The first asymmetric synthesis of trialkyl phosphates on the basis of dynamic kinetic resolution in the phosphite method using a chiral source in a catalytic manner

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Supporting Information

General methods. NMR spectra we3re obtained in $CDCl_3$ on a JEOL EX-270, α-400 or ECA-500 instrument. The ^{1}H and ^{13}C chemical shifts are described as δ values in ppm relative to $(CH_3)_4Si$. Chemical shifts reported in ^{31}P NMR spectra are downfield from 85% H_3PO_4. High-resolution mass spectra (HRMS) were measured on a Applied Biosystems Mariner Biospectrometry Workstation. High-performance liquid chromatography (HPLC) was carried out on a JASCO PU-980 chromatograph with a JASCO CD-1595 detector. E. Merck Kieselgel 60 (70–230 mesh) deactivated by adding 6% of water was used for column chromatography. Acetonitrile, benzyl alcohol, dichloromethane, diisopropylethylamine, 2-propanol and triethylamine were distilled from CaH_2. Toluene was distilled form sodium benzophenone ketyl. THF was continuously refluxed from sodium benzophenone ketyl and distilled before used.

Materials. Phosphorus trichloride (Kishida), 2,6-lutidine (Kishida), 3-methyl-1,3-butanediol (Tokyo Kasei), hydroquinidine hydrochloride (Tokyo Kasei), the compound **6** (Aldrich), (*E,E*)-2,4-hexadien-1-ol (Aldrich) were commercially supplied. 2-Ethyl-1,2-butanediol[1] **3**,[2] **5**[3] and **7**[4] were prepared by reported methods.

2-Chloro-4,4-dimethyl-1,3-dioxa-2-phosphinane (1). To a solution of phosphorus trichloride (21 g 13 mL, 150 mmol) in THF (600 mL) was added dropwise a mixture of 3-methyl-1,3-butanediol (15 g, 15 mL, 150 mmol) and triethylamine (30 g, 45 mL, 300 mmol) at –78 °C over 2 h and the resulting mixture was stirred for 12 h. The reaction mixture was passed through a Celite 545 pad and the filtrate was concentrated to give a colorless liquid. This liquid material was distilled under reduced pressure to give **1** (9.3 g, 37% yield): bp 35–37 °C (0.56 mmHg); ^{1}H NMR (400 MHz) 1.38 (s, 3H), 1.62 (s, 3H), 1.95–2.00 (m, 1H), 2.16–

2.24 (m, 1H), 4.04–4.12 (m, 1H), 4.61–4.68 (m, 1H); ^{13}C NMR (100 MHz) 27.92, 27.94, 31.78, 31.81, 38.01, 38.09, 59.05, 59.08, 78.89, 78.96; ^{31}P NMR (166 MHz) 150.16.

2-Chloro-4,4-diethyl-1,3-dioxa-2-phospholane (2). To a solution of phosphorus trichloride (5.5 g, 3.5 mL, 40 mmol) in THF (200 mL) was added dropwise a mixture of 2-ethyl-1,2-butanediol (4.7 g, 40 mmol) and triethylamine (8.1 g, 12 mL, 80 mmol) at –78 °C over 2 h and the resulting mixture was stirred for 12 h. The reaction mixture was passed through a Celite 545 pad and the filtrate was concentrated to give a colorless liquid. Distillation of this liquid under reduced pressure gave **2** (3.3 g, 18 mmol, 45% yield); bp 51–53 °C (2.2 mmHg); ^{1}H NMR (400 MHz) 0.88 (t, 3H, *J* = 7.2 Hz), 1.03 (t, 3H, *J* = 7.2 Hz), 1.54–1.67 (m, 2H), 1.83–2.04 (m, 2H), 4.12–4.19 (m, 2H); ^{13}C NMR (100 MHz) 7.81, 8.71, 30.08, 31.00, 30.49, 72.85, 72.92, 91.00, 91.09; ^{31}P NMR (166 MHz) 173.63.

Hydroquinidine *tert*-butyldimethylsilyl ether (4). To a solution of hydroquinidine hydrochloride (1.8 g, 5 mmol) and 2,6-lutidine (2.1 g, 2.3 mL, 20 mmol) in CH_2Cl_2 was added dropwise *tert*-butyldimethylsilyl trifluoromethanesulfonate (2.6 g, 2.3 mL, 10 mmol) at 0 °C over 10 min. After stirring for 4 h, the reaction mixture was washed with an aqueous solution saturated with $NaHCO_3$ (20 mL) and then with brine (20 mL). The organic layer was dried over Na_2SO_4 and concentrated. The resulting residual oil was subjected to column chromatography on silica gel (50 g) with a 1:10:10 mixture of methanol, hexane and ethyl acetate as an eluent to afford **4** (1.4 g, 3.2 mmol, 64% yield); ^{1}H NMR (400 MHz) –0.26 (s, 3H), 0.28 (s, 3H), 0.96 (t, 3H, *J* = 7.2 Hz), 1.02 (s, 9H), 1.18–1.27 (m, 1H), 1.60–2.04 (m, 6H), 2.45–2.51 (t, 1H, *J* = 7.6 Hz), 3.25–3.34 (m, 2H), 3.45–3.57 (m, 2H), 3.74–3.80 (m, 1H), 4.04 (s, 3H), 6.27 (s, 1H), 7.37 (d, 1H, *J* = 2.4 Hz), 7.40 (dd, 1H, *J* = 9.2, 2.7 Hz), 7.54 (d, 1H, *J* = 4.4 Hz), 8.03 (d, 1H, *J* = 9.2 Hz), 8.76 (d, 1H, *J* = 4.4 Hz); ^{13}C NMR (100 MHz) –4.96, –4.73, 11.43, 17.81, 17.90, 23.53, 24.36, 25.29, 35.10, 50.01, 50.11, 56.76, 60.93, 68.55, 98.93, 118.71, 118.96, 121.88, 123.58, 125.39, 131.95, 143.12, 145.54, 146.57, 159.53.; HRMS (ESI^+) calcd for $C_{26}H_{41}N_2O_2Si^+$ ($M + H^+$) 441.2932, found 441.2943.

A Typical Procedure for the Preparation of a Phosphate via the Phosphite Method Using a Chiral Amine as a Catalytic Promoter. The synthesis of the phosphate **8** through the condensation of **1** and benzyl alcohol using **3** as a promoter and the subsequent TBHP oxidation is representatively described. To a solution of a chiral amine **3** (78 mg, 0.1 mmol) in THF (10 mL) was added the phosphorochloridite **1** (168 mg, 1 mmol) at –78 °C. After 10 min, benzyl alcohol (108 mg, 1 mmol) and diisopropylethylamine (129 mg, 1 mmol) were successively added at the same temperature. The resulting mixture was warmed up to 25 °C over 12 h. To the mixture was added a 3.0 M solution of TBHP in toluene (0.67 mL, 2.0 mmol) and stirring was continued for 30 min. The reaction mixture was diluted with ethyl acetate (20 mL) and washed with an aqueous solution saturated with $NaHCO_3$ (20 mL) and then with brine (20 mL). The organic layer was dried over Na_2SO_4 and concentrated. The resulting residual oil was subjected to column chromatography on silica gel (20 g) with a 1:2 mixture of hexane and ethyl acetate as an eluent to afford the phosphate **8**.

2-Benzyloxy-4,4-dimethyl-1,3,2-dioxaphosphinane 2-oxide (8): colorless oil; ^{1}H NMR (400 MHz) 1.42 (s, 3H), 1.47 (s, 3H), 1.77–1.81 (m, 1H), 2.03–2.08 (m, 1H), 4.28–4.34 (m, 2H), 5.05–5.10 (m, 2H), 7.31–7.39 (m, 5H); ^{13}C NMR (100 MHz) 26.67, 26.68, 30.03, 30.10, 36.54, 36.61, 64.65, 64.72, 83.60, 83.67, 127.83, 128.36, 128.45, 136.01, 136.08; ^{31}P NMR (166 MHz) –7.32; HRMS (ESI^{+}) calcd for $C_{12}H_{18}O_4P^{+}$ (M + H^{+}) 257.0937, found 257.0926.

2-Benzyloxy-4,4-diethyl-1,3,2-dioxaphospholane 2-oxide (9). Colorless oil; ^{1}H NMR (400 MHz) 0.88 (t, 3H, J = 7.2 Hz), 0.96 (t, 3H, J = 7.2 Hz), 1.46–1.80 (m, 4H), 3.98–4.13 (m, 2H), 5.14 (d, 2H, J = 9.6 Hz), 7.30–7.38 (m, 5H); ^{13}C NMR (100 MHz) 7.40, 7.49, 23.49, 24.70, 29.38, 29.42, 29.67, 36.66, 69.99, 70.05, 72.91, 72.93, 88.43, 127.81, 128.49, 128.58, 135.96, 136.03; ^{31}P NMR (166 MHz) 17.39; HRMS (ESI^{+}) calcd for $C_{13}H_{20}O_4P^{+}$ (M + H^{+}) 271.1094, found 271.1065.

