Experimental Section (Supporting Information)

Facile and Efficient Total Synthesis of (+)-Preussin

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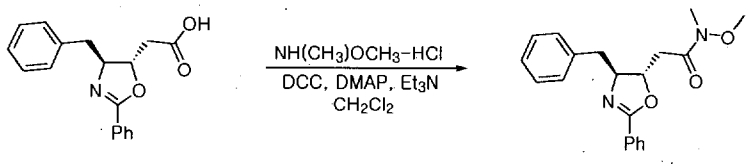
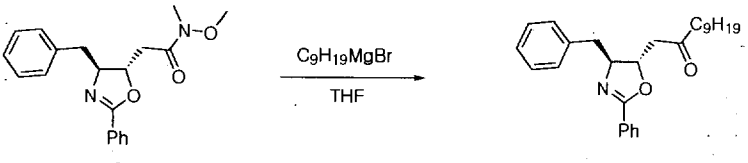


9

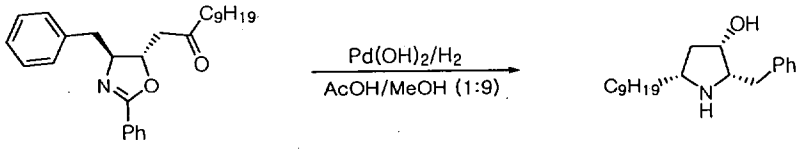
2-((4S,5S)-4-Benzyl-2-phenyl-4,5-dihydro-oxazol-5-yl)-N-methoxy-N-methyl-acetamide (9). To a solution of acid (680 mg, 2.3 mmol) in CH_2Cl_2, N, O-dimethylhydroxylamine hydrochloride (225 mg, 2.3 mmol), triethylamine (0.32 mL, 2.3 mmol), DMAP (28 mg, 0.23 mmol) were successively added. The reaction mixture was cooled to 0 °C, DCC (475 mg, 2.3 mmol) was added. The mixture was stirred at ambient temperature for 12h and filtered. The filtrate was washed with 0.5N-HCl, saturated aqueous $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, and concentrated. Purifiaction by column chromatography over silica gel (1:1 ethyl acetate-hexane) gave the Weinreb amide **9** (661 mg, 85%). $[\alpha]^D_{25}$ = -7.5 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, CDCl3) δ 2.36 (dd, J = 5.5, 16.0 Hz, 1H), 2.88 (m, 2H), 3.15 (s, 3H), 3.18 (dd, J = 5.5, 13.5 Hz, 1H), 3.56 (s, 3H), 4.24 (m, 1H), 4.87 (ddd, J = 5.6, 5.6, 13.5 Hz), 7.18-7.49 (m, 8H), 7.92-7.94 (m, 2H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 33.9, 37.8, 41.5, 61.2, 73.2, 80.0, 126.4, 127.7, 128.2, 128.3, 128.4, 129.6, 131.3, 137.6, 162.9, 170.5; IR (neat): 1652 cm^{-1}; HRMS m/e calcd for $C_{20}H_{22}N_2O_3$ (M^+) 338.1630, found 338.1625.



9 **10**

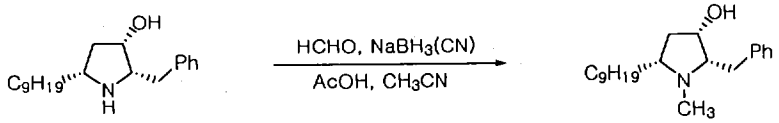
1-((4S,5S)-4-Benzyl-2-phenyl-4,5-dihydro-oxazol-5-yl)-undecan-2-one (10). To a solution of **9** (750 mg, 2.22mmol) in 10 mL of dry THF was added 22 mL of nonylmagnesium bromide (0.2 M, 4.44 mmol) at –30 °C. The reaction mixture was stirred at 0 °C for an hour. The reaction was poured into 0.5N HCl at 0 °C and the mixture was extracted with ether. The organic extract was dried with anhydrous $MgSO_4$ and evaporated *in vacuo*. The product was purified by column chromatography over silica gel (1:4 ethyl acetate-hexane) gave the ketone **10** (713 mg, 80%). $[\alpha]^D_{25}$ = -23.9 (c 1.0 , $CHCl_3$); ^1H NMR (500 MHz, CDCl3) δ 0.87 (t, J = 6.5 Hz, 3H), 1.27 (m, 17H), 2.30 (dd, J = 5.0, 17.0 Hz, 1H), 2.34 (t, J = 7.5 Hz, 2H), 2.78 (dd, J = 7.5, 17.0 Hz, 1H), 2.84 (dd, J = 8.0, 13.5 Hz, 1 H), 3.20 (dd, J = 5.5, 13.5 Hz, 1H), 4.13

(ddd, J = 5.5, 6.0, 8.5 Hz, 1H), 4.80 (ddd, J = 5.0, 6.0, 7.5 Hz, 1H), 7.20-7.49 (m, 8H), 7.90-7.92 (m, 2H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 14.1, 22.6, 23.6, 29.1, 29.2, 29.3, 29.4, 31.8, 41.5, 43.6, 47.8, 73.3, 79.6, 126.6, 127.7, 128.3, 128.5, 129.5, 131.4, 137.5, 162.9, 207.8; IR (neat): 2925, 1715, 1649 cm^{-1}; HRMS m/e calcd for $C_{27}H_{35}NO_2$ (M^+) 405.2668, found 405.2662.



