Highly Convergent Route to Cyclopeptide Alkaloids. Total Synthesis of Ziziphine N

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Supporting Information

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Experimental

Synthesis of 7. To a solution of **6** (5.0 g, 15.7 mmol), Meldrum's acid (2.25 g, 15.7 mmol) and DMAP (2.87 g, 23.5 mmol) in 80 mL of methylene chloride was added DCC (3.9 g, 18.8 mmol) at 0 ^{o}C. The temperature was slowly raised to room temperature and stirring was continued for 3 h. The mixture was filtered and the filtration was diluted with 800 mL cold ethyl acetate. The solution was washed subsequently with cold 5% $KHSO_4$ solution, water and brine, dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was refluxed with 200 mL of methanol for 40 min. The solvent was evaporated again and the residue was dissolved in 80 mL dichloromethane, sodium borohydride (1.0 g, 26.6 mmol) was added portion-wise at 0 ^{o}C. Stirring was continued at 0 ^{o}C for 8 h, the reaction was quenched with 100 mL water. After common work-up and flash chromatography, 2.8 g (50%) of **7** was obtained. . ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (d, J = 6.3 Hz, 6H), 0.89 (s, 9H), 1.50 (s, 9H), 2.57 (dd, J = 8.1, 15.4 Hz, 1H), 2.79 (dd, J = 9.3 Hz, 18 Hz, 1H), 2.88 (bs, 1H), 4.10 (d, J = 2.7 Hz, 2H), 4.18 (dt, J = 7.8 Hz, 2.7 Hz, 1H), 4.55-4.58 (m, 1H); ESI-MS *m/z* 368.4 $[M + Na]^+$.

Reduction of 7. To a solution of **7** (415 mg, 1.2 mmol) in 6 mL anhydrous THF at room temperature was added boran-dimethylsulfide (0.36 mL, 3.6 mmol). The mixture was refluxed for 4 h. The reaction mixture was cooled to room temperature, diluted with ether (50 mL), and quenched with saturated ammonium chloride (5 mL). The organic phase was separated and washed with 0.1 N HCl, saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated to dryness. The residue was purified by

column chromatography to give **3** (376 mg, 90% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0 08 (d, *J* = 3.9 Hz, 6H), 0.89 (s, 9H), 1.46 (s, 9H), 1.91-1.97 (m, 1H), 2.02-2.08 (m, 1H), 3.40-3.45 (m, 3H), 3.77-4.10 (m, 3H), 4.44-4.49 (m, 1H).

Preparation of aldehyde 9. The solution of **8** (6.0 g, 30.9 mmol) and sodium hydroxide (9.9 g, 247 mmol) in 100 mL ethanol/H_2O (2:1) was heated to 70 ^oC, chloroform (5.0 mL, 61.8 mmol) was added over 1 h. The resulting mixture was stirred 3 h, cooled to room temperature, evaporated to remove ethanol. The left water solution was adjust to pH 4~5, extracted with ethyl acetate. Common work-up and purification gave 2.1 g (41% yield) of aldehyde, which was dissolved in 10 mL DMF. To this solution K_2CO_3 (1.6 g, 11.3 mmol) and methyl iodide (0.7 mL, 11.3 mmol) were added. The mixture was then stirred at room temperature for 1 h, quenched with water. Common work-up and purification gave product **9** (1.9 g, 87% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68-1.87 (m, 7H), 2.82-2.85 (m, 1H), 3.90 (s, 3H), 5.35 (t, *J* = 3.0 Hz, 1H), 6.93 (d, *J* = 9.0 Hz, 1H), 7.27 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.51 (d, *J* = 3.3 Hz, 1H), 10.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.82, 25.15, 30.30, 56.01, 62.11, 97.15, 112.88, 115.38, 117.52, 124.96, 125.11, 150.87, 157.09, 189.38; MS *m/z* 259.1 $[M + Na]^+$; HRMS Calcd. for $C_{13}H_{16}O_4Na$ $[M + Na]^+$ 259.0948, found 259.0941. IR (KBr) 1027, 1162, 1220, 1282, 1496, 1676, 2879, 2941 cm^{-1}.