2-(*E*,*E*)-hexa-2,4-dienyloxy-4,4-dimethyl-1,3,2-dioxaphosphinane 2-oxide (10). Colorless oil; ^{1}H NMR (400 MHz) 1.43 (s, 6H), 1.70 (d, 3H, J = 6.0 Hz),1.80 (m, 1H), 2.01 (m, 1H), 4.28–4.35 (m, 2H), 4.47–4.52 (m, 2H), 5.58–5.73 (m, 2H), 5.96–6.03 (m, 1H), 6.17–6.24 (m, 1H); ^{13}C NMR (100 MHz) 18.06, 26.78, 30.04, 30.11, 36.59, 36.62, 64.65, 64.72, 67.66, 67.71, 83.46, 83.53, 124.04, 124.11, 130.21, 131.61, 134.65; ^{31}P NMR (166 MHz) –8.64; HRMS (ESI^{+}) calcd for $C_{11}H_{19}O_4PK^{+}$ (M + K^{+}) 285.0653, found 285.0660.

References for Supplementary Data

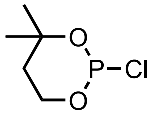
(1) Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Org. Synth. Coll. Vol. 8* 1993, 315–321.

(2) Amberg, W.; Bennani, Y.; Chadha, R. K.; Crispino, G. A.; Davis, W. D.; Hartung, J.; Jeong, K.-S.; Ogino, Y.; Shibata, T.; Sharpless, K. B. *J. Org. Chem*. 1993, **58**, 844–849.

(3) Shindo, M.; Koga, K.; Tomioka, K. *J. Org. Chem.* 1998, **63**, 9351–9357.

(4) Katrizky, A. R.; Aslan, D. C.; Leeming, P.; Steel, P. J. *Tetrahedron Asym.* 1997, **8**, 1491–1500.

[1]H NMR spectrum of **1**



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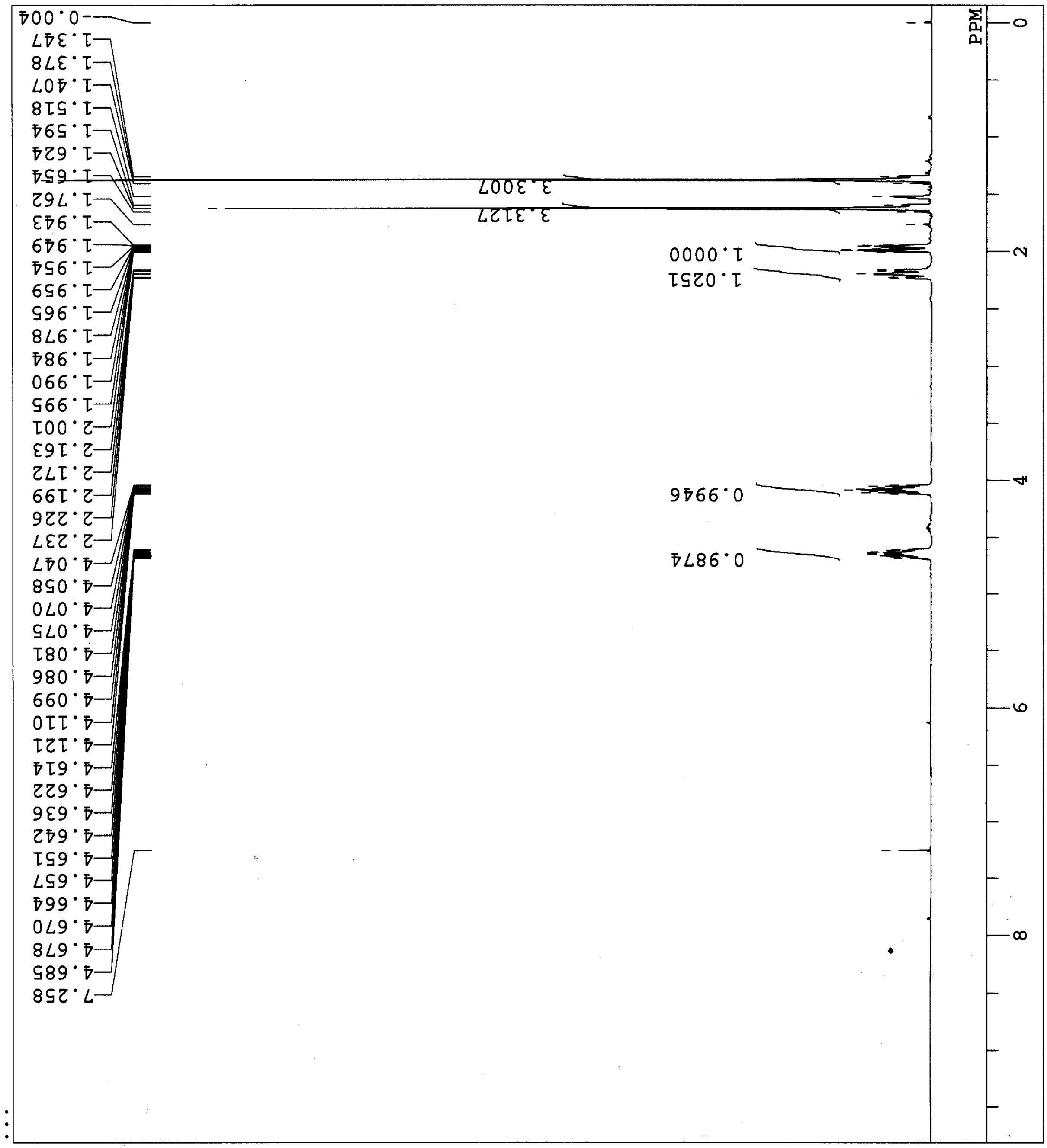

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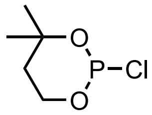

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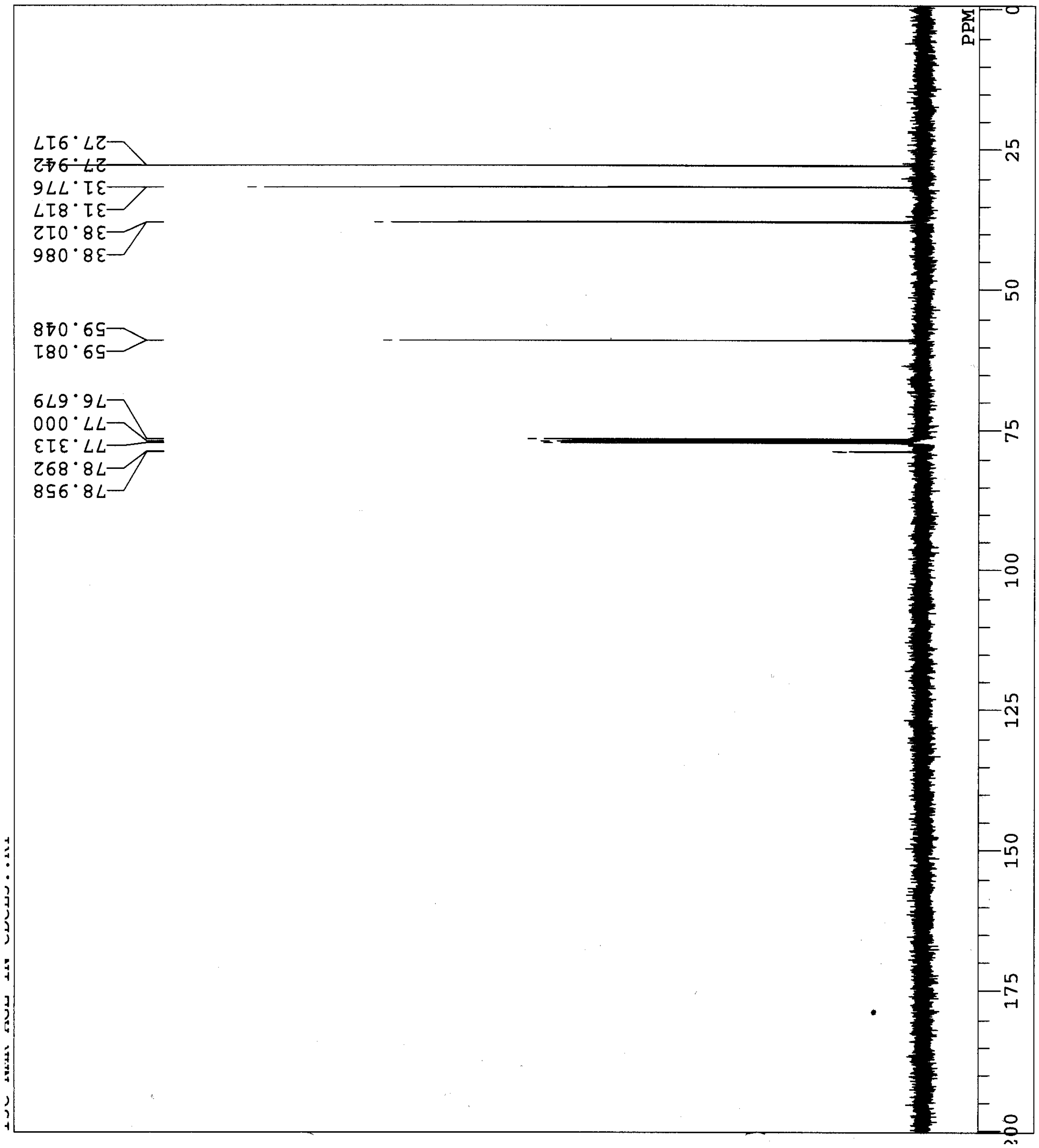

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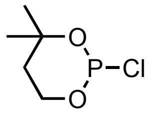

