THF) (flow rate: 6.00 mL min^{-1}) and a solution of *n*-BuLi (0.40 M in *n*-hexane) (flow rate: 1.5 mL min^{-1}) were introduced to **M1** ($\phi = 250 \mu\text{m}$). The resulting solution was passed through **R1** ($\phi_1 = 500 \mu\text{m}$, $L_1 = 3.5 \text{ cm}$) and was mixed with a solution of a first electrophile (E^1 : Electrophile-1) (0.24 M in THF) (flow rate: 3.0 mL min^{-1}) in **M2** ($\phi = 500 \mu\text{m}$). The resulting solution was passed through **R2** ($\phi_2 = 1000 \mu\text{m}$, $L_2 = 310 \text{ cm}$ (200 cm at 0°C , 10 cm at ambient temperature, and 100 cm at -28°C)), and was introduced to **M3** ($\phi = 500 \mu\text{m}$) where the solution was mixed with a solution of *n*-BuLi (0.40 M in *n*-hexane) (flow rate: 2.25 mL min^{-1}). The resulting solution was passed through **R3** ($\phi_3 = 1000 \mu\text{m}$, $L_3 = 12.5$ or 25 cm) and was introduced to **M4** ($\phi = 500 \mu\text{m}$) where the solution was mixed with a solution of a second electrophile (E^2 : Electrophile-2) (0.24 M in THF) (flow rate: 4.0 or 5.0 or 6.0 mL min^{-1}). The resulting solution was passed through **R4** ($\phi_4 = 1000 \mu\text{m}$, $L_4 = 200 \text{ cm}$). After a steady state was reached, the product solution was collected for 30 s while being quenched with H_2O . The organic phase was separated and the aqueous phase was extracted with diethyl ether. The combined organic phase was concentrated, and the resulting crude product was purified by flash chromatography on silica gel.

2-(α -Hydroxybenzyl)-3-methylpyridine. The reaction was performed under the following condition; flow rate of a solution of benzaldehyde (Electrophile-2): 4.0 mL min^{-1} , **R3**: $\phi = 1000 \mu\text{m}$, $L = 12.5 \text{ cm}$. After extraction with Et_2O , the crude product was purified by silica gel chromatography (hexane/AcOEt = 2/1) to afford 2-(α -hydroxybenzyl)-3-methylpyridine (40.4 mg, 68% yield, 88% purity (determined by GC)). 3-(α -Hydroxybenzyl)-2-methylpyridine was observed by GCMS as a major byproduct (9%, GC). ^1H NMR for title compound (400 MHz, CDCl_3) δ 2.07 (s, 3H), 5.73 (s, 1H), 5.92-6.12 (s, 1H), 7.14-7.46 (m, 8H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 17.8, 72.5, 122.6, 127.7, 127.8, 128.4, 130.4, 138.5, 142.3, 144.9, 157.9 ppm; HRMS (CI) m/z calcd for (MH^+) $\text{C}_{13}\text{H}_{14}\text{NO}$: 200.1076, found: 200.1073. When the reactions in **R3** and **R4** were carried out at 0°C , the yield was lower (23.0 mg, 38%).

2-Benzoyl-3-methylpyridine. The reaction was performed under the following condition; flow rate of a solution of benzonitrile (Electrophile-2): 5.0 mL min^{-1} , **R3**: $\phi_3 = 1000 \mu\text{m}$, $L_3 = 25 \text{ cm}$. After extraction with Et_2O , the crude product was purified by silica gel chromatography (hexane/AcOEt = 2/1) to afford 27.9 mg of 2-benzoyl-3-methylpyridine (47% yield, 97% purity (GC)). ^1H NMR (400 MHz, CDCl_3) δ 2.42 (s, 3H), 7.33 (dd, $J = 8.0, 4.8 \text{ Hz}$, 1H), 7.42-7.50 (m, 2H), 7.54-7.62 (m, 1H), 7.66 (dd, $J = 6.8, 0.8 \text{ Hz}$, 1H), 7.84-7.90 (m, 2H), 8.51 (dd, $J = 4.8, 1.2 \text{ Hz}$, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 18.4, 124.6, 128.4, 130.5, 132.8, 133.4, 136.4, 139.0, 146.0, 155.0, 195.3 ppm; HRMS (EI) m/z calcd for (M^+) $\text{C}_{13}\text{H}_{11}\text{NO}$: 197.0841, found: 197.0840.

2-(α -Hydroxybenzyl)-5-methylpyridine. The reaction was performed under the following condition; flow rate of a solution of benzaldehyde (Electrophile-2): 4.0 mL min^{-1} , **R3**: $\phi = 1000 \mu\text{m}$, $L = 25 \text{ cm}$. After extraction with Et_2O , the crude product was purified by silica gel chromatography (hexane/AcOEt = 1/2) to afford 2-(α -hydroxybenzyl)-5-methylpyridine (44.9 mg, 75% yield, 81% purity (GC)).

5-(α -Hydroxybenzyl)-2-methylpyridine was observed by GCMS as a major byproduct (9%, GC). 2- and 3-Hydroxybenzylpyridines as unpurified byproducts were also observed by GCMS (total 10%, GC). ^1H NMR for title compound (400 MHz, CDCl_3) δ 2.31 (s, 3H), 4.65-5.50 (m, 1H), 5.72 (s, 1H), 7.03 (d, J = 7.6 Hz, 1H), 7.21-7.45 (m, 6H), 8.35-8.40 (m, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 18.0, 74.7, 120.74, 126.9, 127.7, 128.5, 131.9, 137.5, 143.4, 148.0, 158.1 ppm; HRMS (ESI) m/z calcd for (MH^+) $\text{C}_{13}\text{H}_{14}\text{NO}$: 200.1076, found: 200.1073.

2-(α -Hydroxybenzyl)-5-trimethylsilylpyridine. The reaction was performed under the following condition; flow rate of a solution of benzaldehyde (Electrophile-2): 4.0 mL min^{-1} , **R3**: ϕ_3 = 1000 μm , L_3 = 12.5 cm. After extraction with Et_2O , the crude product was purified by silica gel chromatography (hexane/AcOEt = 2/1) to afford 39.6 mg of 2-(α -hydroxybenzyl)-5-trimethylsilylpyridine (51% yield, 93% purity (GC)). 5-(α -Hydroxybenzyl)-2-trimethylsilylpyridine was observed by GCMS as a major byproduct (7%, GC). ^1H NMR (400 MHz, CDCl_3) δ 0.29 (s, 9H), 5.74 (s, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.22-7.42 (m, 5H), 7.72 (dd, J = 7.6, 7.6 Hz, 1H), 8.60-8.64 (m, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 1.3, 74.8, 120.8, 127.0, 127.8, 128.5, 133.8, 124.0, 143.2, 151.8, 160.9 ppm; HRMS (APCI) m/z calcd for (MH^+) $\text{C}_{15}\text{H}_{20}\text{NOSi}$: 258.1315, found: 258.1238.

2-(α -Hydroxybenzyl)-6-methylpyridine. The reaction was performed under the following condition; flow rate of a solution of benzaldehyde (Electrophile-2): 4.0 mL min^{-1} , **R3**: ϕ_3 = 1000 μm , L_3 = 25 cm. After extraction with Et_2O , the crude product was purified by silica gel chromatography (hexane/AcOEt = 2/1) to afford 40.0 mg of 2-(α -hydroxybenzyl)-6-methylpyridine (67% yield, >99% purity (GC)). ^1H NMR (400 MHz, CDCl_3) δ 2.57 (s, 3H), 5.69 (s, 1H), 6.88 (d, J = 7.6 Hz, 1H), 7.02 (d, J = 7.6 Hz, 1H), 7.22-7.42 (m, 5H), 7.47 (dd, J = 7.6, 7.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 24.2, 74.5, 118.3, 121.8, 127.1, 127.6, 128.4, 137.0, 143.4, 156.6, 159.8 ppm; HRMS (APCI) m/z calcd for (MH^+) $\text{C}_{13}\text{H}_{14}\text{NO}$: 200.1076, found: 200.1074.

2-Benzoyl-6-methylpyridine. The reaction was performed under the following condition; flow rate of a solution of benzonitrile (Electrophile-2): 6.0 mL min^{-1} , **R3**: ϕ_3 = 1000 μm , L_3 = 25 cm. After extraction with Et_2O , the crude product was purified by silica gel chromatography (hexane/AcOEt = 2/1) to afford 32.9 mg of 2-benzoyl-6-methylpyridine (56% yield, >99% purity (GC)). ^1H NMR (400 MHz, CDCl_3) δ 2.63 (s, 3H), 7.31-7.36 (m, 1H), 7.44-7.52 (m, 2H), 7.54-7.62 (m, 1H), 7.72-7.80 (m, 2H), 8.06-8.12 (m, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 24.5, 121.6, 125.7, 128.0, 131.2, 132.8, 136.2, 137.0, 154.7, 157.7, 193.9 ppm; HRMS (APCI) m/z calcd for (MH^+) $\text{C}_{13}\text{H}_{12}\text{NO}$: 198.0920, found: 198.0913.