Synthesis of vinyl iodide 4. To a suspension of iodomethyltriphenylphosphonium iodide (10.7 g, 20.3 mmol) in 60 mL anhydrous THF at room temperature was slowly added 20.3 mL of a 1 M solution of lithium hexamethyldisilazane in THF. After stirring for 10 min, the solution was cooled to –78

^{o}C and HMPA (5.0 mL) was added. It was stirred for another 10 min before a solution of aldehyde **9** (4.0 g, 16.9 mmol) in 15 mL THF was slowly added. After addition was completed, the mixture was stirred at the same temperature for 10 min, then warmed to room temperature, and stirred for another 1 h. The mixture was diluted with 500 mL of hexane and then filtered. The filtrate was washed with brine, dried over Na_2SO_4 and evaporated to dryness. The residue was dissolved in 50 mL methanol before PPTS (200 mg) was added. The reaction was monitored until the substrate was completely consumed. Common work-up and purification give product **4** (3.3 g, 56% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3H), 4.87 (bs, 1H), 6.58 (dd, *J* = 2.1, 8.4 Hz, 1H), 6.75-6.84 (m, 2H), 7.26-7.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.28, 81.24, 112.13, 115.72, 116.05, 126.87, 134.46, 148.63, 151.21; MS *m/z* 277.0 $[M]^+$, HRMS Calcd. for $C_9H_{10}O_2I$ 276.9718, found 276.9720; IR (KBr) 1031, 1217, 1491, 1600, 2835, 2939, 3348 $cm^{-1.}$

Mitsunobu reaction of 3 and 4. DIAD (0.75 mL, 3.6 mmol) was added dropwise to a solution of **3** (600 mg, 1.8 mmol), **4** (600 mg, 2.2 mmol), and triphenylphosphine (950 mg, 3.6 mmol) in THF (30 mL). The mixture was heated at 80 ^{o}C for 3 h and the solvent was evaporated. The crude product was extracted with ether (25 mL) and filtered. The solution was dried and concentrated under reduced pressure. Chromatography on silica gel gave **10** (570 mg, 54% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.71 (s, 6H), 0.91 (s, 9H), 1.47 (s, 9H), 2.15-2.19 (m, 2H), 3.46-3.59 (m, 2H), 3.79 (s, 3H), 3.85-3.89 (m, 2H), 3.94-4.05 (m, 2H), 4.81 (d, *J* = 9.3 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 9.32 (m, 1H), 7.33-7.39 (m, 2H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ -5.39, 14.09, 18.24, 21.76, 22.67, 25.84, 28.54, 30.12, 44.99, 56.07, 62.35, 62.94, 64.27, 80.41, 111.78, 116.33, 117.15, 134.73, 150.45, 151.46, 154.55; MS *m/z* 612.1 $[M + Na]^+$; HRMS Calcd. for $C_{25}H_{40}NO_5SiINa$ $[M + Na]^+$ 612.1613, found 612.1616; IR (KBr) 777, 836, 1116, 1227, 1393, 1508, 1698, 2857, 2930, 2955 cm^{-1}; $[\alpha]_D^{22}$ = -12.7 (*c* = 0.84 in $CHCl_3$).

Cross coupling of 10 and 5. A mixture of **10** (36 mg, 0.06 mmol), *N*-alloxycarbonyl-L-proline amide **5** (18 mg, 0.09 mmol), CuI (12 mg, 0.06 mmol), *N*,*N*-dimethylglycine hydrochloride (9 mg, 0.06 mmol), cesium carbonate (60 mg, 0.18 mmol) in dry 1,4-dioxane (5 mL) was heated to 80 ^oC under argon atmosphere for 12 h. The cooled mixture was diluted with ethyl acetate (50 mL), filtered through celite. The filtrate was concentrated, and the residue was purified via chromatography to afford **11 (**24 mg, 75% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.92 (s, 9H), 1.46 (s, 9H), 1.91 (s, 2H), 2.05-2.19 (m, 4H), 3.49 (m, 5H), 3.81 (s, 3H), 3.87 (m, 1H), 4.37 (s, 1H), 4.54 (s, 2H), 4.80 (d, *J* = 8.7 Hz, 1H), 5.18 (m, 2H), 5.65 (d, *J* = 10.2 Hz, 1H), 5.88 (m, 1H), 6.73 (s, 1H), 6.88 (m, 3H), 9.33(d, *J* = 14.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.37, 0.99, 18.25, 21.93, 23.77, 25.75, 28.52, 28.81, 44.94, 45.28, 46.91, 47.26, 57.55, 61.13, 62.38, 62.97, 63.98, 66.21, 79.32, 79.68, 114.56, 117.67, 118.17, 122.30, 126.18, 151.94, 154.53, 169.74; MS *m/z* 682.3 $[M + Na]^+$; HRMS Calcd. for $C_{34}H_{53}N_3O_8SiNa$ $[M + Na]^+$ 682.3494, found 682.3496; IR (KBr) 775, 837, 1117, 1178, 1398, 1494, 1651, 1698, 2857, 2887, 2954 cm^{-1}; $[\alpha]_D^{22}$ = -36.8 (*c* = 0.96 in $CHCl_3$).