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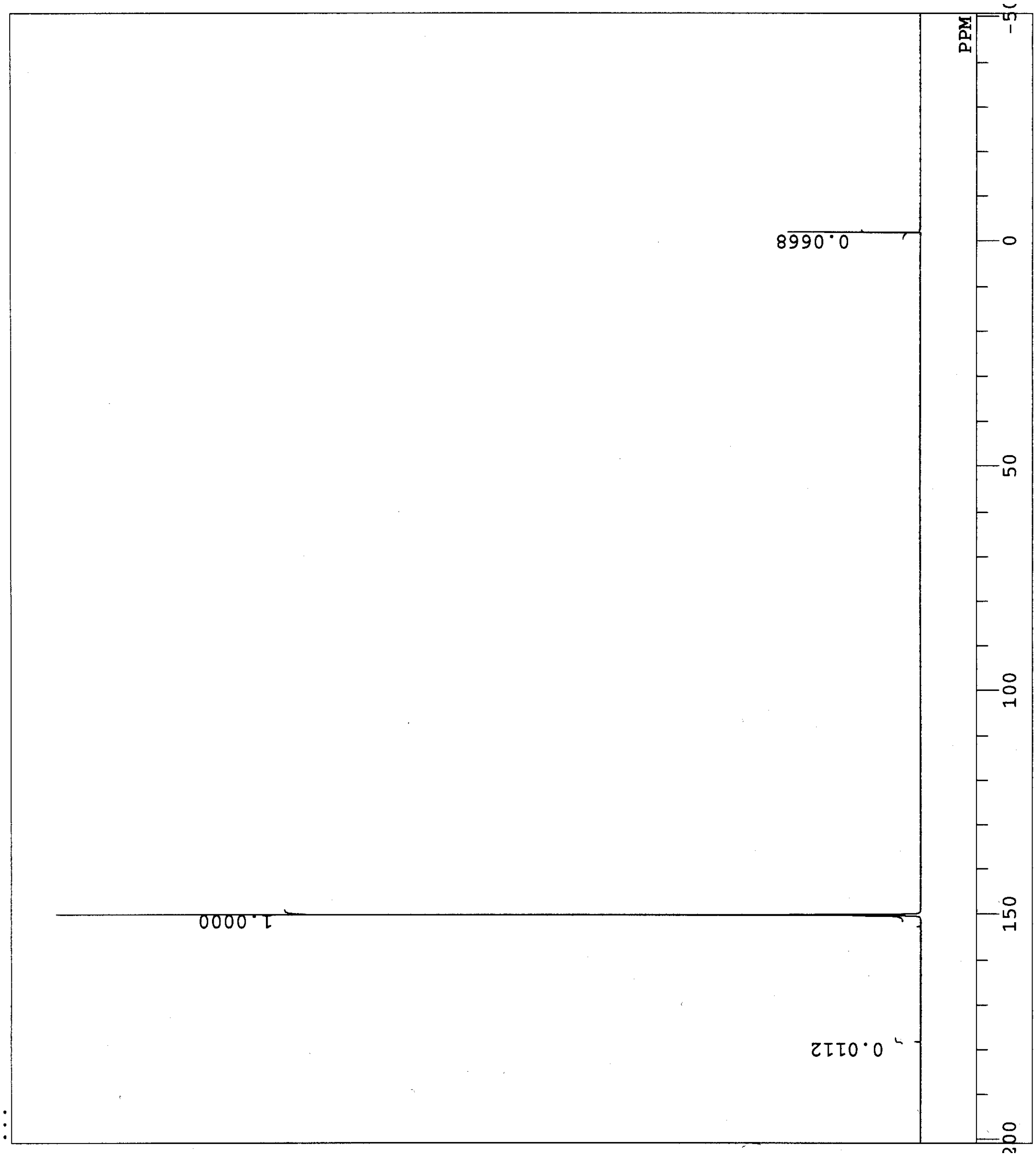

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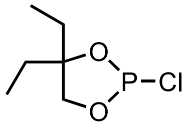

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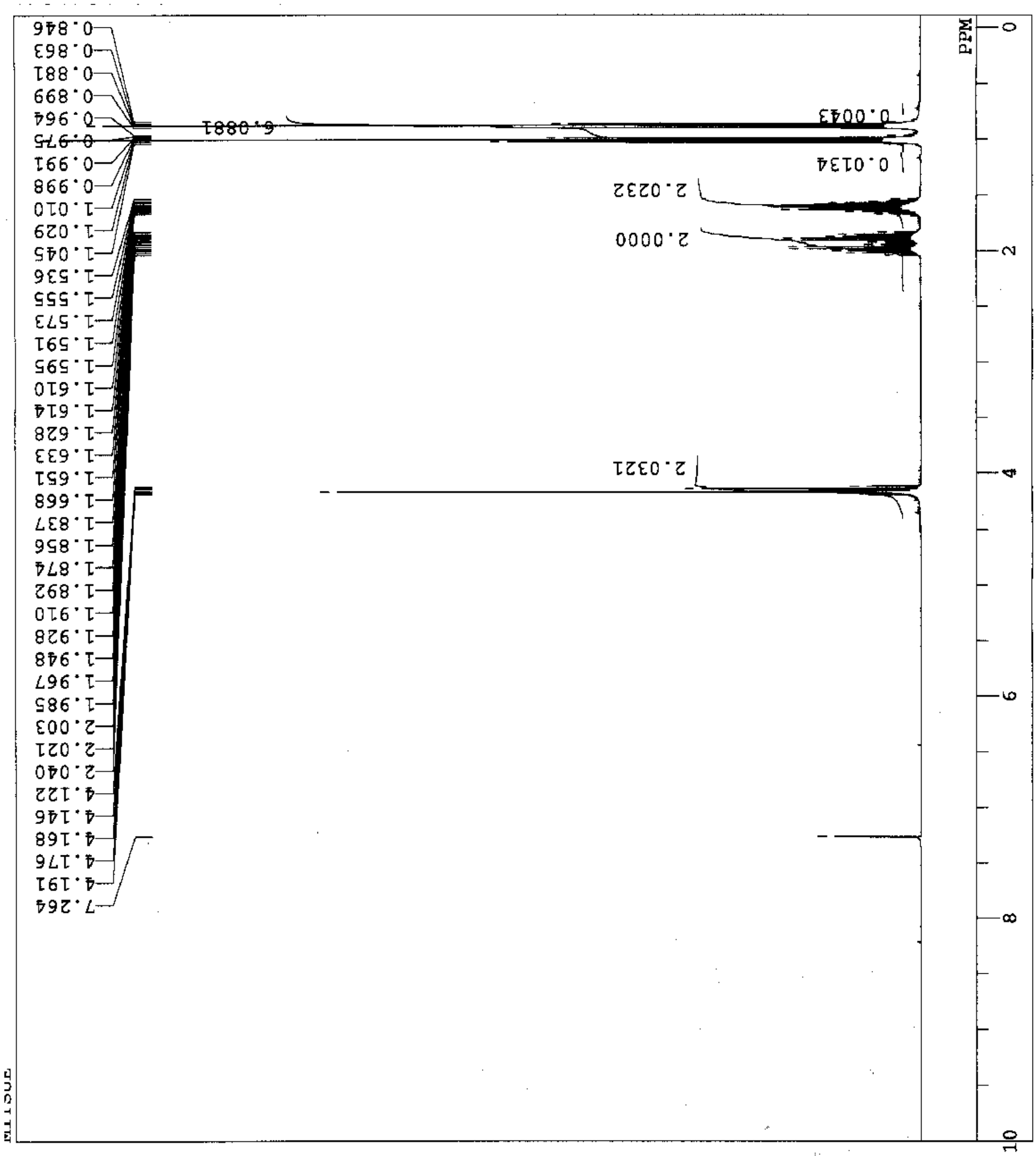

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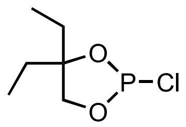