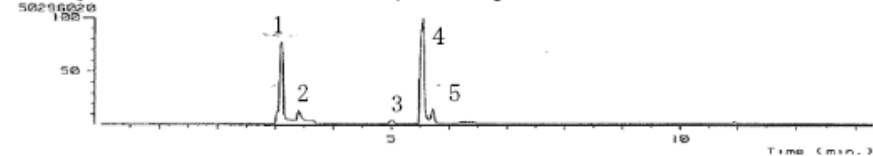
2-(1-Hydroxy-1-phenylethyl)-6-trimethylsilylpyridine. The reaction was performed under the following condition; flow rate of a solution of acetophenone (Electrophile-2): 4.0 mL min^{-1} , **R3**: ϕ_3 = 1000 μm , L_3 = 25 cm. After extraction with Et_2O , the crude product was purified by silica gel chromatography (hexane/AcOEt = 2/1) to afford 45.7 mg of 2-(1-hydroxy-1-phenylethyl)-6-trimethylsilylpyridine (56% yield, >99% purity (GC)). ^1H NMR (400 MHz, CDCl_3) δ 0.33 (s, 9H), 1.92 (s, 3H), 6.82 (s, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.17-7.24 (m, 1H), 7.28-7.34 (m, 2H), 7.39 (d, J = 7.2 Hz, 1H), 7.46-7.56 (m, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ -1.9, 29.1, 74.6, 119.5, 126.0, 126.8, 127.1, 128.1, 135.1, 147.3, 163.7, 165.3 ppm; HRMS (ESI) m/z calcd for (MH^+) $\text{C}_{16}\text{H}_{21}\text{NOSi}$: 272.1471, found: 272.1465.

References

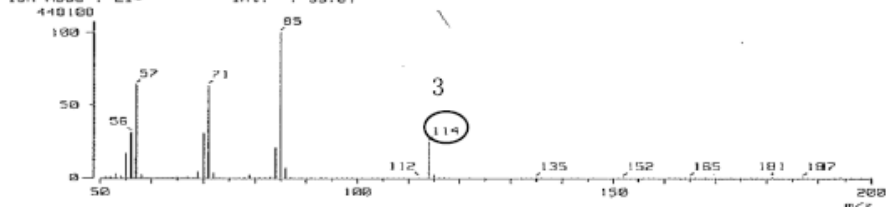
¹ Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron*, **2000**, 56, 1349-1360.

² For the spectral data of 2-bromo-5-trimethylsilylpyridine; Stange, A. F.; Tokura, S.; Kira, M. *J. Organomet. Chem.* **2000**, 612, 117-124.