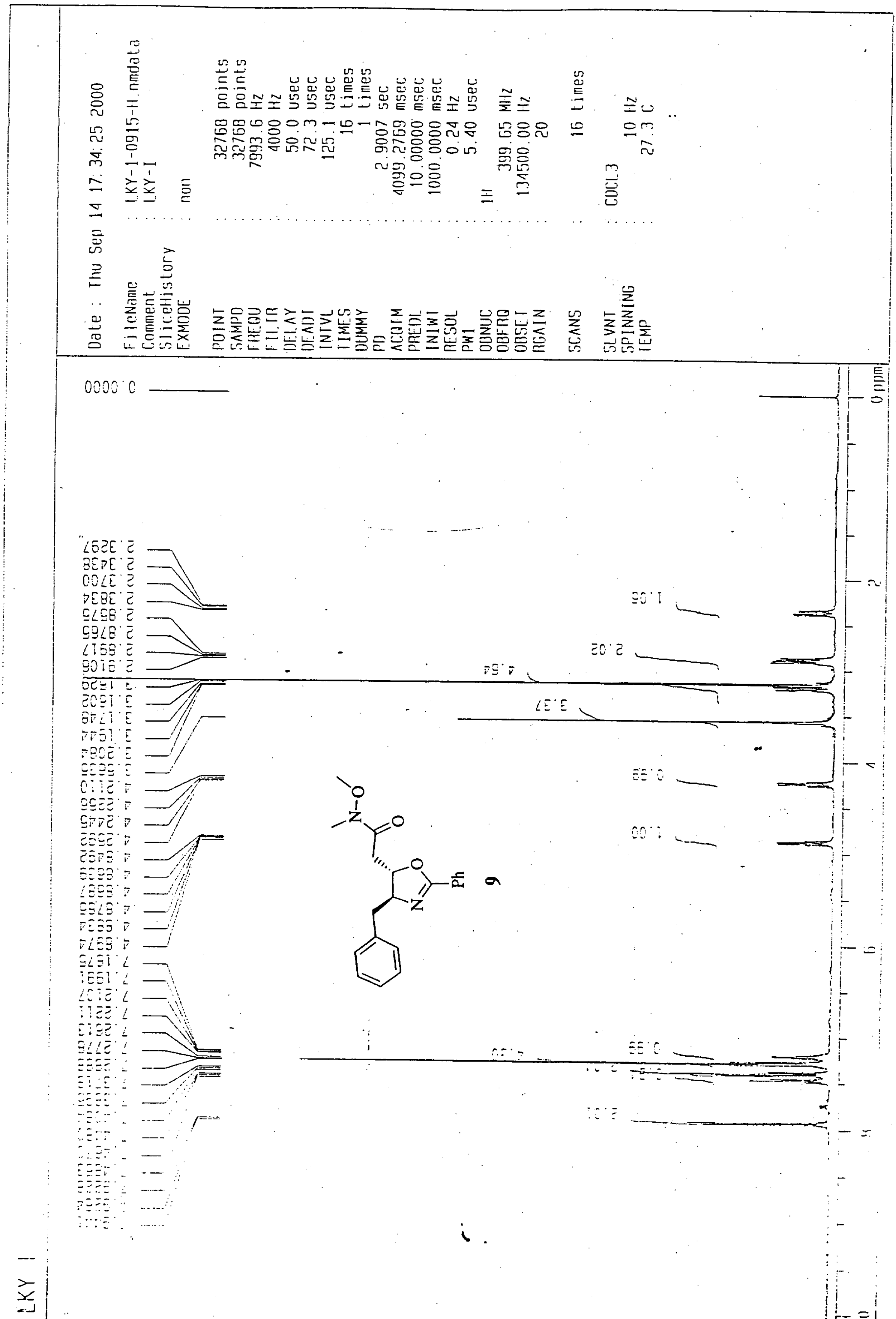
10 **11**

(+)-(2S,3S,5R)-2-Benzyl-3-hydroxy-5-nonylpyrrolidine (11). A solution of **10** (335 mg, 0.83 mmol) in 10 mL of 1:9 AcOH/MeOH, to which was added 335 mg 20% $Pd(OH)_2$, was vigorously shaken under 70 psi H_2 for 24 h at ambient temperature. The mixture was then filtered and concentrated *in vacuo*. Purification