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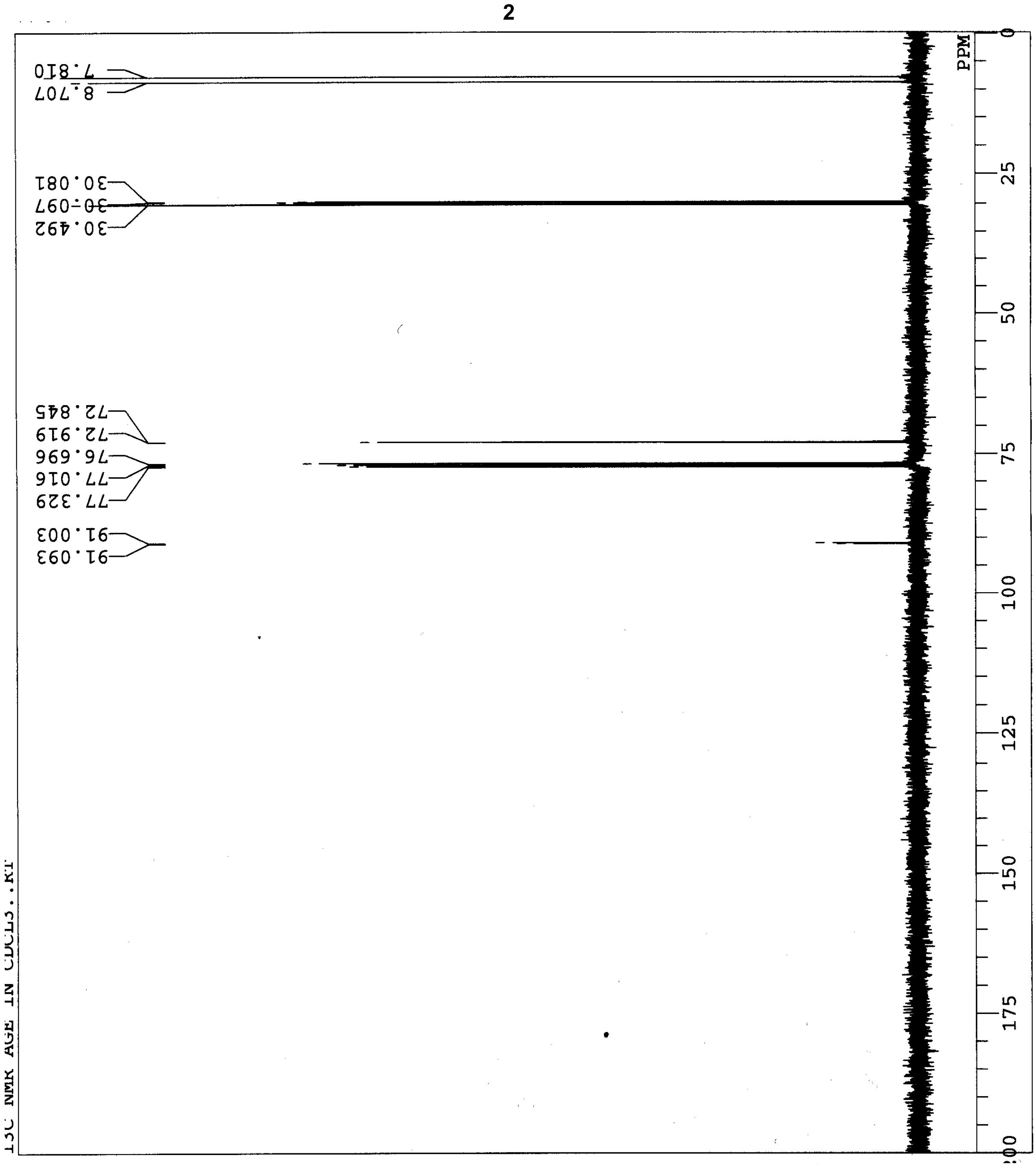

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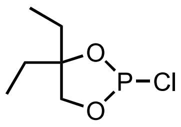

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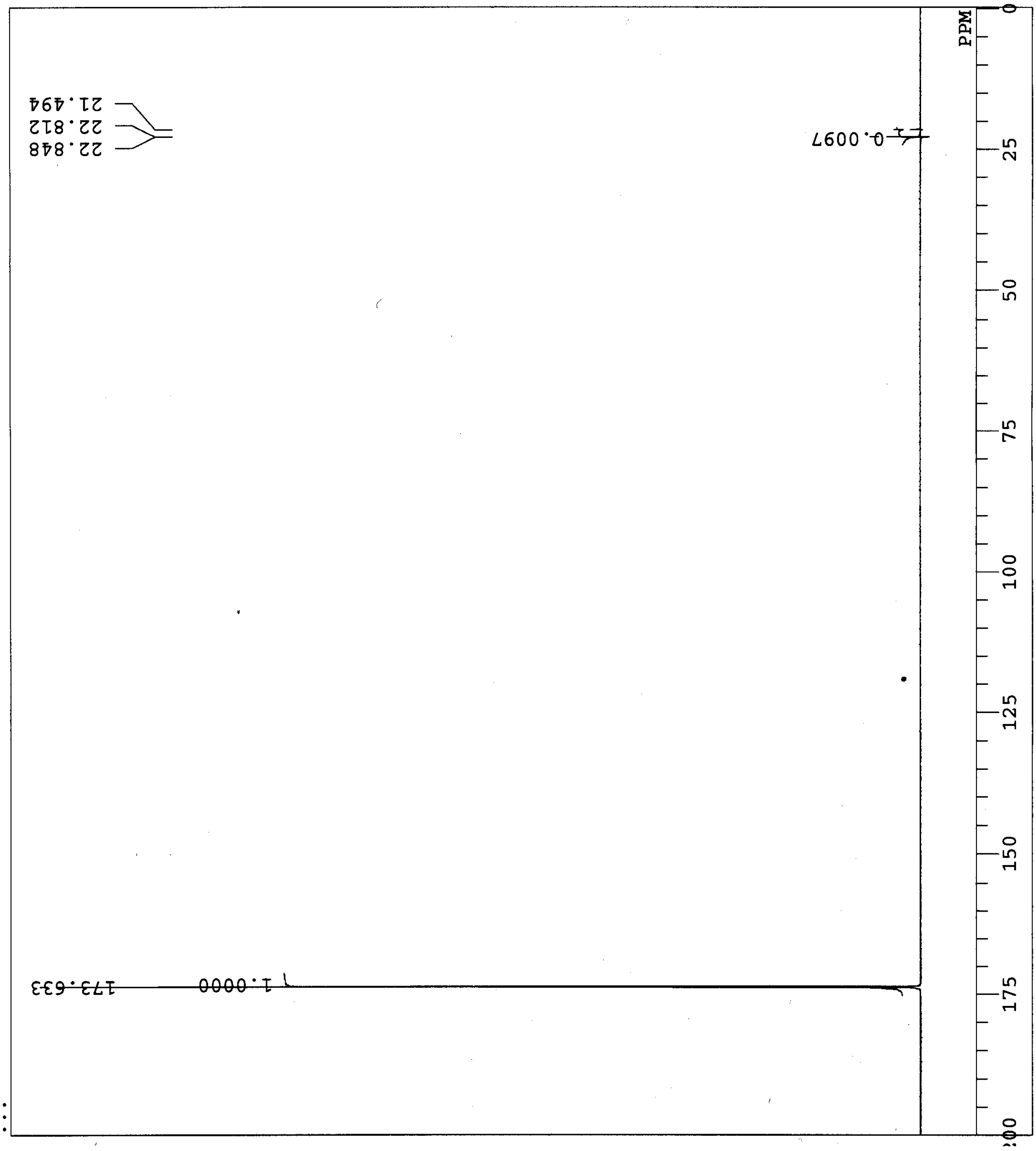

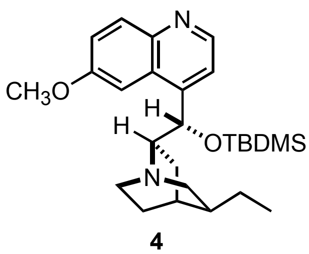

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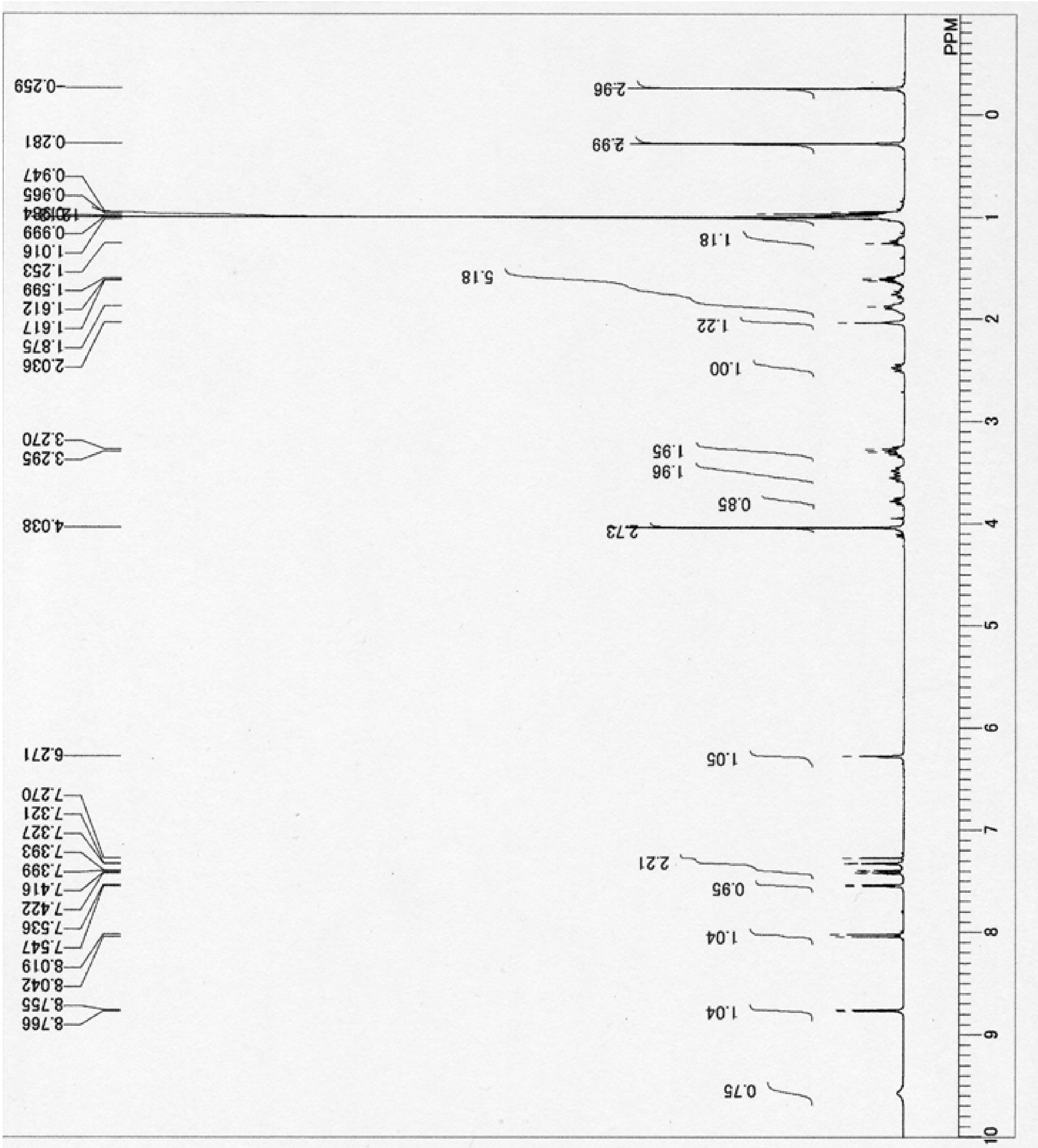