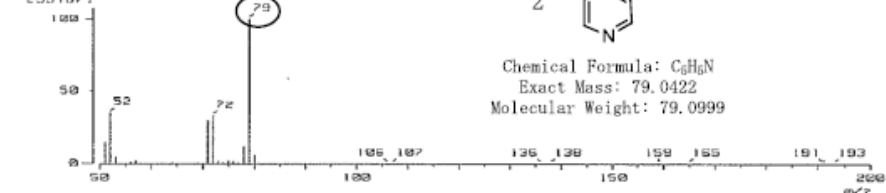
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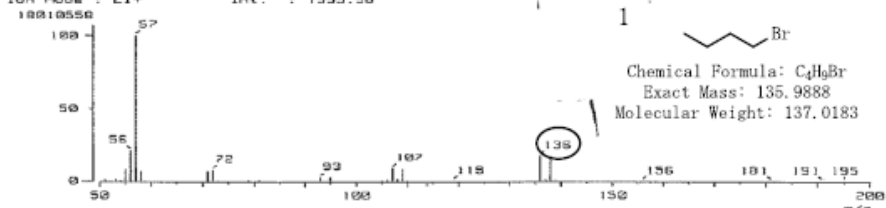
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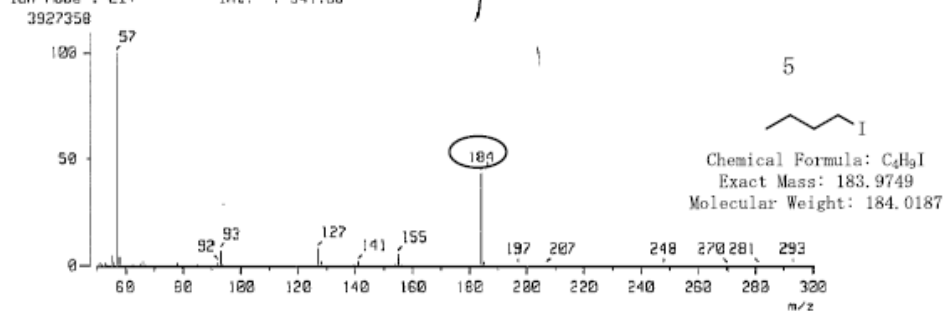
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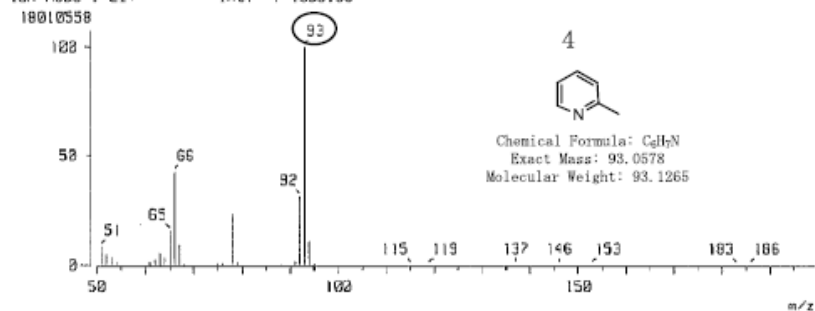
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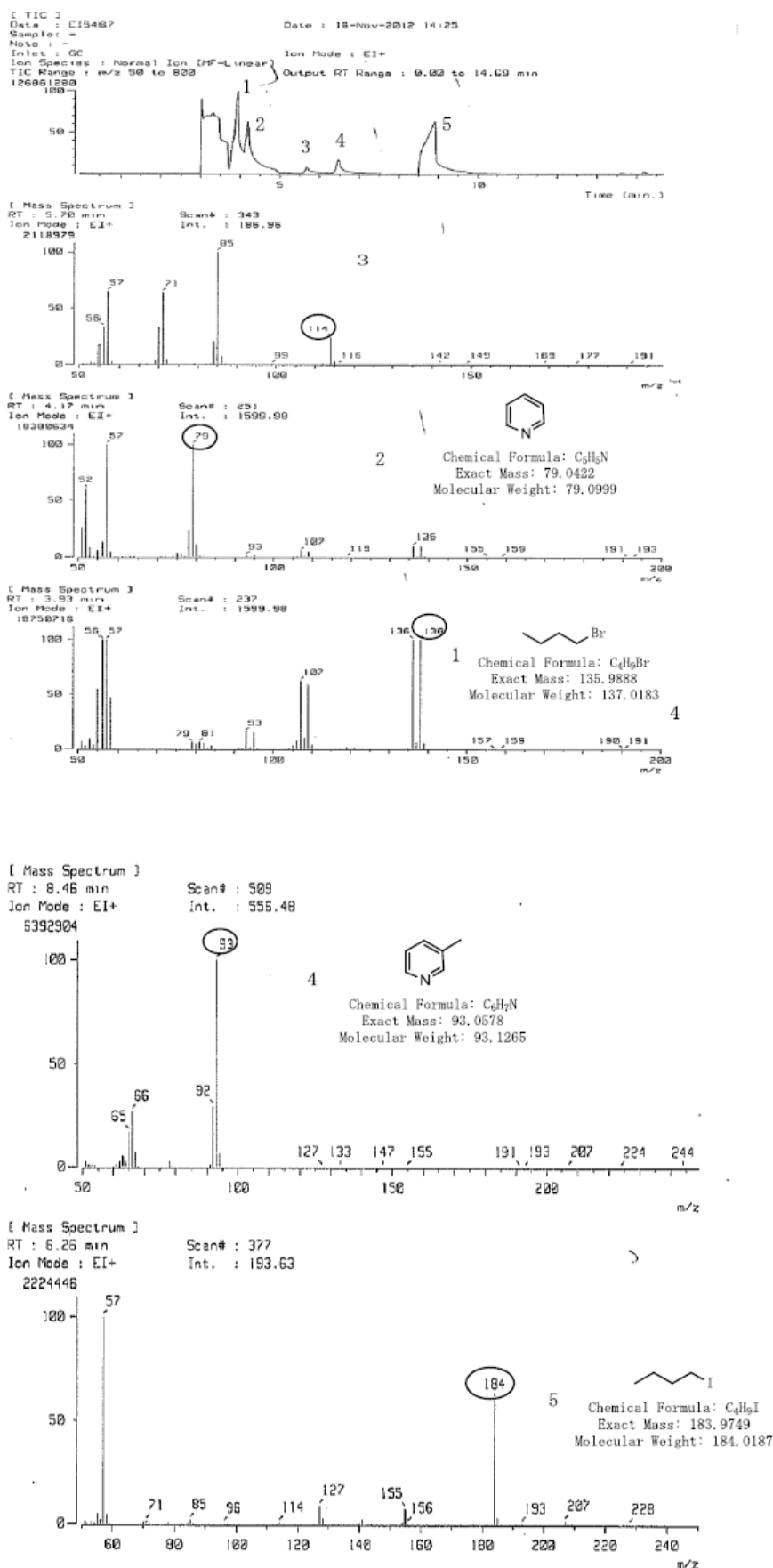
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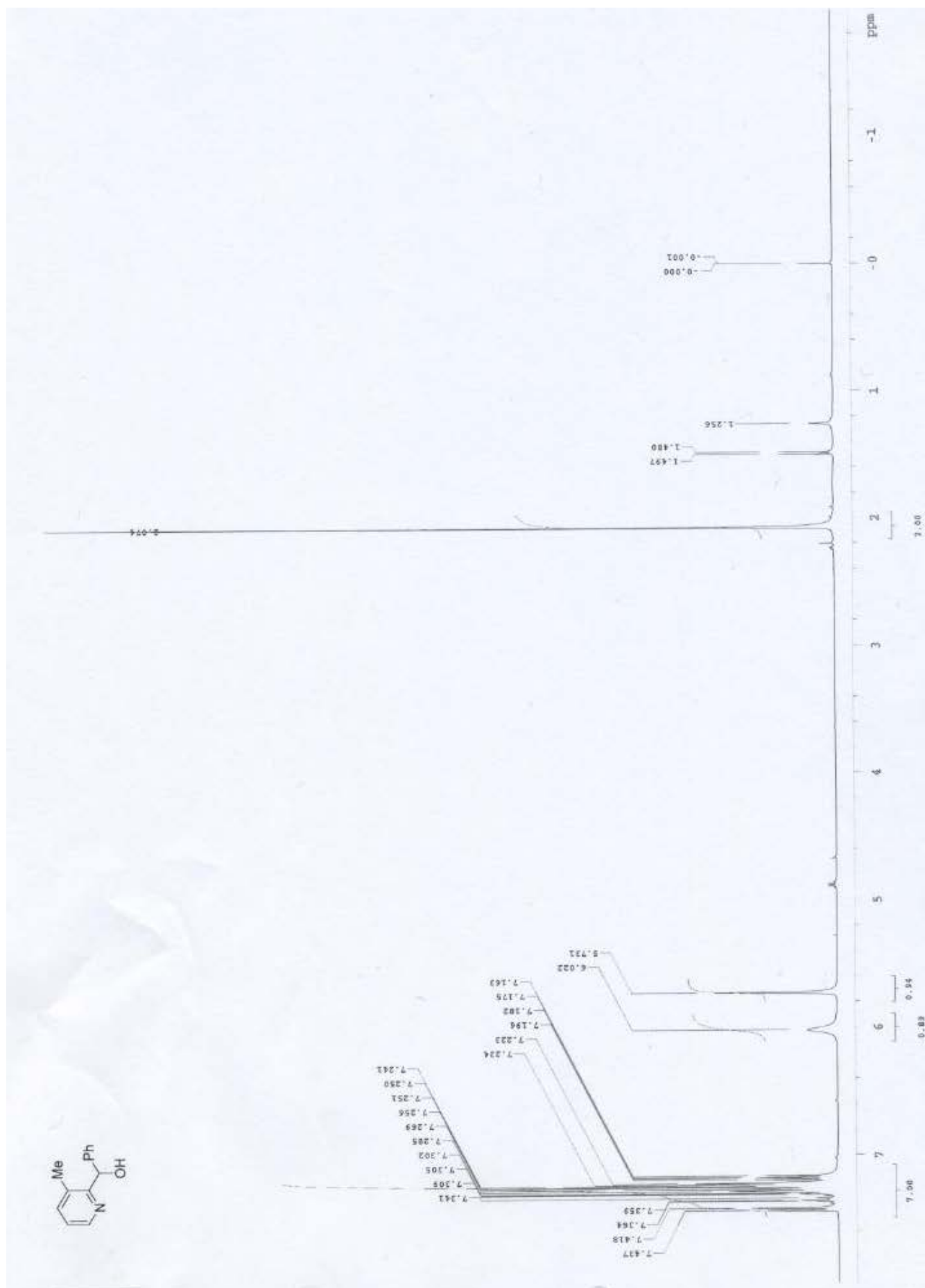
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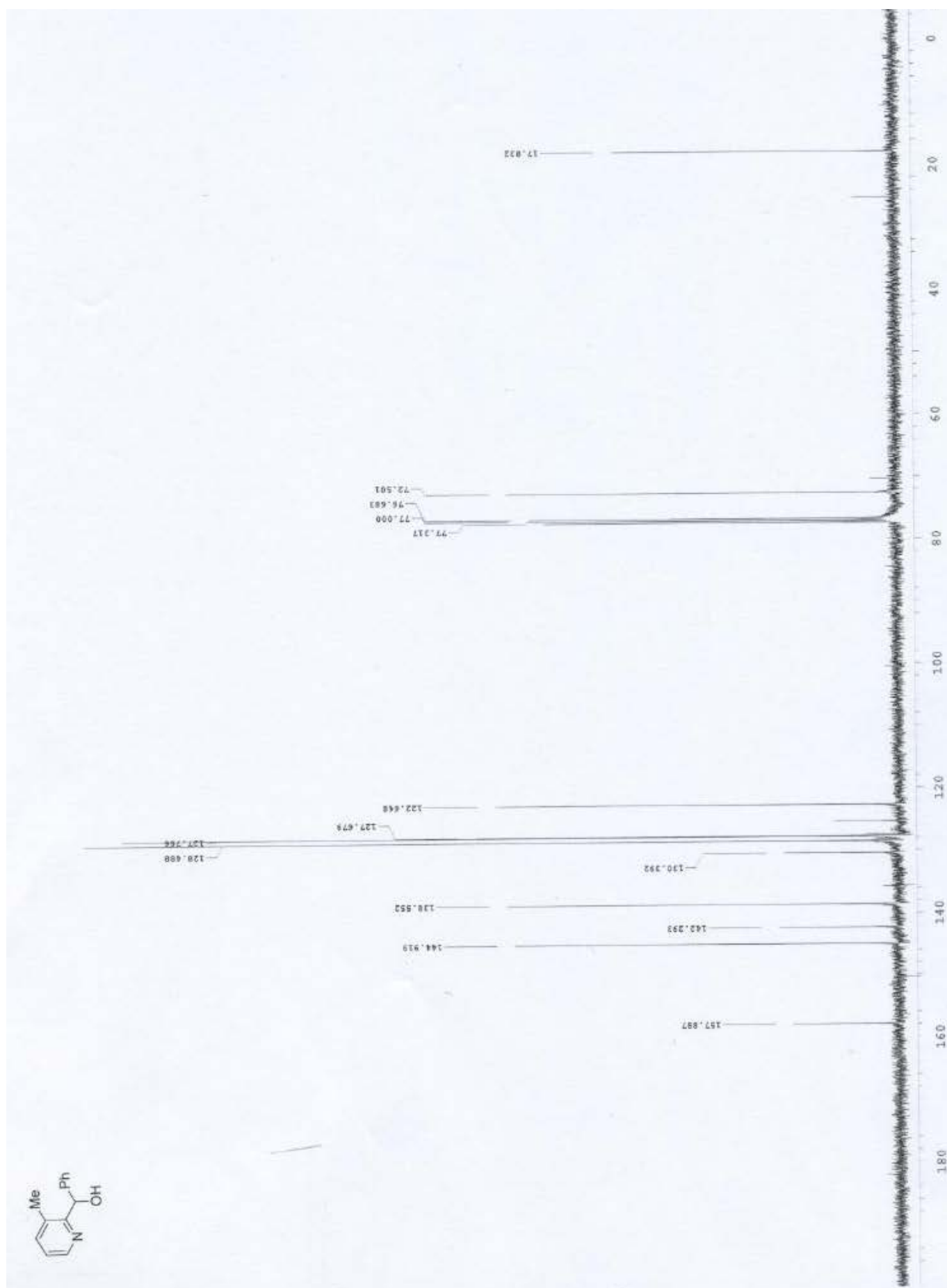
GCMS trace of the crude reaction product on the lithiation of 2-bromopyridine followed by the reaction with iodomethane in a conventional macro batch reactor