Amino acid 12. To a solution of **11** (140 mg, 0.21 mmol) in THF (2 mL) was

added 0.25 mL of 1.0 M TBAF in THF. The resulting solution was stirred at room temperature until the substrate was completely consumed monitored by TLC. The reaction mixture was diluted with ethyl acetate (20 mL), washed with water and brine, and dried over Na_2SO_4. Common purification afford the corresponding alcohol (110 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 9H), 1.91 (m, 2H), 2.14-2.30 (m, 4H), 3.50-3.54 (m, 5H), 3.75 (m, 1H), 3.81 (s, 3H), 4.37 (m, 1H), 4.55 (m, 2H), 5.07-5.24 (m, 2H), 5.18 (m, 2H), 5.67 (d, *J* = 9.9 Hz, 1H), 5.88 (m, 1H), 6.75-6.88(m, 4H), 8.94 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.07, 23.72, 24.49, 28.44, 44.94, 45.31, 46.96, 47.57, 57.03, 57.37, 60.87, 61.20, 62.69, 64.21, 65.01, 66.37, 78.94, 80.18, 106.47, 107.54, 117.54, 122.19, 125.55, 125.84, 132.45, 150.83, 151.54, 156.08, 169.56 cm^{-1}; MS *m/z* 568.2 $[M + Na]^+$; HRMS Calcd. for $C_{28}H_{39}N_3O_8Na$ $[M + Na]^+$ 568.2629, found 568.2624; IR (KBr) 733, 772, 1122, 1222, 1405, 1495, 1693, 2888, 2976, 3420; $[\alpha]_D^{22}$ = -33.7 (*c* = 0.97 in $CHCl_3$).

A mixture of the above alcohol (110 mg, 0.2 mmol) and Dess-Martin periodinane (128 mg, 0.3 mmol) in dichloromethane (10 mL) was stirred at room temperature for 2 h, quenched with saturated $Na_2S_2O_3$. The organic phase was separated and the aqueous phase was extracted with dichloromethane (20 mL × 3). The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated to dryness. The residue was dissolved in the mixture of *t*-BuOH (4 mL), acetonitrile (2 mL) and 2-methyl-1-butene (1 mL). The mixture was cooled to 0 ^{o}C followed by addition of a newly prepared solution of NaH_2PO_4 (120 mg) and $NaClO_2$ (100 mg) in water (6 mL). The mixture was then slowly warmed to room

temperature before it was quenched with saturated $Na_2S_2O_3$. After common work-up, the product obtained was dissolved in dry methylene chloride (10 mL),. To this solution $Pd(PPh_3)_4$ (30 mg, 0.02 mmol) and diethylamine (100 μL, 1 mmol) were added. After the mixture was stirred at room temperature for 50 min, the solvent was removed and the residue was purified via silica gel column to afford amino acid **2** (56 mg, 56% yield); ^{1}H NMR (300 MHz, CD_3OD) δ 1.43 (2s, 9H), 2.08 (m, 5H), 2.43 (m, 1H), 3.37 (m, 2H), 3.55-3.75 (m, 3H), 3.82 (s, 3H), 4.44-4.47 (m, 1H), 4.84 (m, 1H), 6.05 (d, *J* = 9.6 Hz, 1H), 6.77-6.97 (m, 3H), 7.45 (d, *J* = 2.7 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 25.45, 29.05, 30.71, 31.43, 32.23, 46.20, 46.58, 47.46, 57.06, 61.91, 69.41, 81.34, 83.96, 84.49, 109.95, 110.61, 114.13, 116.92, 117.49, 119.25, 122.00, 125.94, 152.94, 153.46, 156.91 cm^{-1}; MS *m/z* 476.1 $[M + H]^+$; HRMS Calcd. for $C_{24}H_{34}N_3O_7$ $[M + H]^+$ 476.2391, found 476.2381; IR (KBr) 776, 1170, 1220, 1417, 1614, 1682, 2928, 2971; $[\alpha]_D^{22}$ = +29.1 (*c* = 0.83 in CH_3OH).