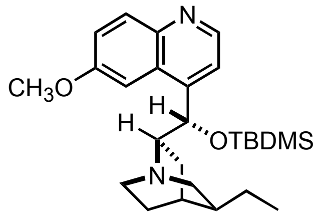

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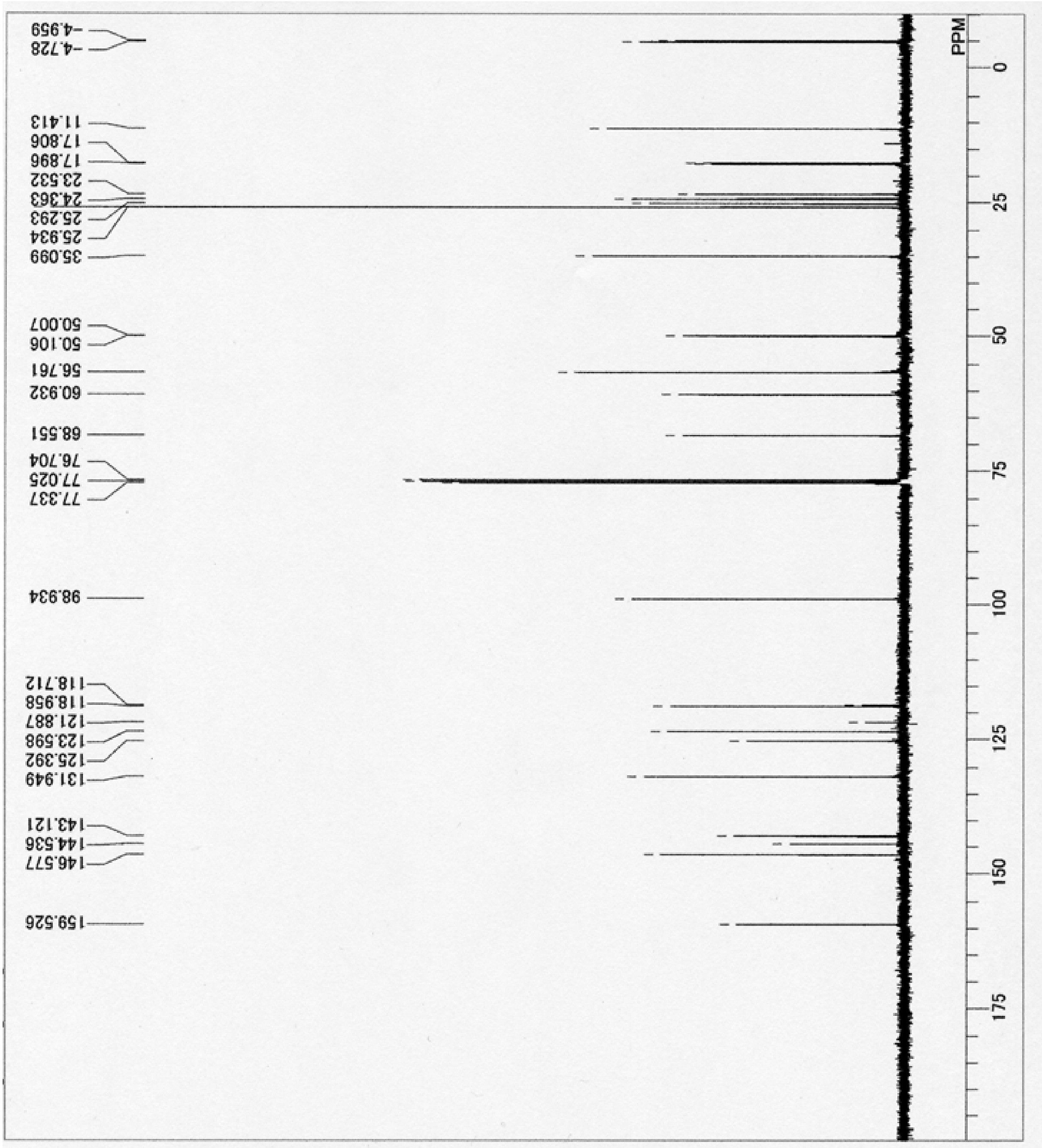

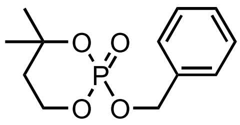

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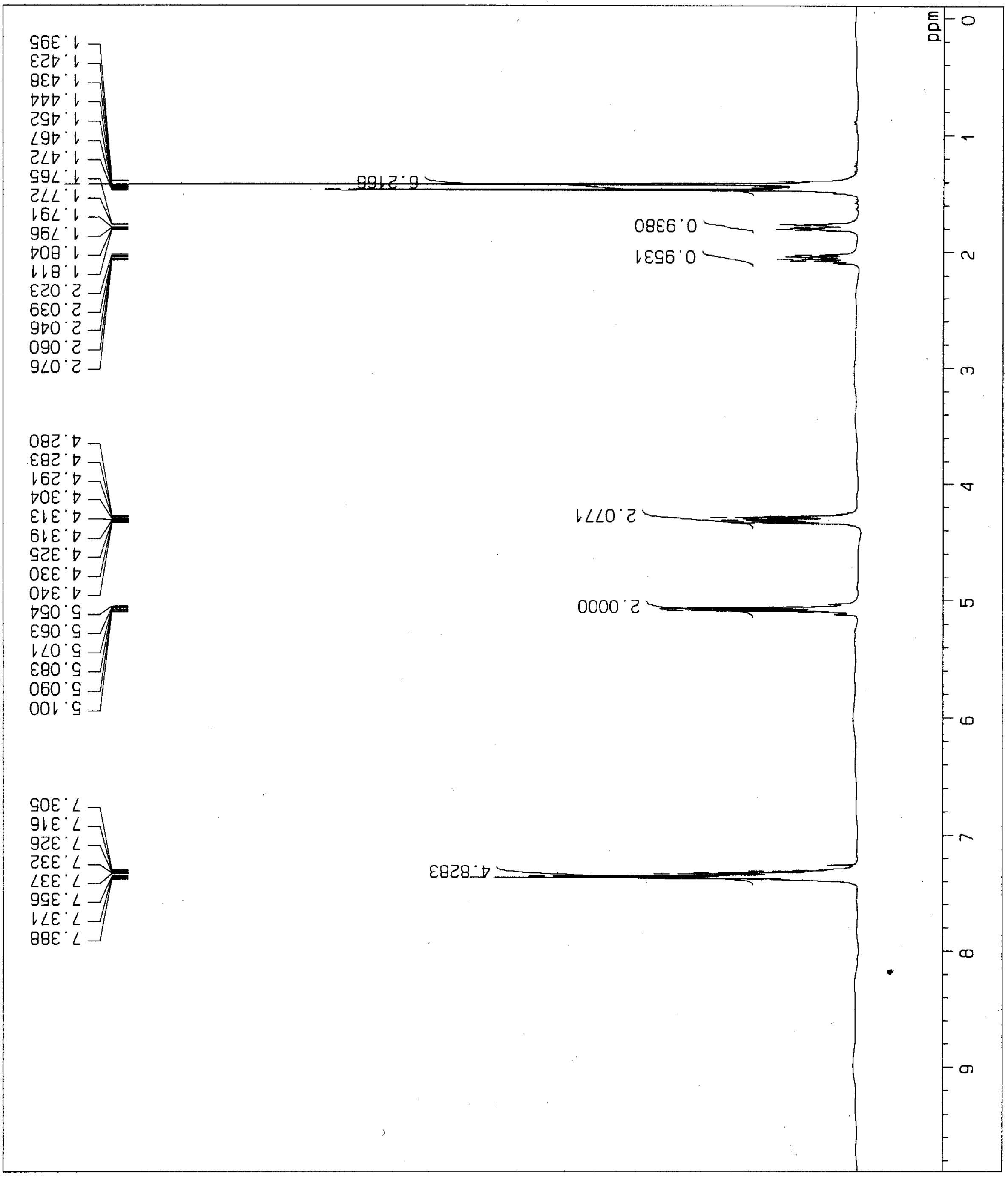

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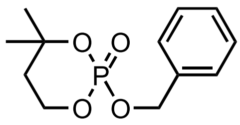