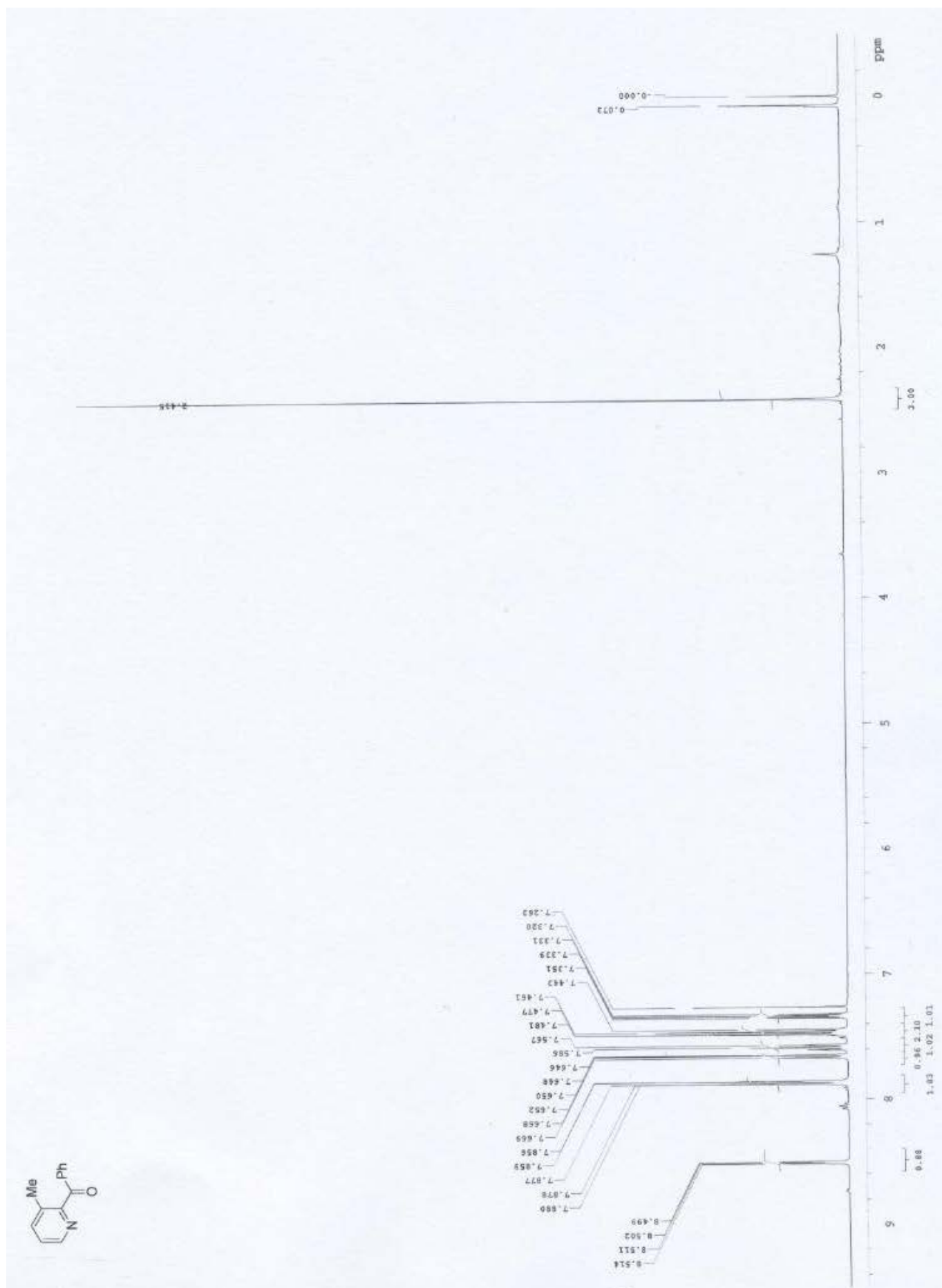
GCMS trace of the crude reaction product on the lithiation of 3-bromopyridine followed by the reaction with iodomethane in a conventional macro batch reactor



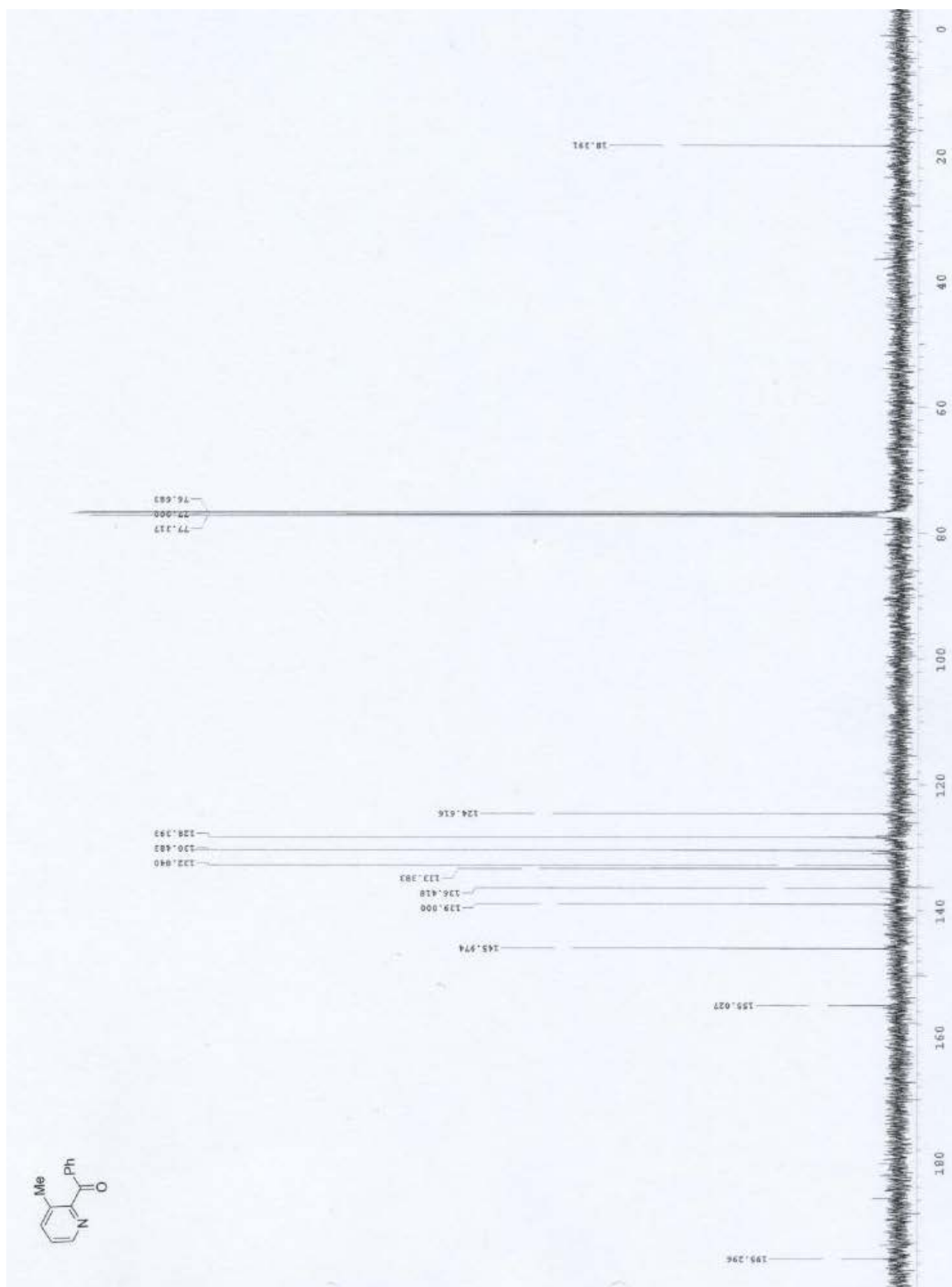
¹H NMR spectrum of 2-(α -hydroxybenzyl)-3-methylpyridine



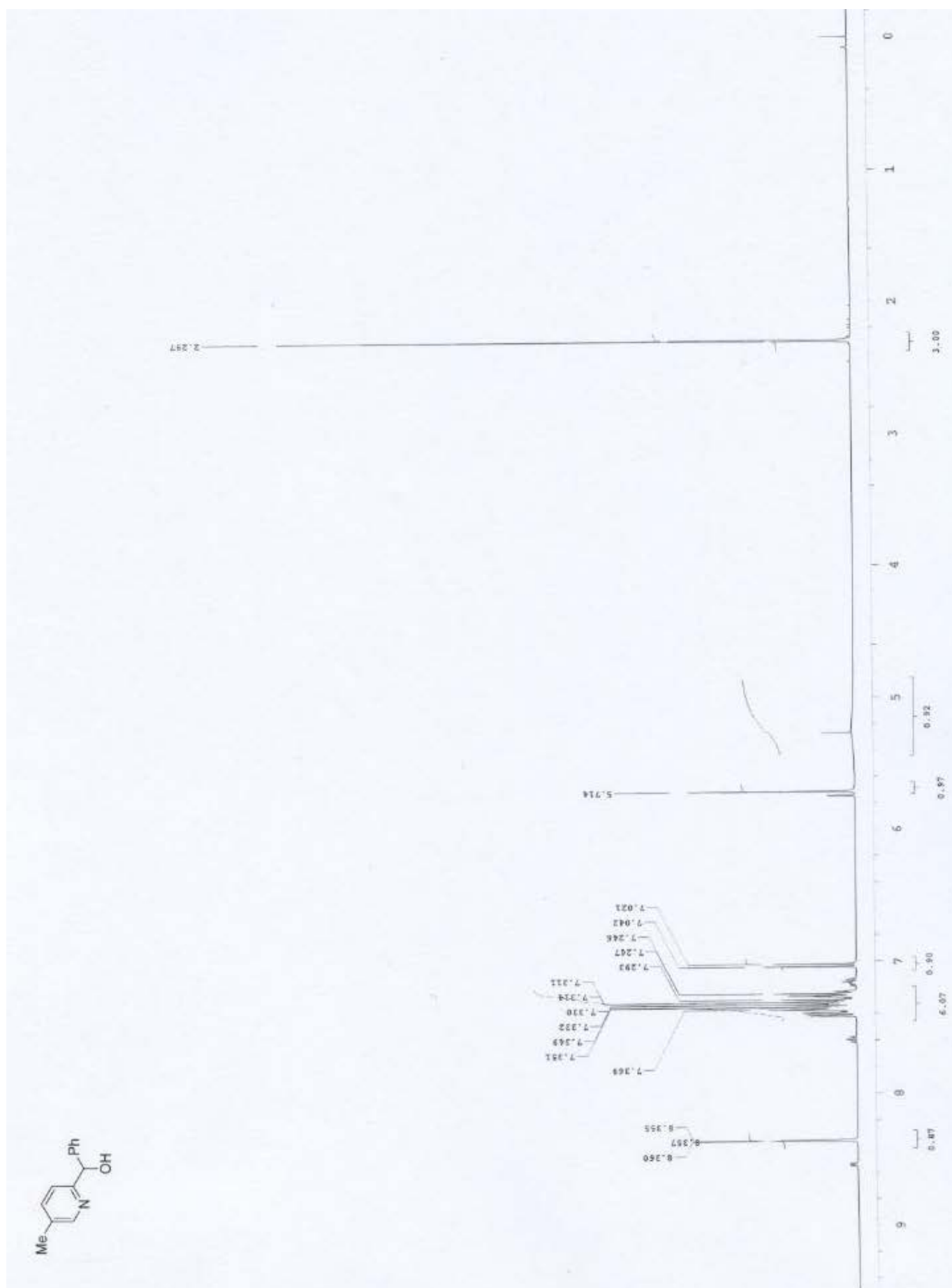
¹³C NMR spectrum of 2-(α-hydroxybenzyl)-3-methylpyridine