Lactam 2. To a solution of FDPP (109 mg, 0.28 mmol), diisopropylethylamine (100 μL, 0.56 mmol) in 40 mL anhydrous DMF was added a solution of **12** (27 mg, 0.05 mmol) in dry DMF (110 mL) in a dropwise manner under Ar atmosphere. The mixture was stirred at room temperature for 24 h before the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate, washed with water and brine, and dried over Na_2SO_4. The solution was concentrated and the residue was chromatographed to give **2** (17 mg, 66%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.74-1.84 (m, 2H), 1.97-2.04 (m, 2H), 2.16-2.25 (m, 2H), 2.35 (m, 1H), 3.31 (m, 1H), 3.39-3.47 (m, 1H), 3.80 (s, 3H), 4.30 (m, 2H), 4.63 (d, *J* = 5.7 Hz, 1H), 5.30 (m, 1H),

5.94 (d, J = 8.4 Hz, 1H), 6.81-6.96 (m, 4H), 8.38 (d, J = 11.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.93, 28.20, 29.33, 32.47, 45.33, 47.85, 53.39, 56.02, 61.83, 62.47, 79.11, 80.26, 106.57, 110.86, 113.92, 117.08, 121.63, 124.21, 151.13, 153.94, 167.87, 172.53; MS *m/z* 480.1 $[M + Na]^+$; HRMS Calcd. for $C_{24}H_{31}N_3O_6Na$ $[M + Na]^+$ 480.2105, found 480.2098; IR (KBr) 731, 1053, 1131, 1224, 1398, 1509, 1640, 1655, 1696, 2930, 2976, 3392 cm^{-1}; $[\alpha]_D^{22}$ = -406.4 (c = 0.56 in $CHCl_3$).

Ziziphine N 1. To a solution of **2** (25 mg, 0.05 mmol) in dry dichloromethane (1 mL) was added $ZnBr_2$ (25 mg, 0.1 mmol) at 0 ^oC. The mixture was stirred for 4 h, quenched with saturated $NaHCO_3$, and then extracted with dichloromethane. After the solvent was removed under reduced pressure, the residue was dissolved in dry DMF (0.5 mL). To this solution *N*,*N*-dimethyl-L-isoleucyl-L-leucine **13** (29 mg, 0.11mmol), HATU (42 mg, 0.11 mmol), K_2CO_3 (30 mg, 0.22 mmol) were added subsequently at 0 ^oC. The mixture was stirred overnight, quenched with water, and then extracted with ethyl acetate. The combined organic layers were washed with water and brine, and dried over Na_2SO_4. The solution was concentrated and the residue was chromatographed to afford **1** (7 mg, 22 % yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.9 Hz, 6H), 0.95 (t, J = 6.8 Hz, 3H), 1.14 (m, 1H), 1.48 (m, 2H), 1.56 (m, 1H), 1.64 (m, 1H), 1.75 (m, 2H), 1.94 (m, 2H), 2.24 (s, 6H), 2.36 (m, 1H), 2.46 (m, 1H), 2.55 (d, J = 5.6 Hz, 1H), 3.26 (m, 1H), 3.57 (m, 1H), 3.80 (s, 3H), 4.21 (m, 2H), 4.38 (d, J = 5.8 Hz, 1H), 4.52 (dd, J = 9.0, 4.2 Hz, 1H), 4.75 (dd, J = 7.9, 7.6 Hz, 1H), 5.94 (d, J = 8.8 Hz, 1H), 6.80 (br s, 1H), 6.82 (d, J = 7.3 Hz, 1H), 6.86 (d, J = 11.6 Hz, 1H), 6.92 (dd, J = 11.5, 8.8 Hz, 1H), 6.94 (d, J = 8.8 Hz, 1H), 8.34 (d, J = 11.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7, 14.3, 21.4, 22.9, 24.4, 24.6,

26.7, 28.8, 32.4, 34.0, 40.6, 42.8, 45.1, 47.6 (2C), 55.7, 61.8, 62.5, 74.1, 78.4, 106.4, 110.5, 113.6, 116.7, 121.4, 123.9, 150.7, 151.0, 167.5, 171.0, 171.3, 171.6; MS *m/z* 634.2 $[M + Na]^+$; HRMS Calcd. for $C_{33}H_{49}N_5O_6Na$ $[M + Na]^+$ 634.3575, found 634.3578; IR (KBr) 802, 1025, 1223, 1260, 1463, 1509, 1643, 2852, 2923, 2958 cm^{-1}; $[\alpha]_D^{22}$ = -324.8 (*c* = 0.24 in $CHCl_3$).