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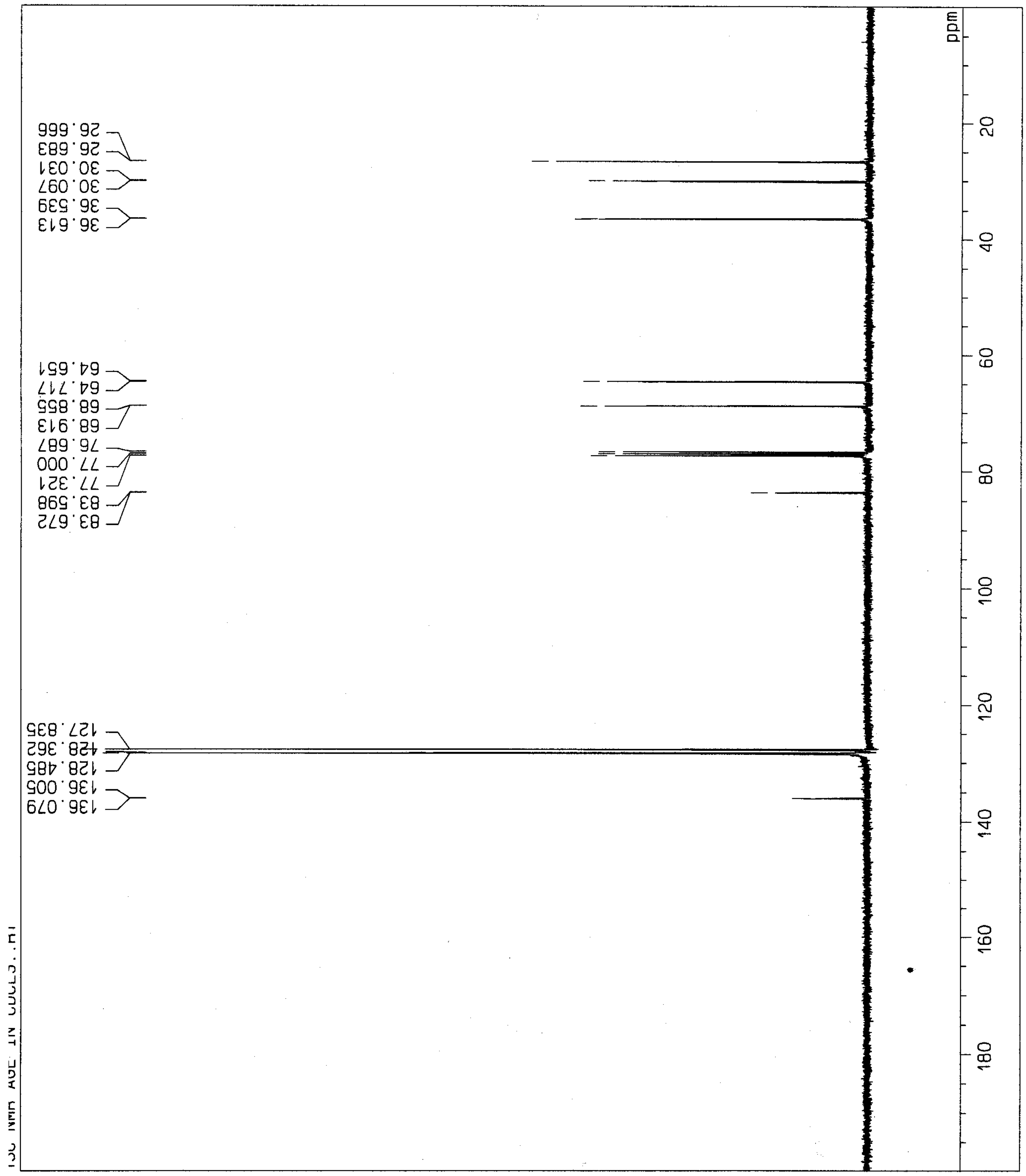

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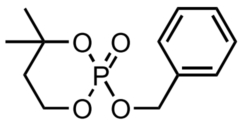

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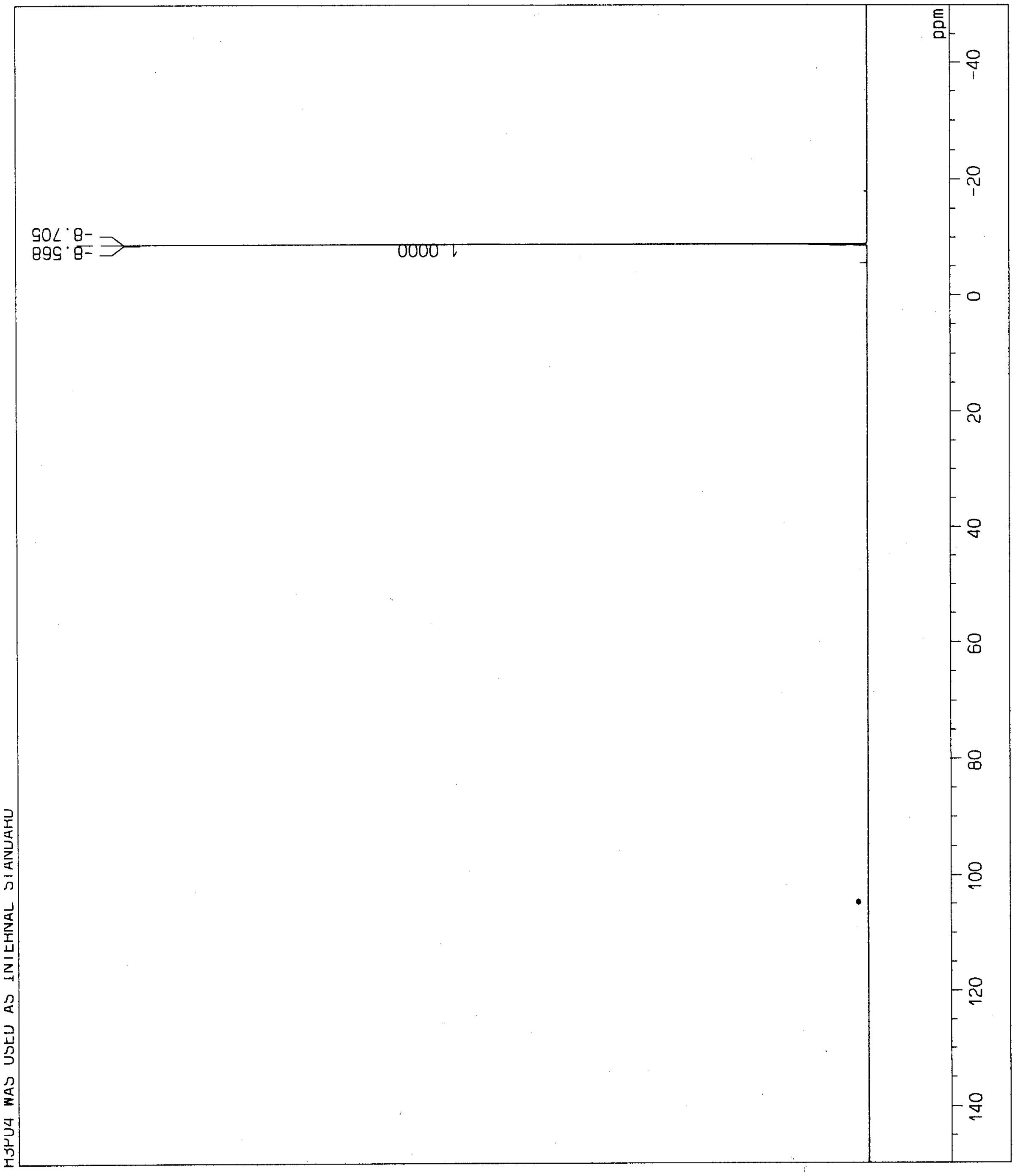

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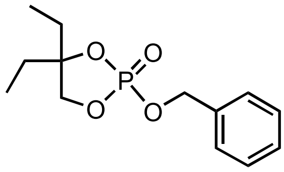