by column chromatography over silica gel (9:1 CH_2Cl_2-MeOH) gave **11** (125mg, 50%). $[\alpha]^D_{25}$ = -16.0 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, CDCl3) δ 0.85 (t, J = 6.5 Hz, 3H), 1.2-1.50 (m, 18H), 2.31 (ddd, J = 6.5, 8.5, 14.0 Hz, 1H), 2.53 (br s, 1H), 2.86-3.04 (m, 4H), 4.01 (m, 1H), 7.20-7.31(m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.8, 23.4, 27.9, 30.0, 30.26, 30.28, 30.4, 32.6, 36.1, 37.9, 42.7, 57.9, 66.5, 72.7, 126.9, 129.1, 129.7, 140.4; IR (neat): 3425, 1638, 1338 cm^{-1}; HRMS m/e calcd for $C_{20}H_{33}NO$ (M^+) 303.2562, found 303.2560.



11 **1**

(+)-(2S,3S,5R)-2-Benzyl-3-hydroxy-1-methyl-5-nonylpyrrolidine ((+)-Preussin (1)). To a solution of **11** (50 mg, 0.165 mmol) in 2.5 mL of acetonitrile was added 0.76 mL of 37% aqueous formaldehyde, 56μL of acetic acid, and 52 mg of sodium cyanoborohydride. The resulting solution was stirred at 20 °C for 4 h and then concentrated under reduced pressure. The crude product was isolated with dichloromethane in the normal manner and purified by silica gel column chromatography (1:3 ethyl acetate-hexane) to afford 41 mg (78%) of (+)-preussin (**1**). $[\alpha]^D_{25}$ = +31.5 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, CDCl3) δ 0.88 (t, J = 6.5 Hz, 3H), 1.27-1.39 (m, 15H), 1.41 (m, 1H), 1.71 (m, 1H), 2.11-2.26 (m, 3H), 2.32 (s, 3H), 2.82-2.89 (m, 2H), 3.79 (m, 1H), 7.20-7.30 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.8, 23.4, 27.0, 30.0, 30.2, 30.3, 32.6, 34.4, 35.7, 39.3, 40.0, 66.5, 71.2, 126.8, 129.1, 130.1, 140.1; IR (neat): 3452, 3032, 1614 cm^{-1}; HRMS m/e calcd for $C_{21}H_{35}NO$ (M^+) 317.2719, found 317.2710.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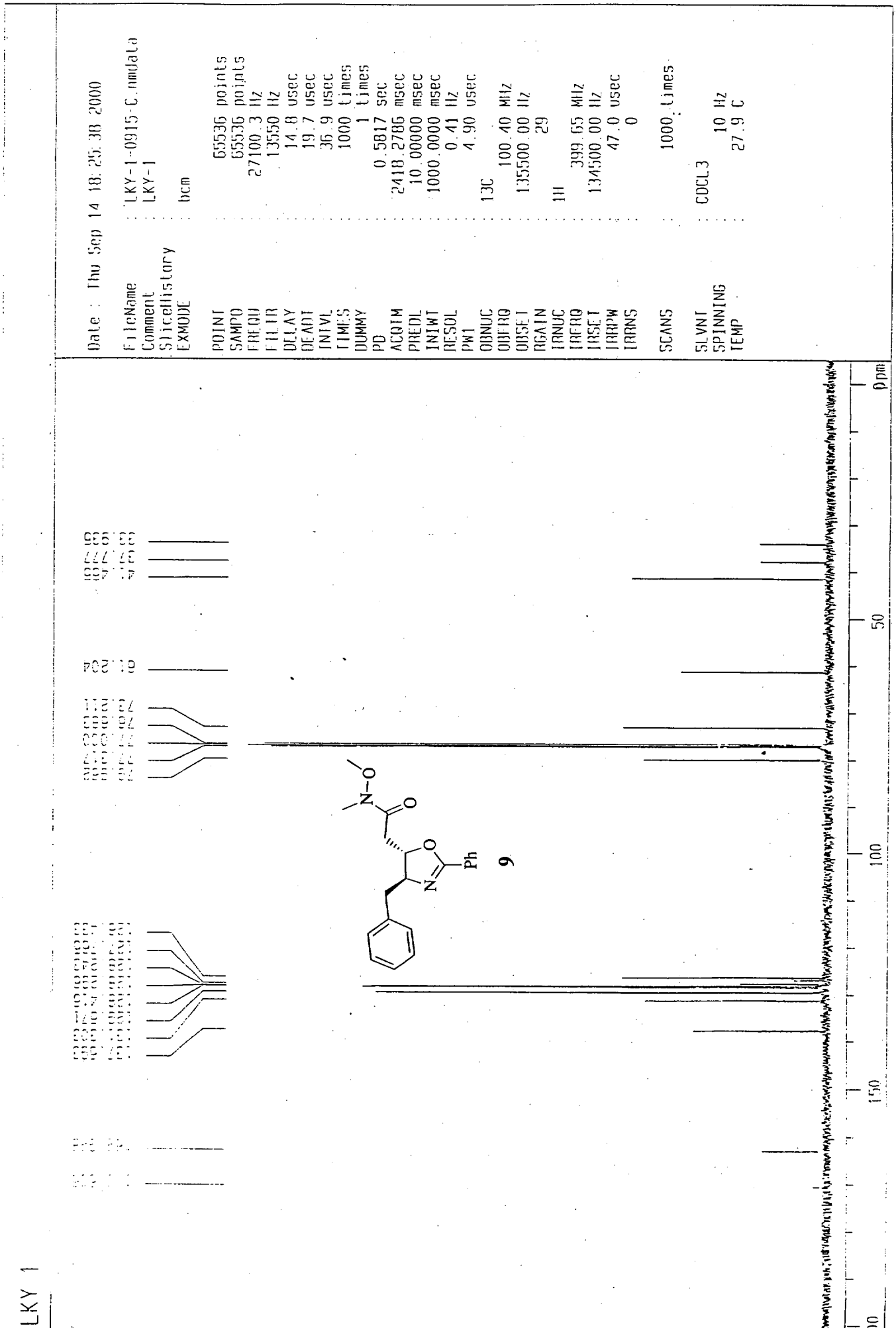
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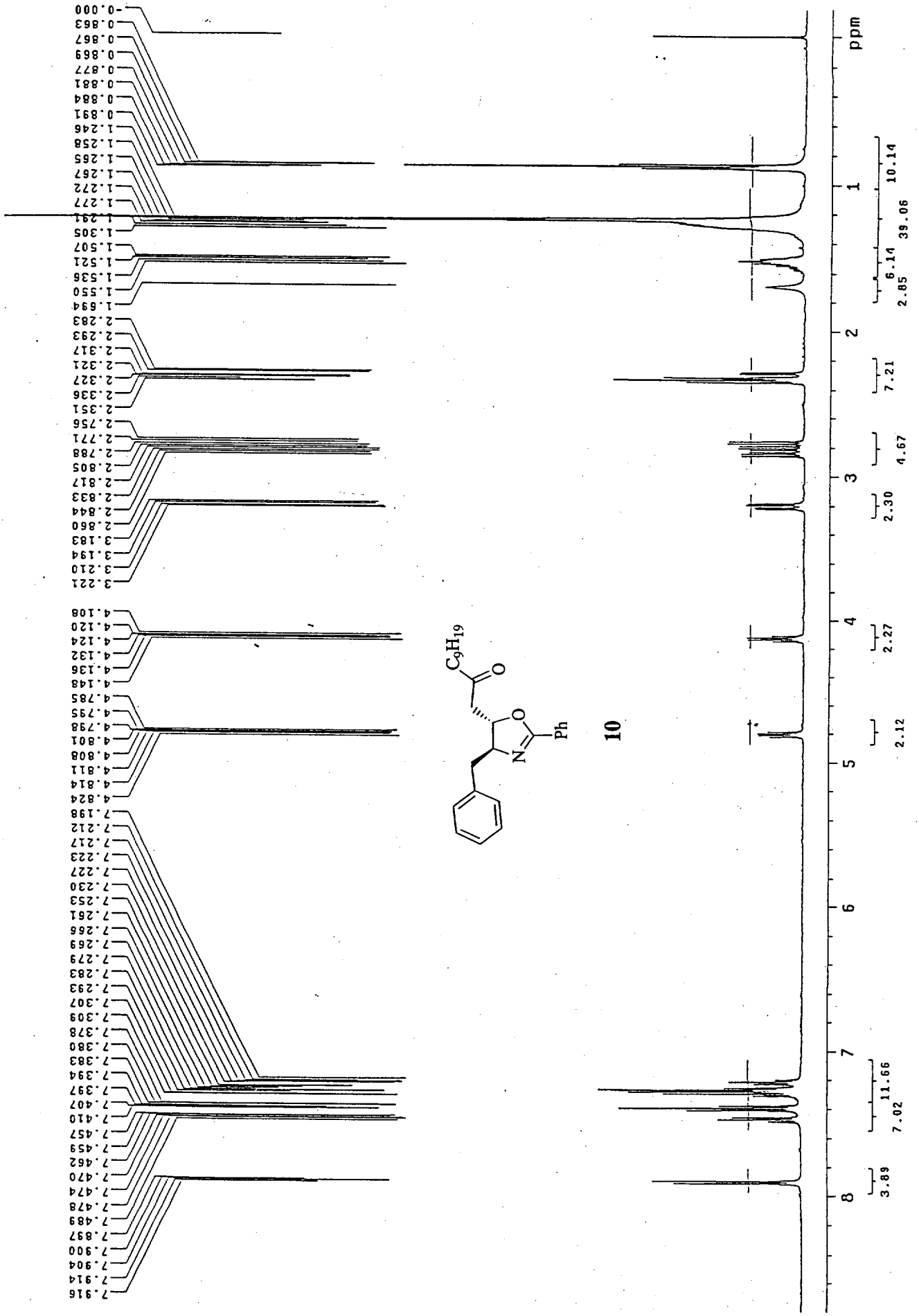