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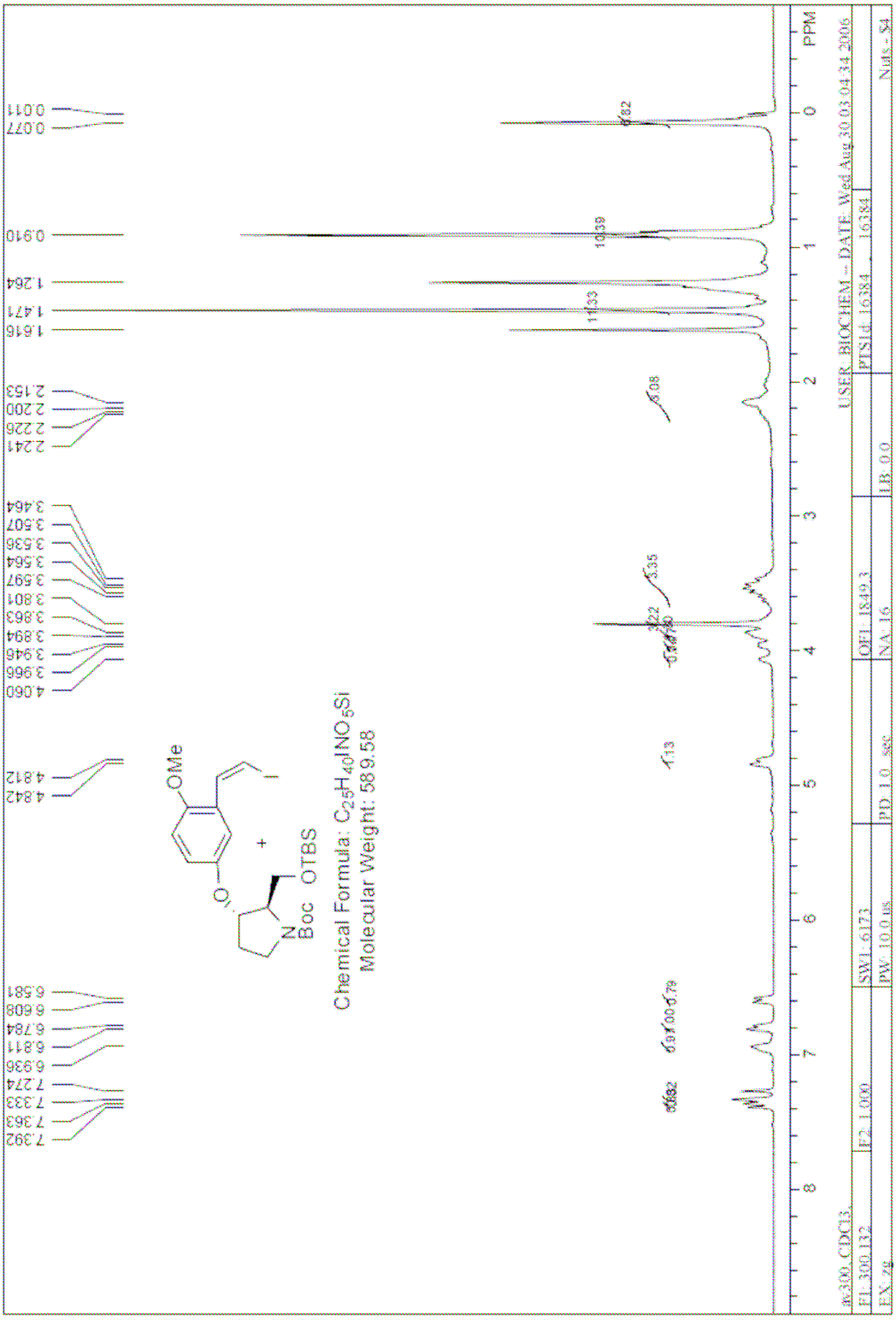
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