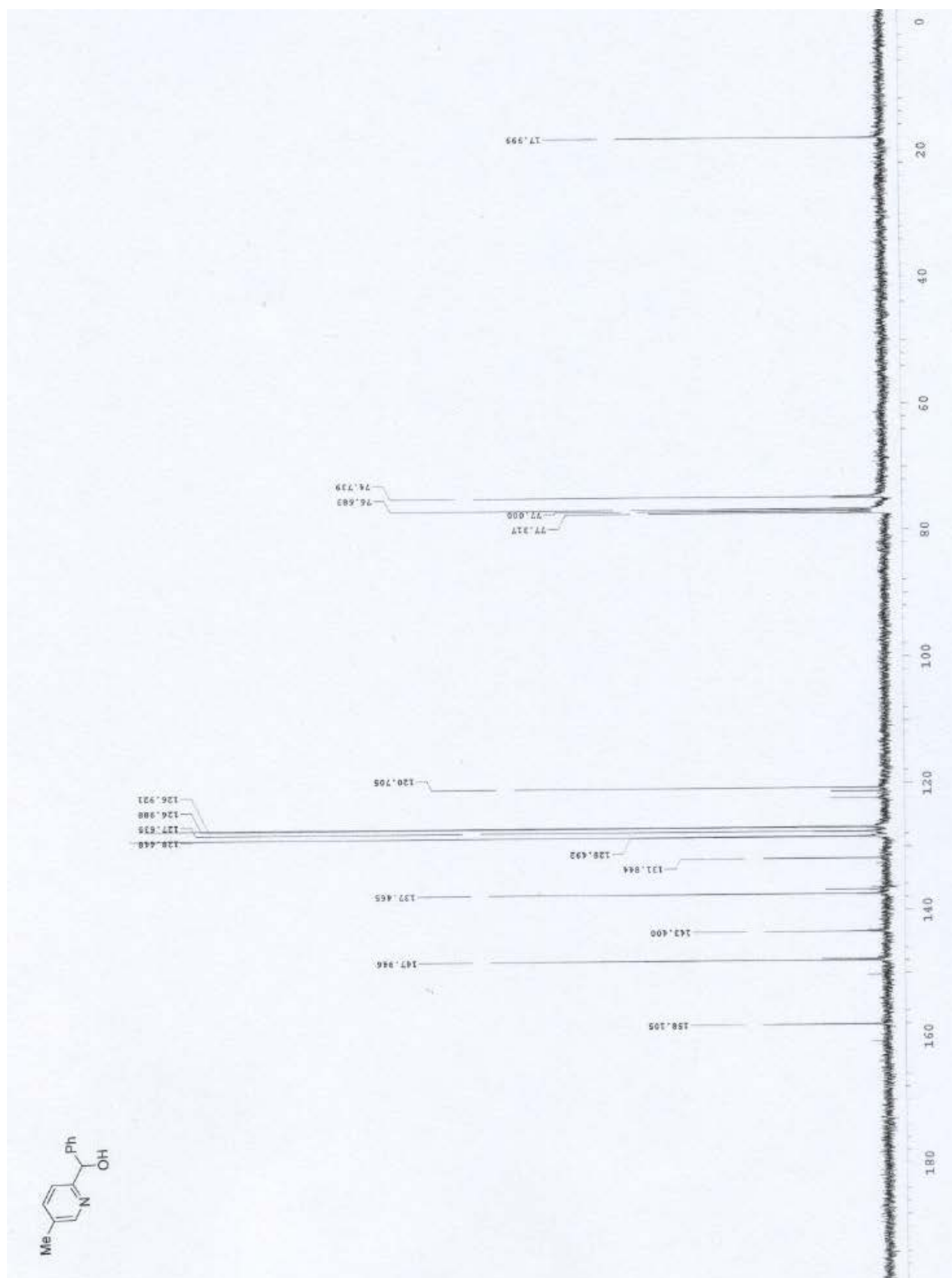
¹H NMR spectrum of 2-benzoyl-3-methylpyridine