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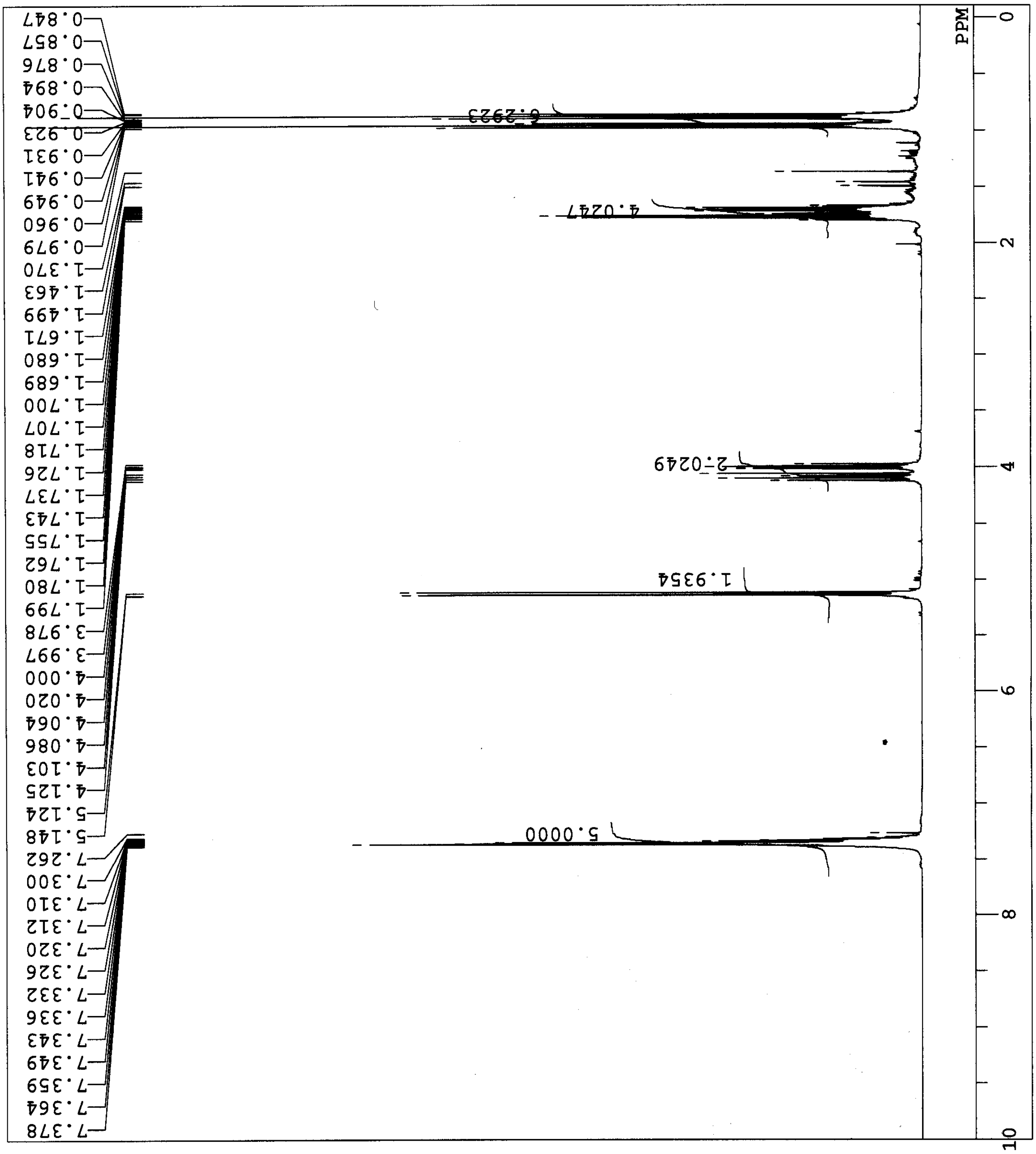

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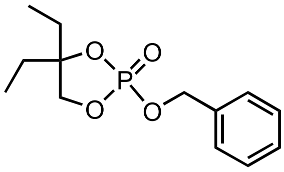

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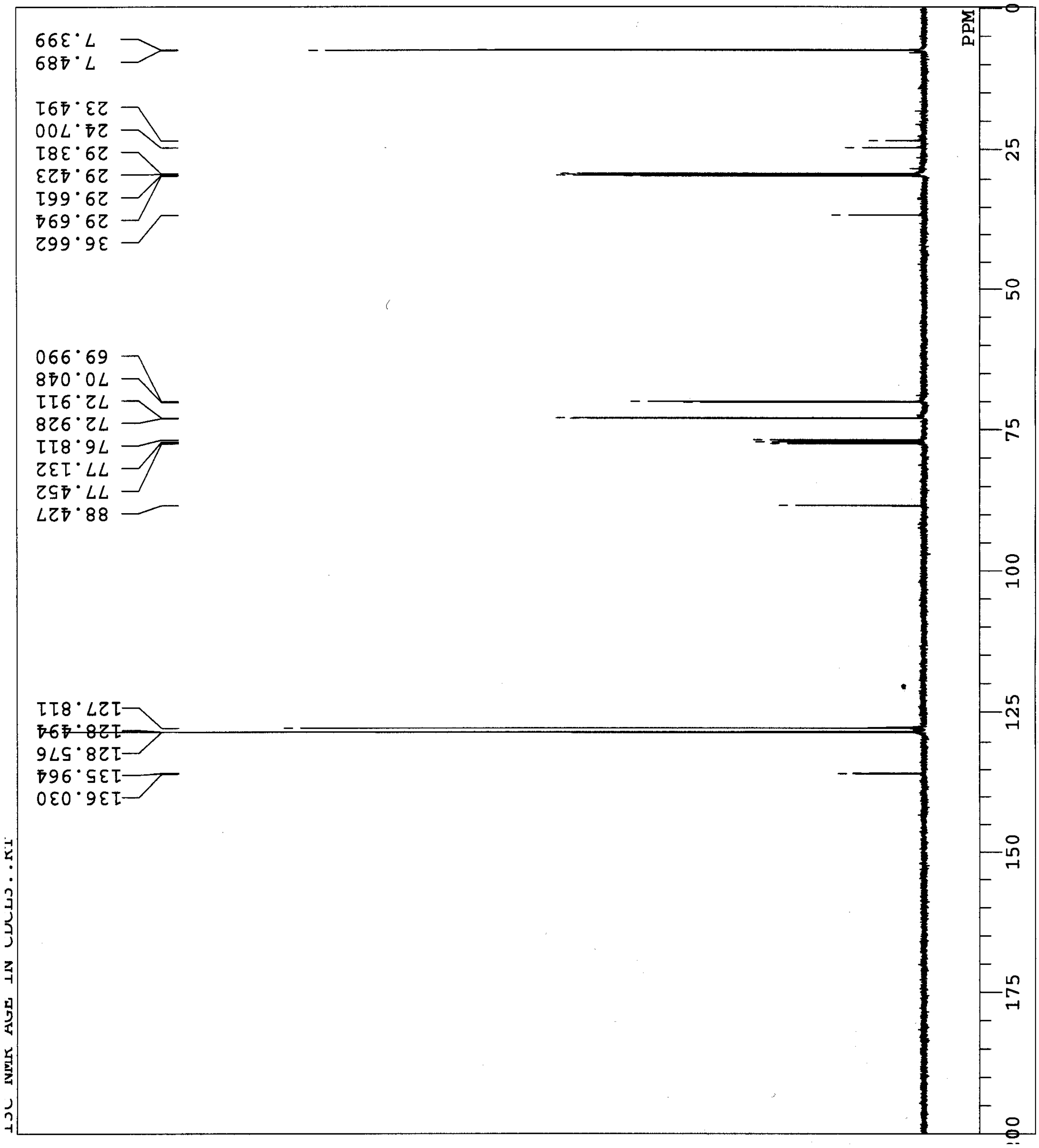

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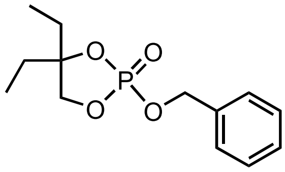

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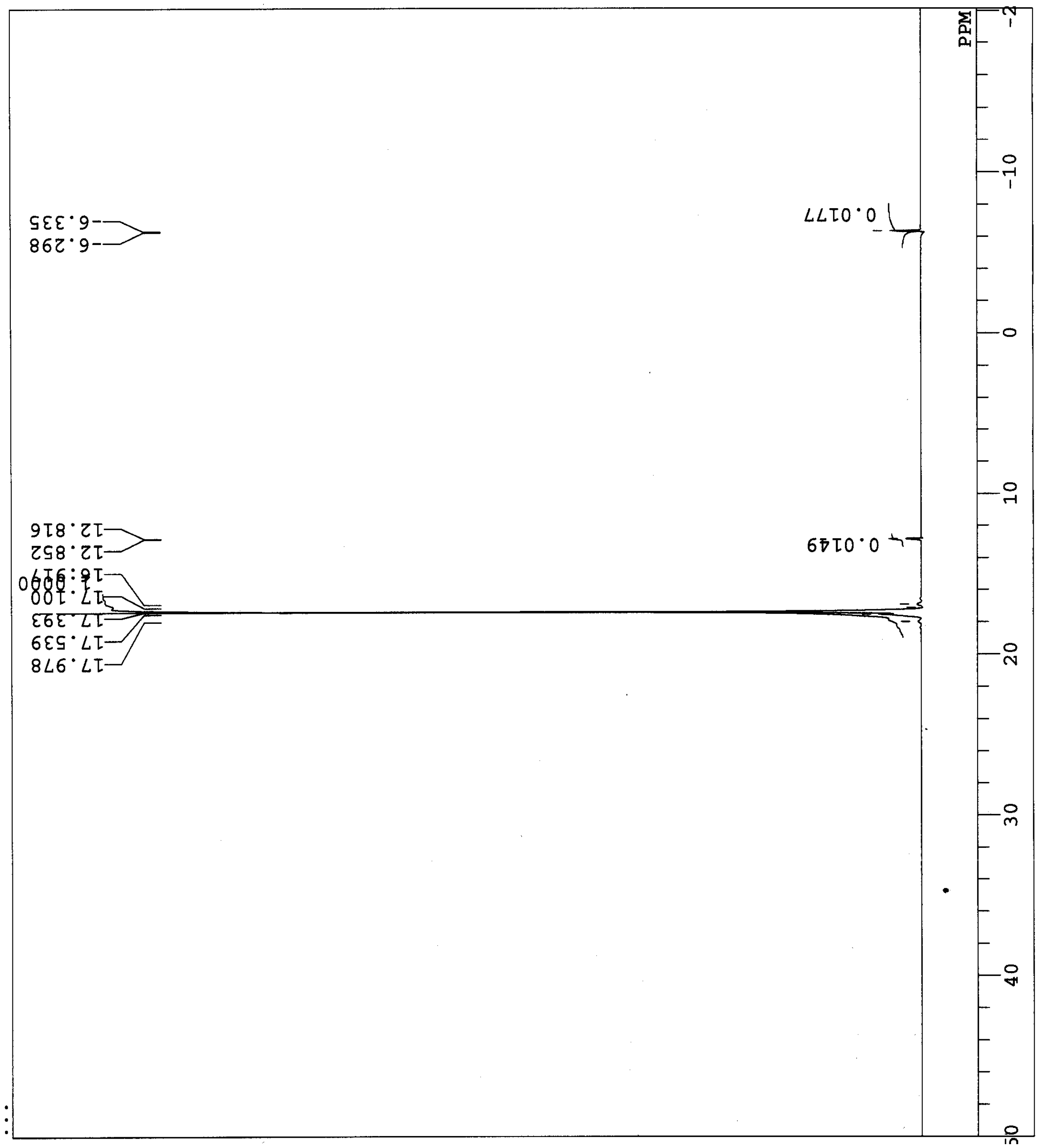