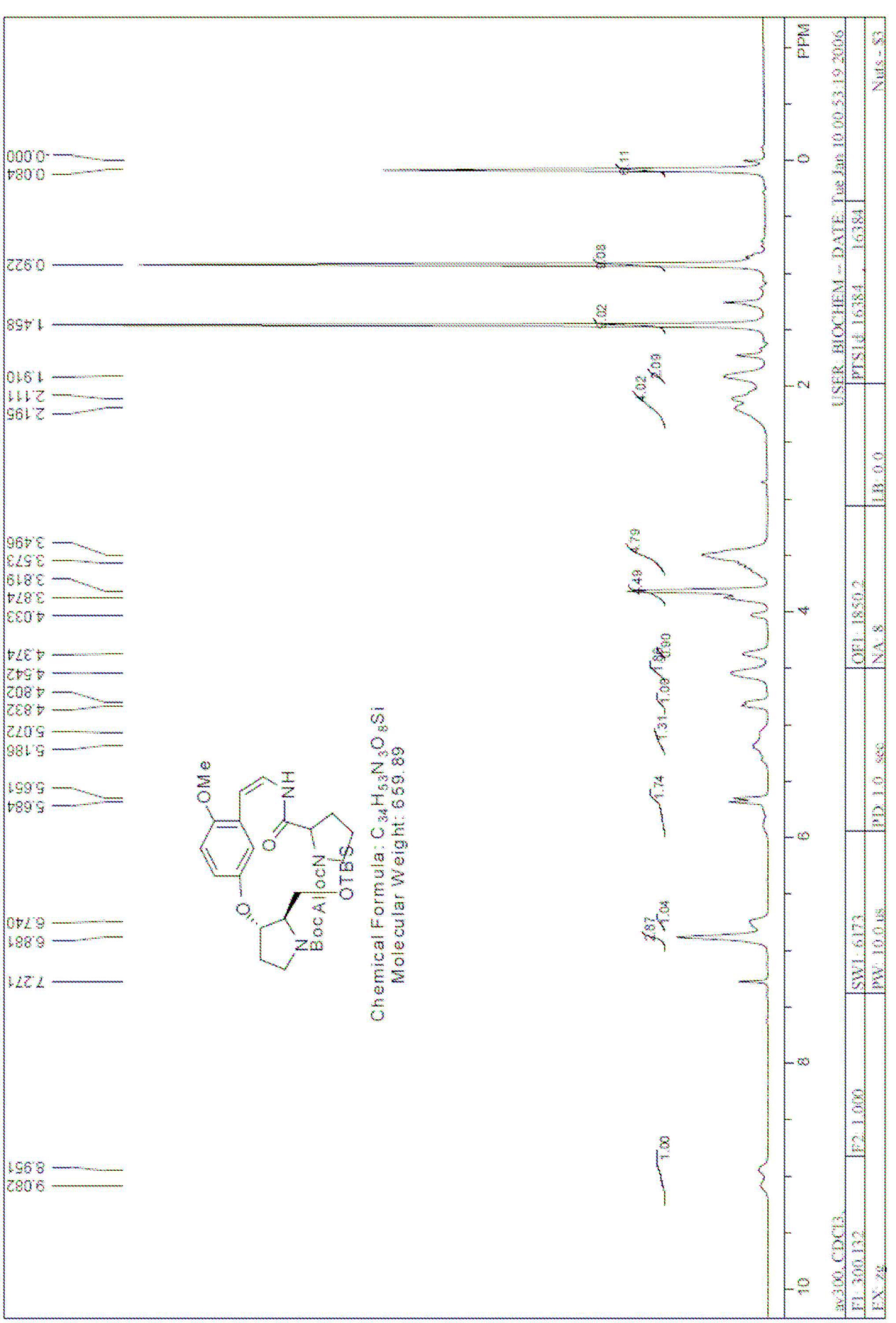
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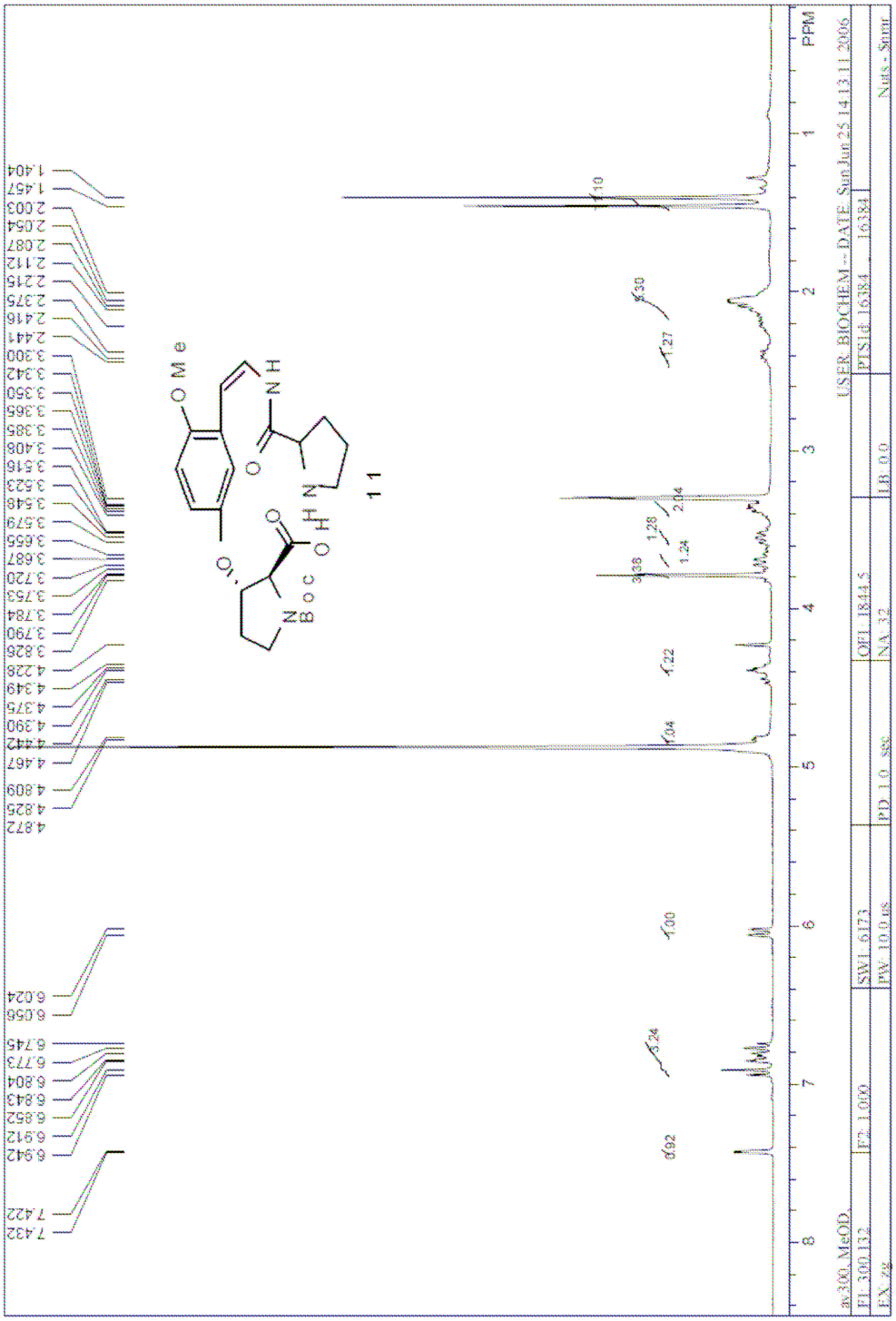