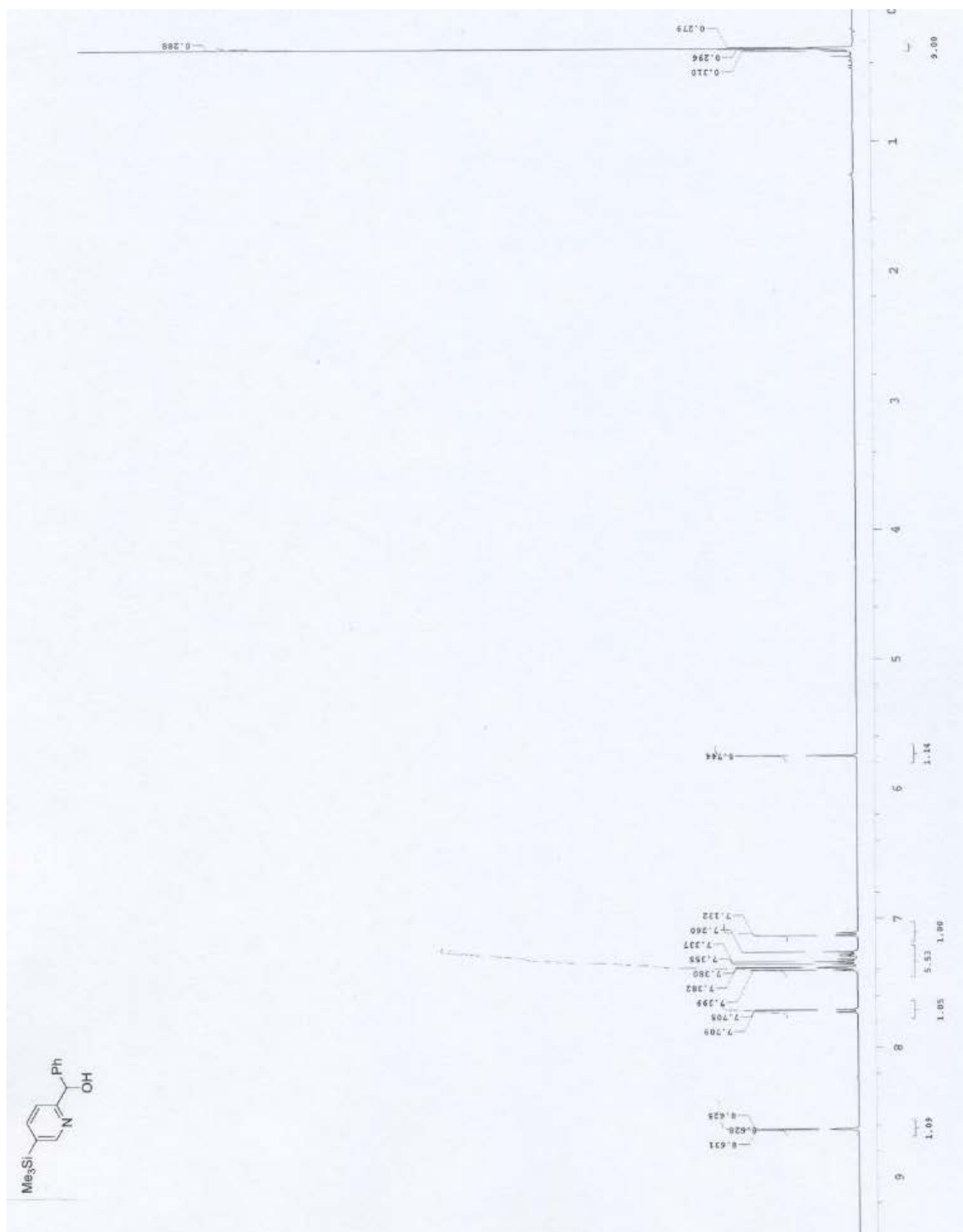
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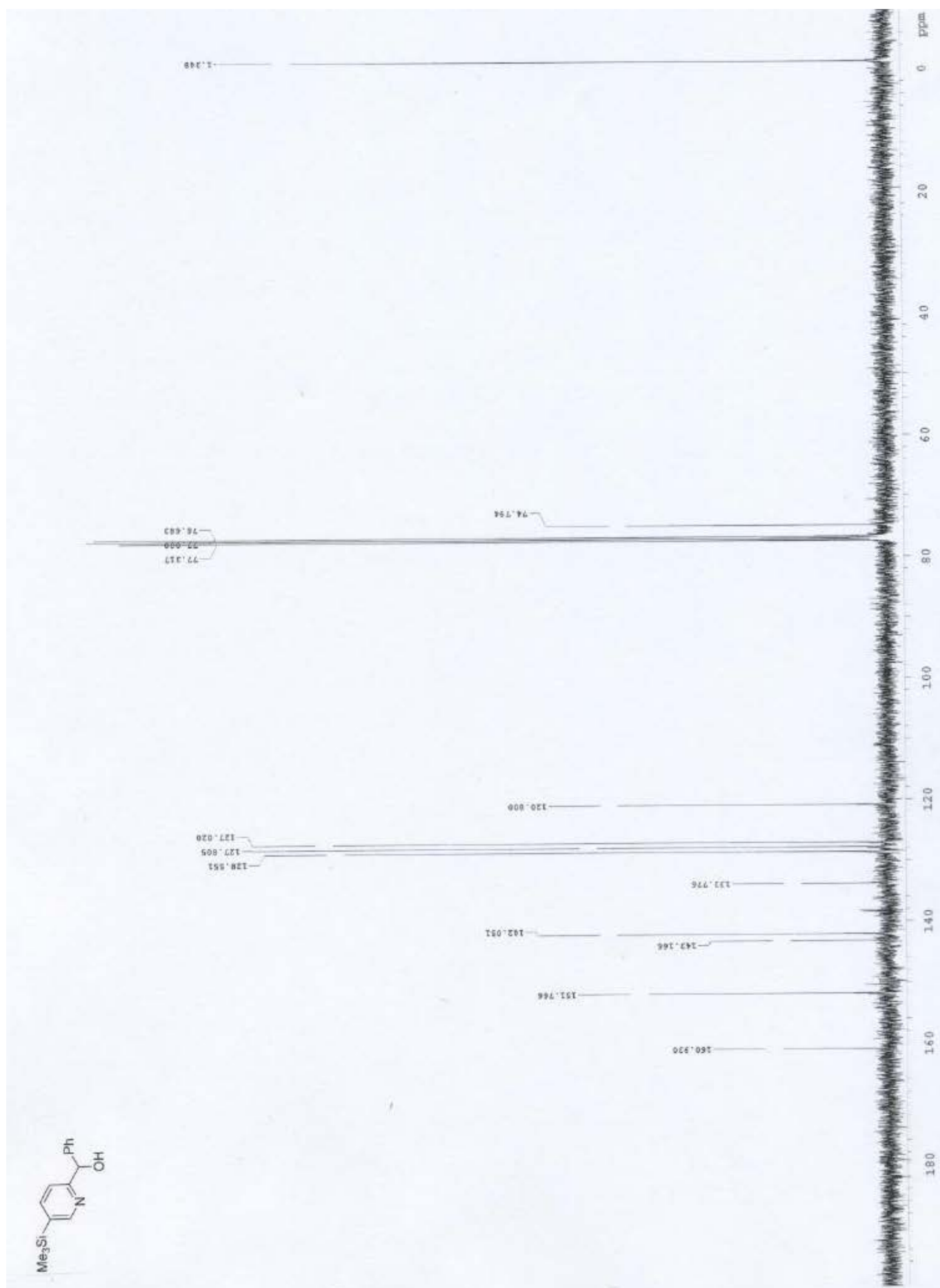
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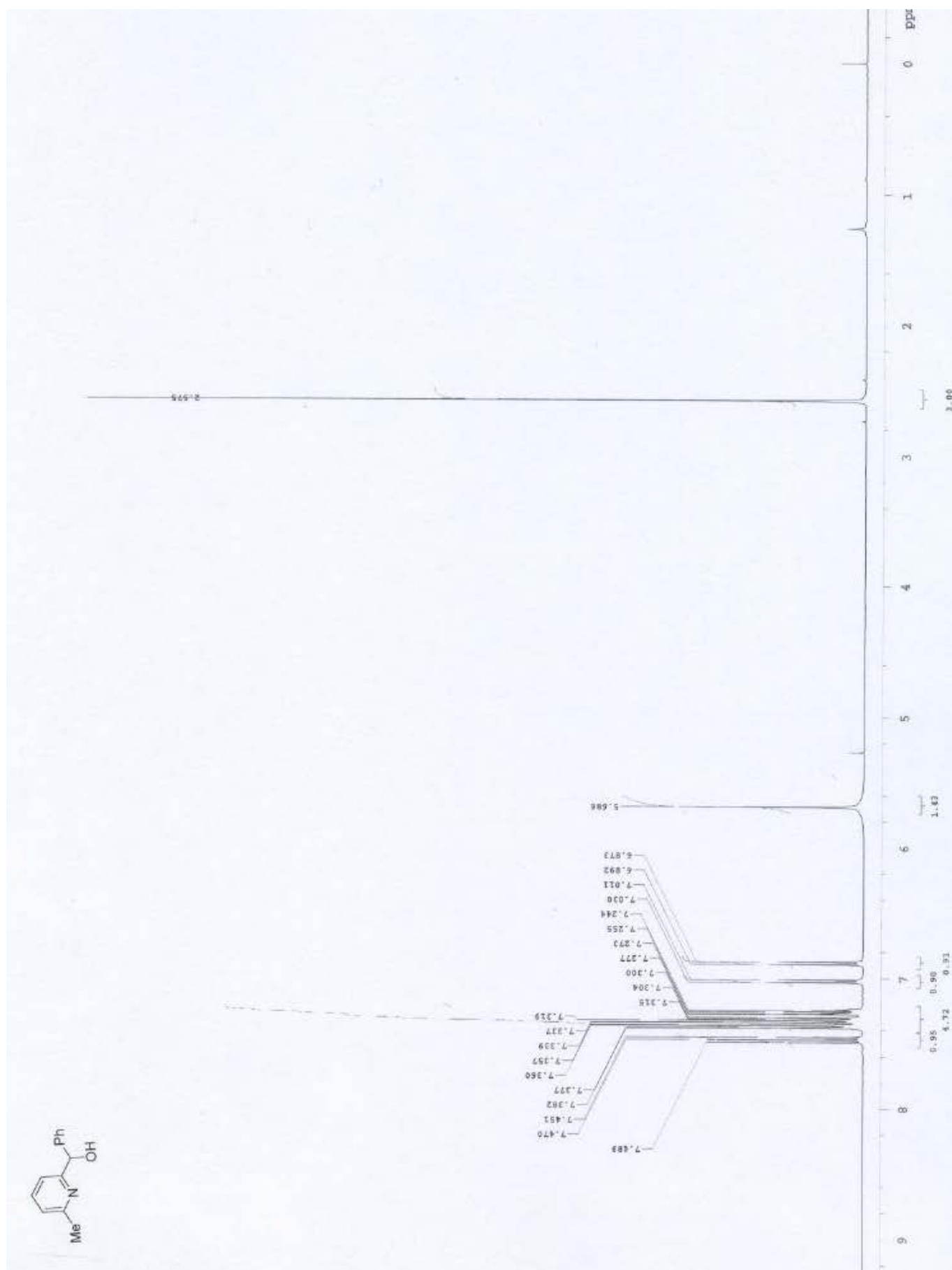
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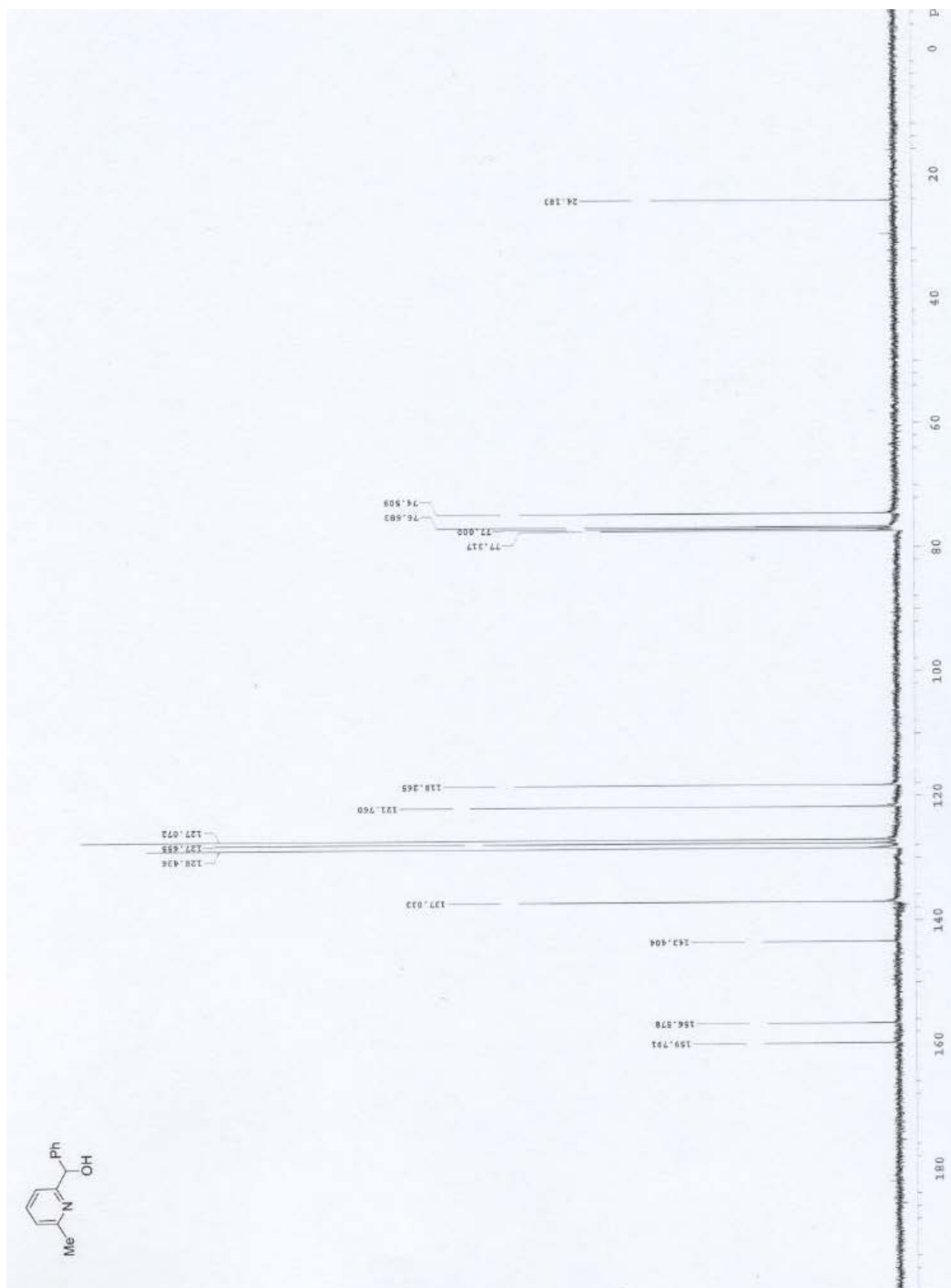
¹H NMR spectrum of 2-(α-hydroxybenzyl)-5-trimethylsilylpyridine