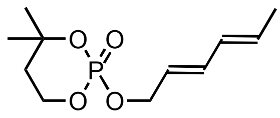

[1]H NMR spectrum of **10**

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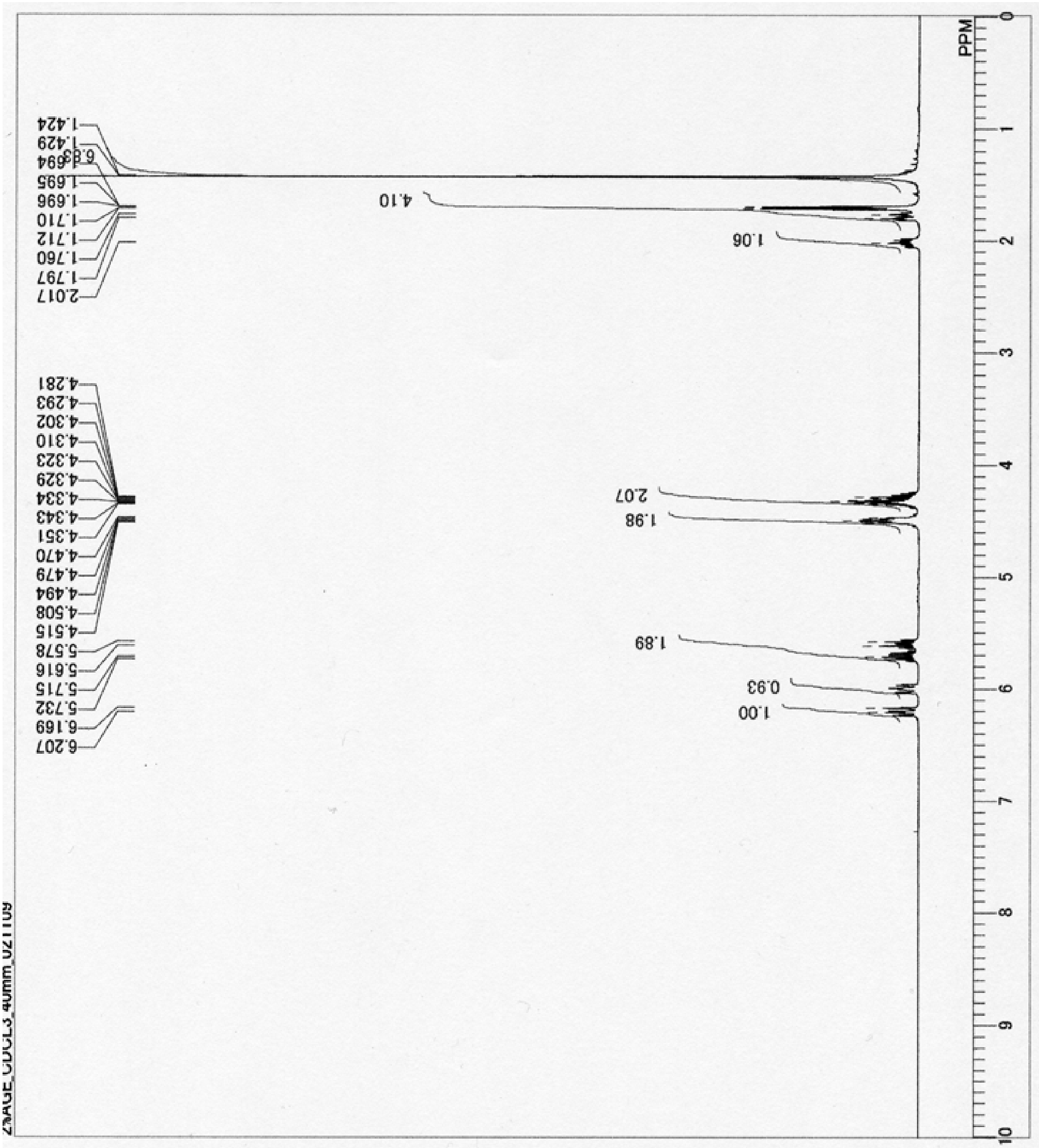

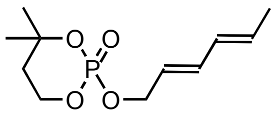

^{13}C NMR spectrum of **10**

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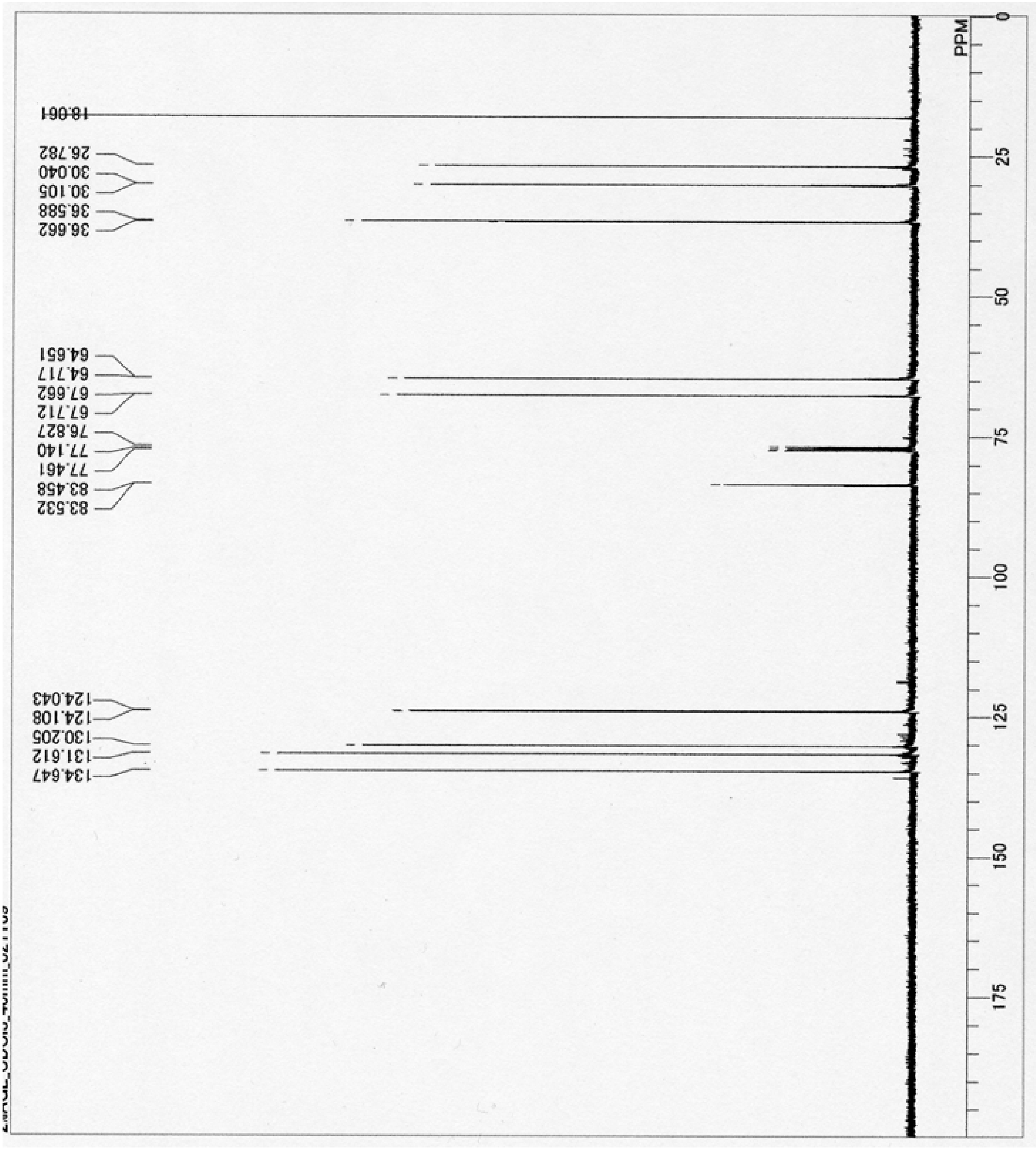

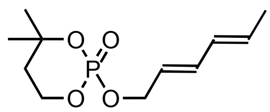

^{31}P NMR spectrum of **10**

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