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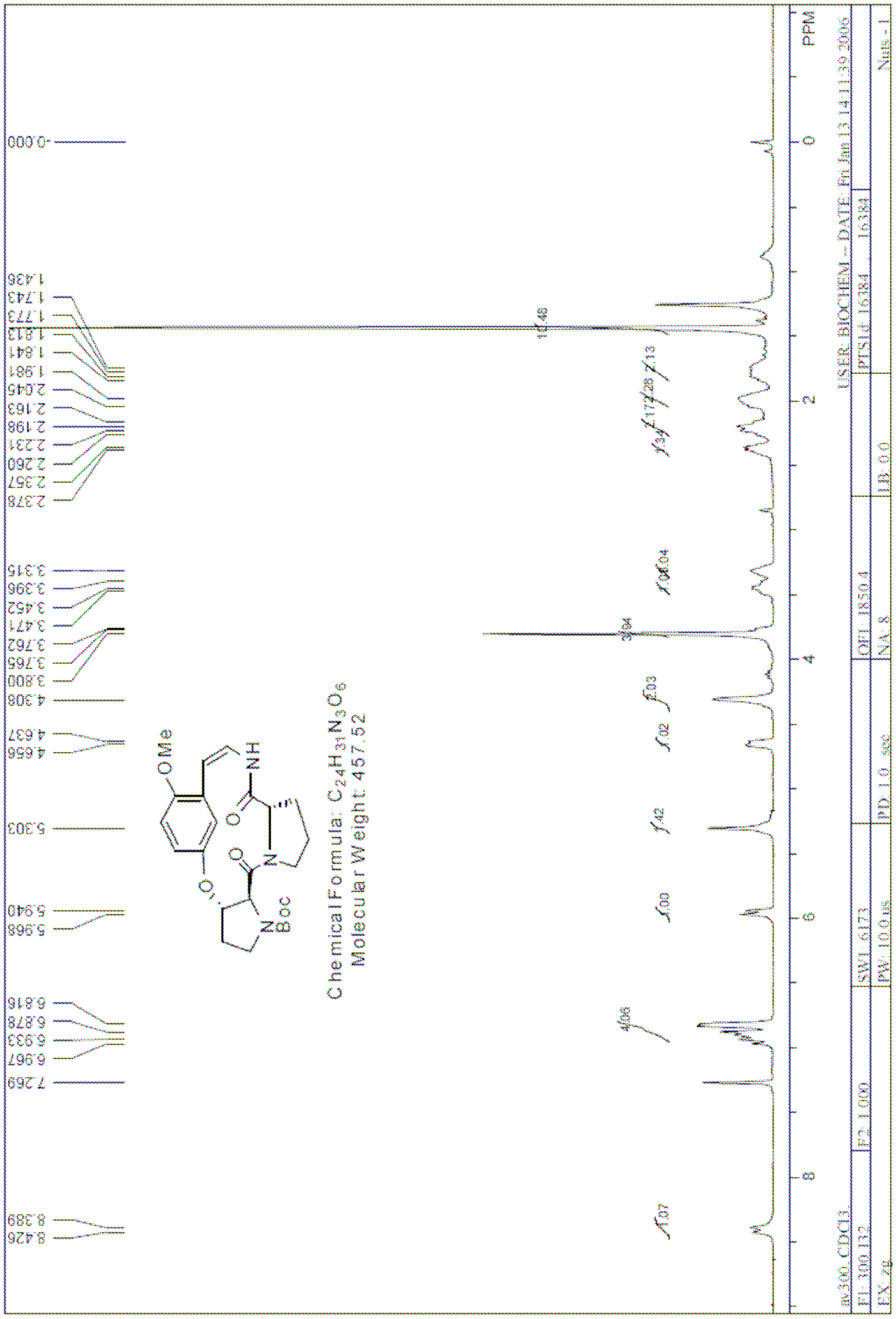