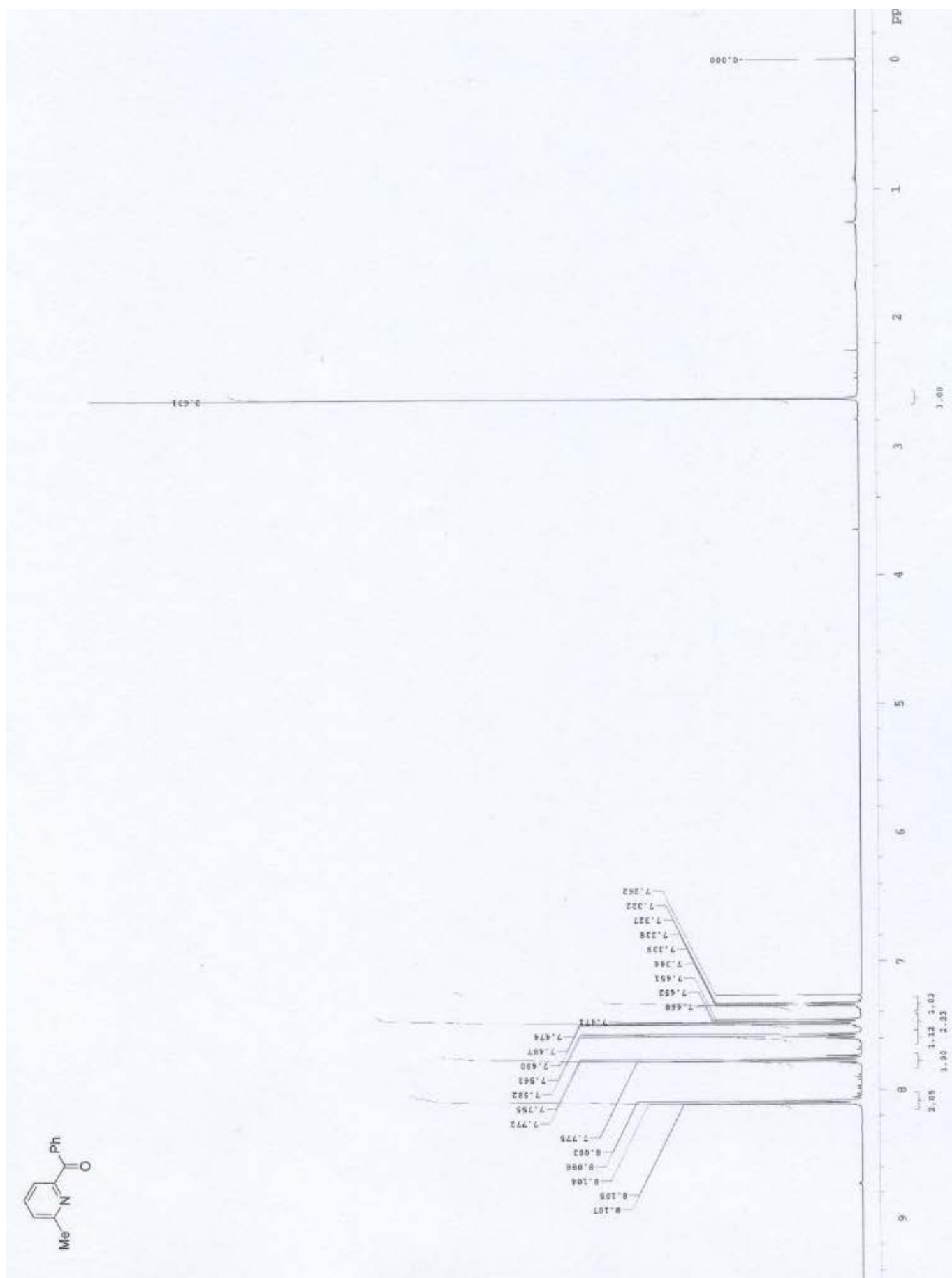
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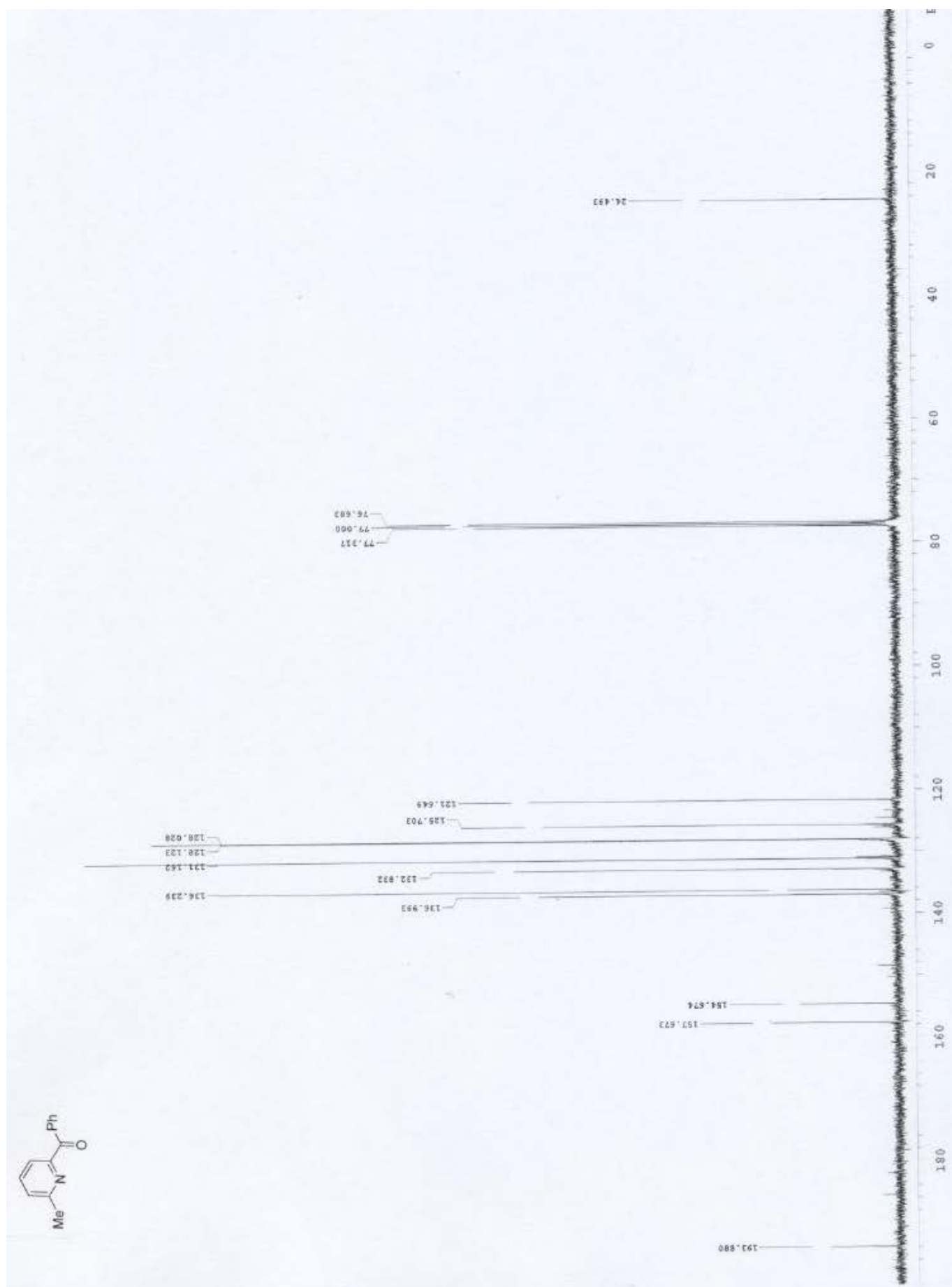
^1H NMR spectrum of 2-(α -hydroxybenzyl)-6-methylpyridine