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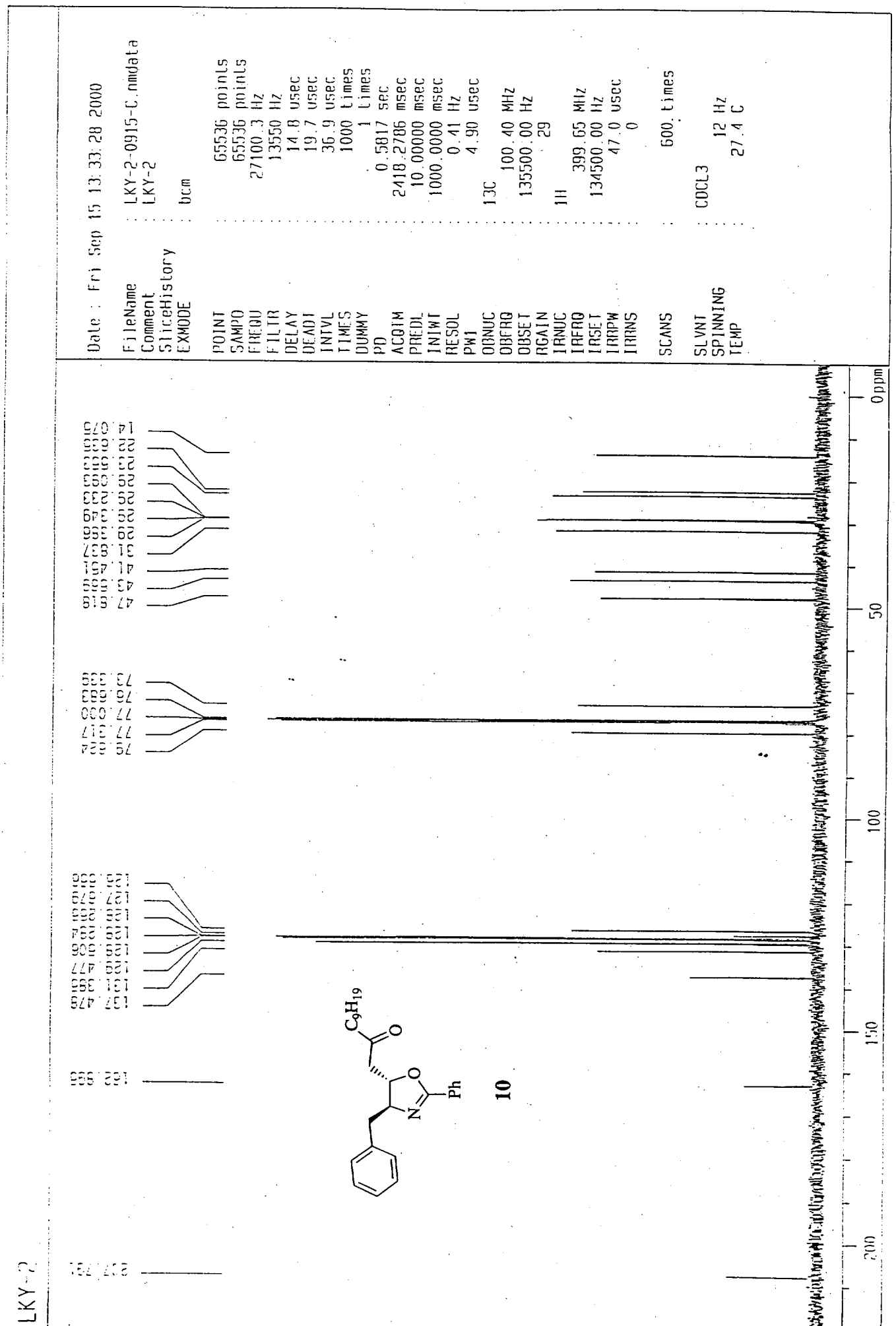

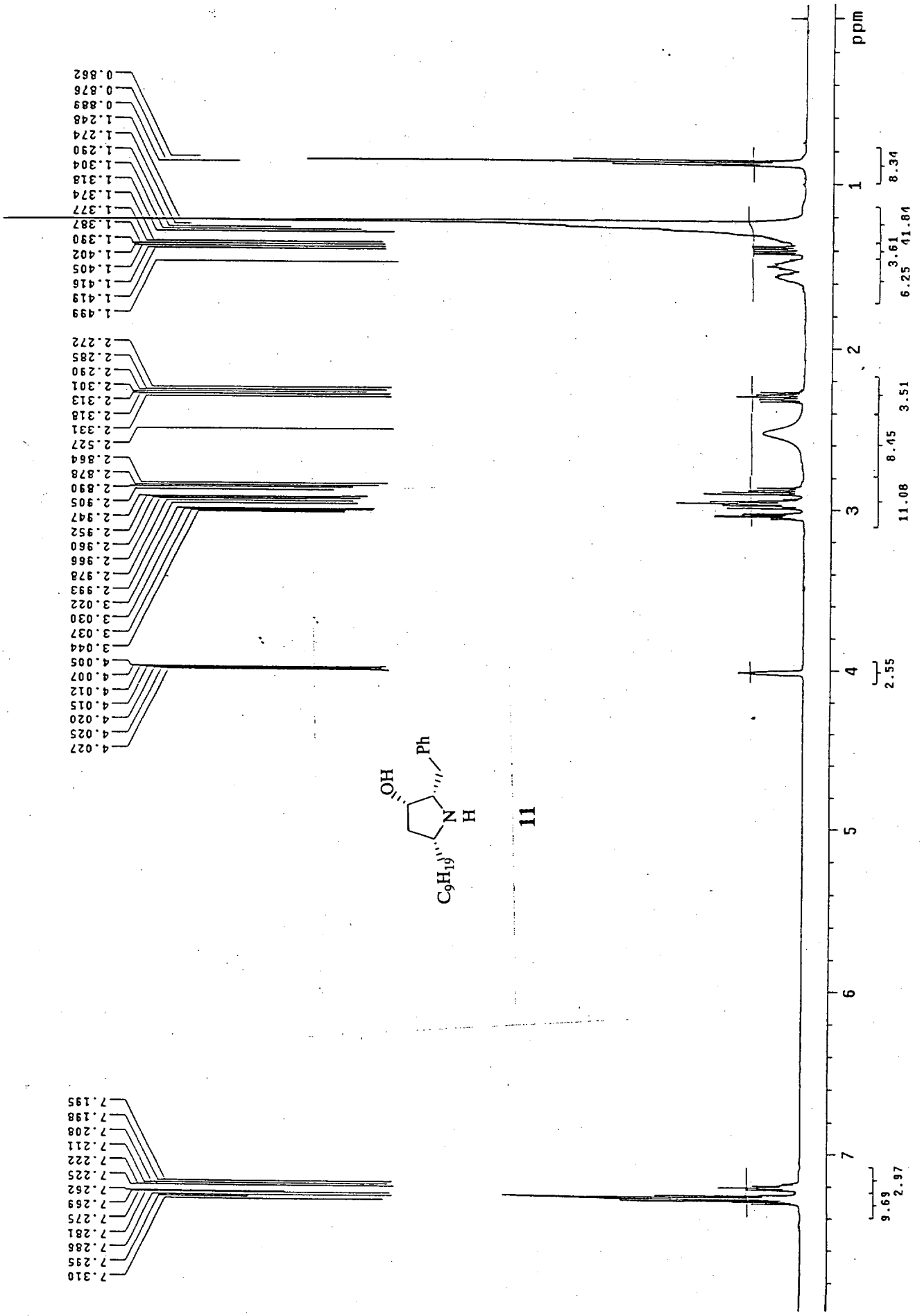
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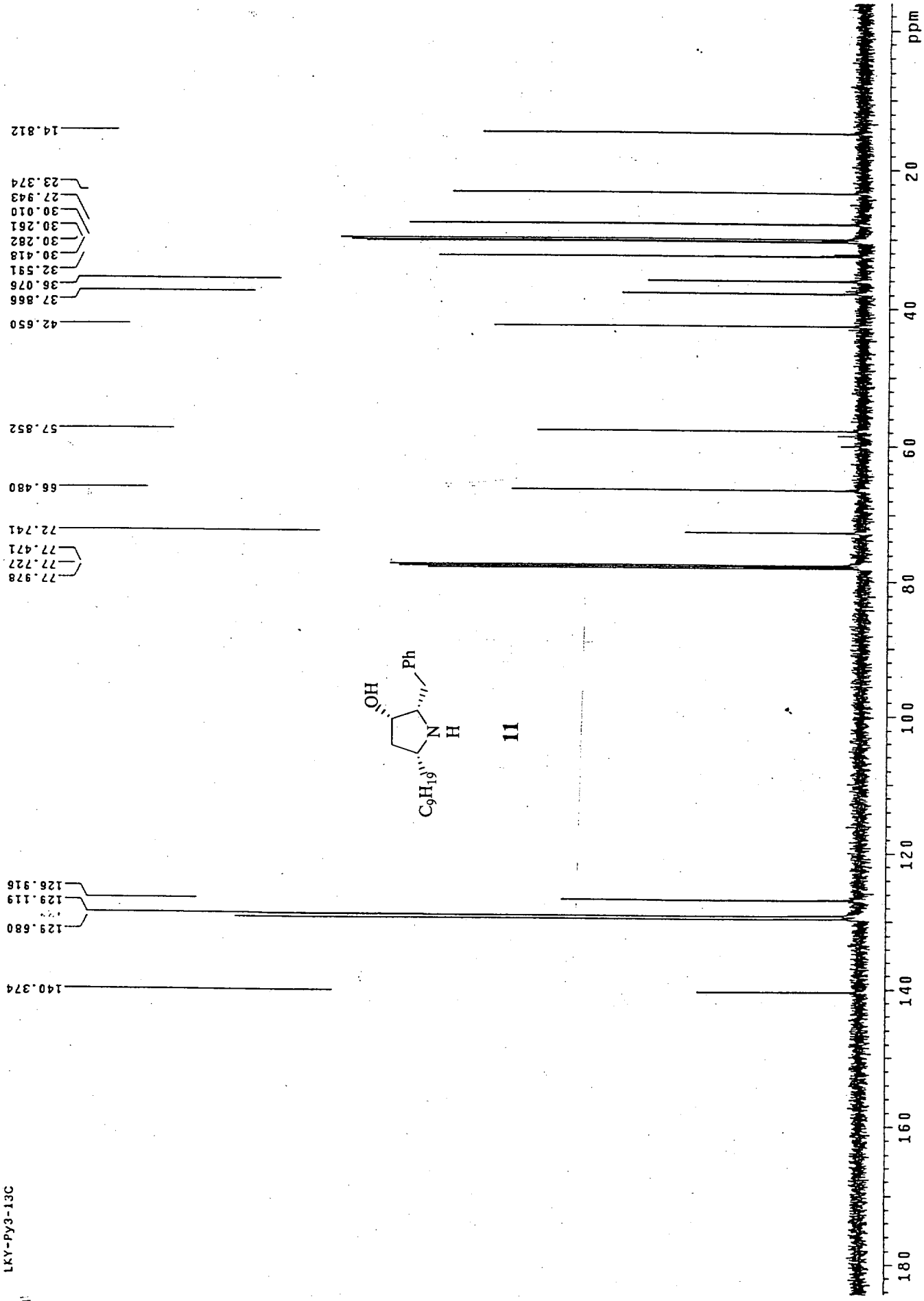

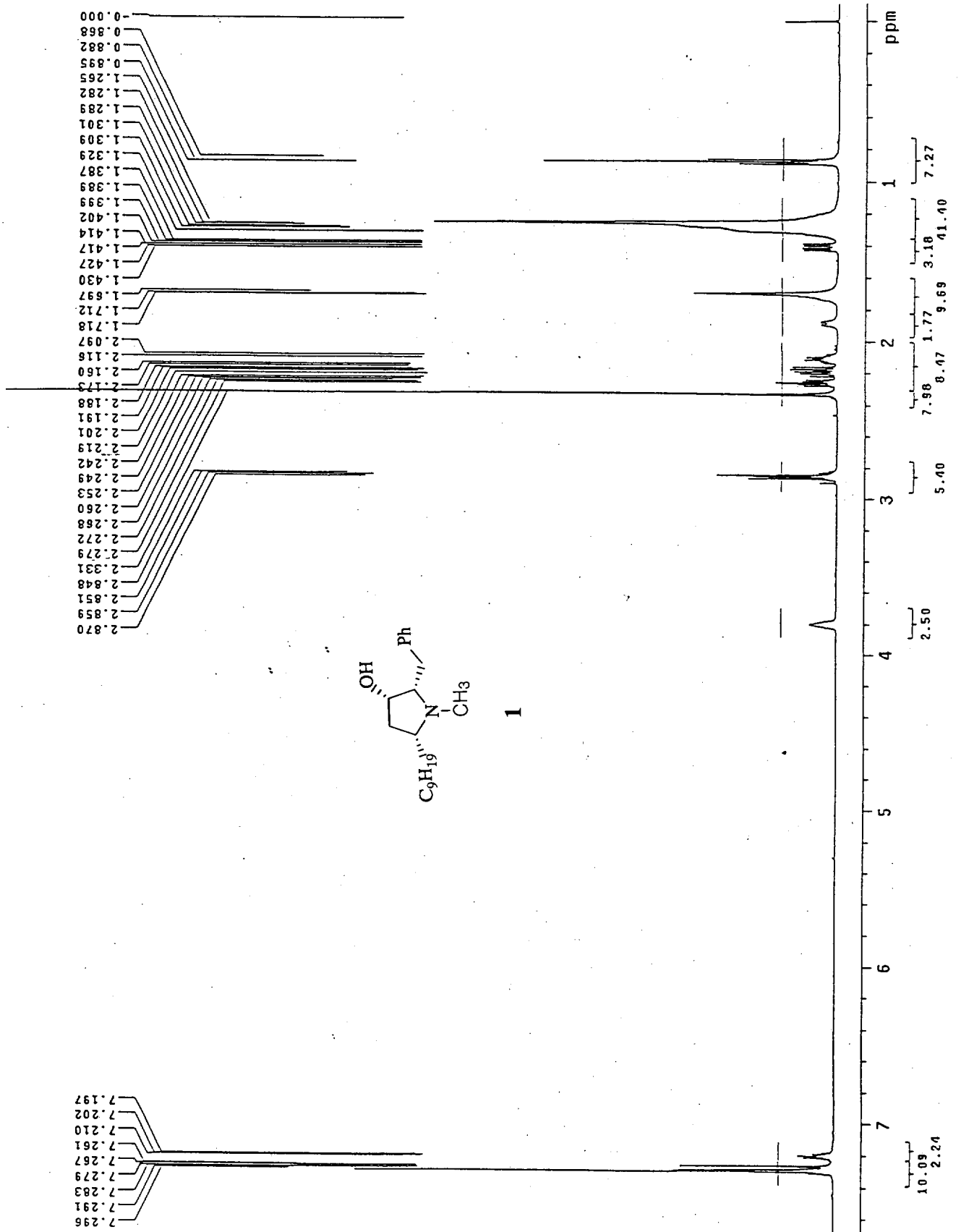
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