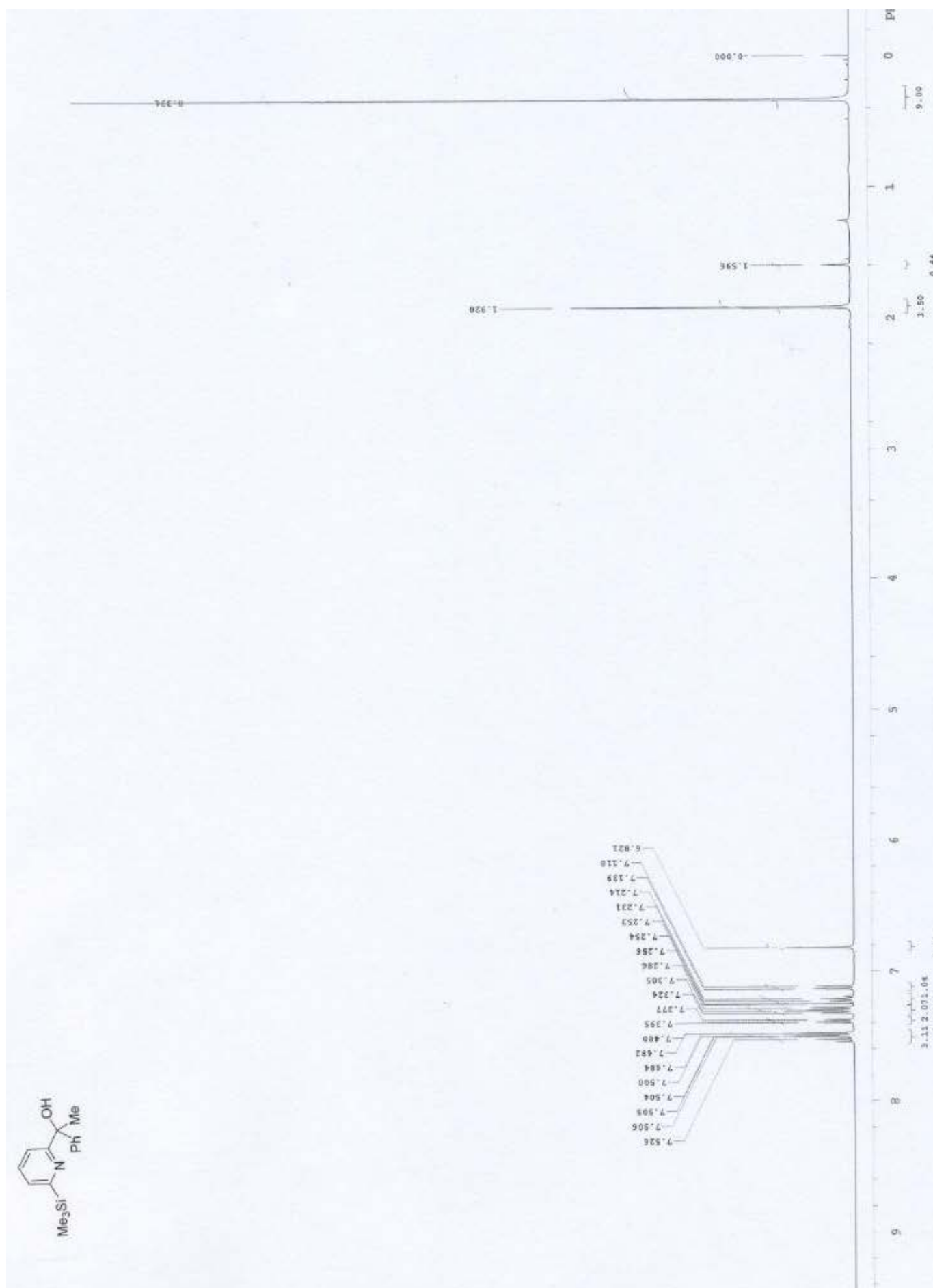
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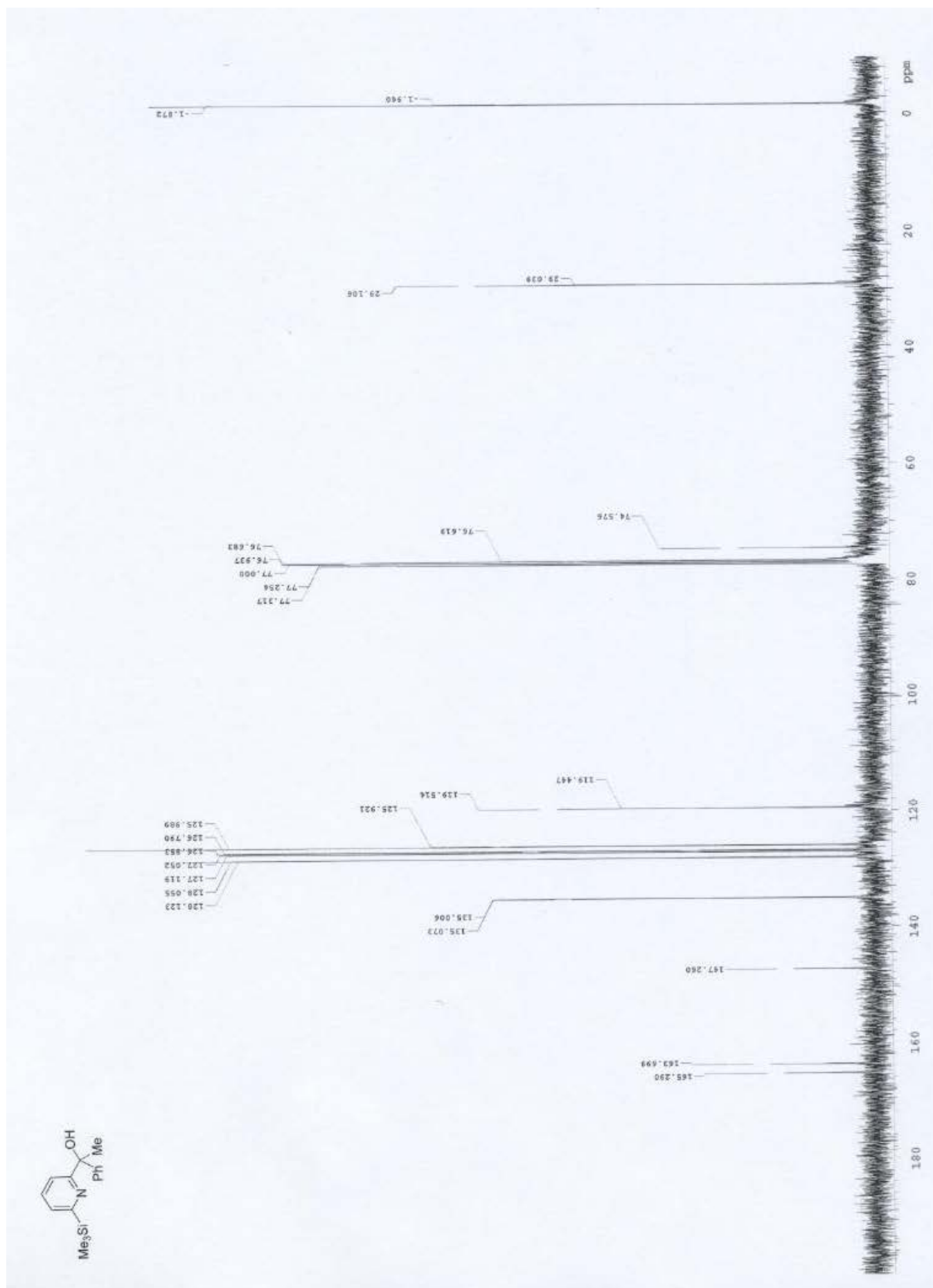
¹H NMR spectrum of 2-benzoyl-6-methylpyridine



¹³C NMR spectrum of 2-benzoyl-6-methylpyridine



¹H NMR spectrum of 2-(1-hydroxy-1-phenylethyl)-6-trimethylsilylpyridine



¹³C NMR spectrum of 2-(1-hydroxy-1-phenylethyl)-6-trimethylsilylpyridine