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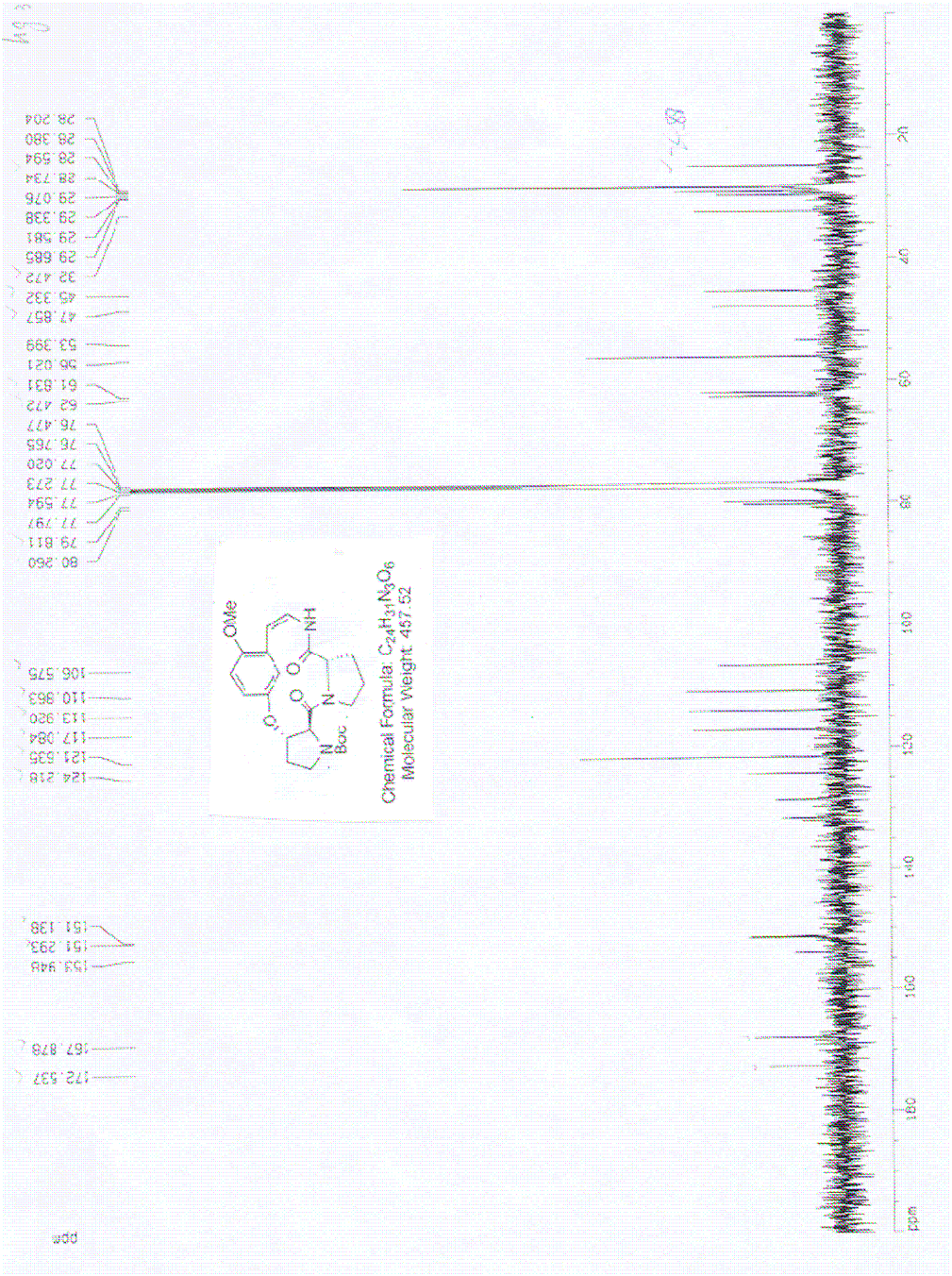
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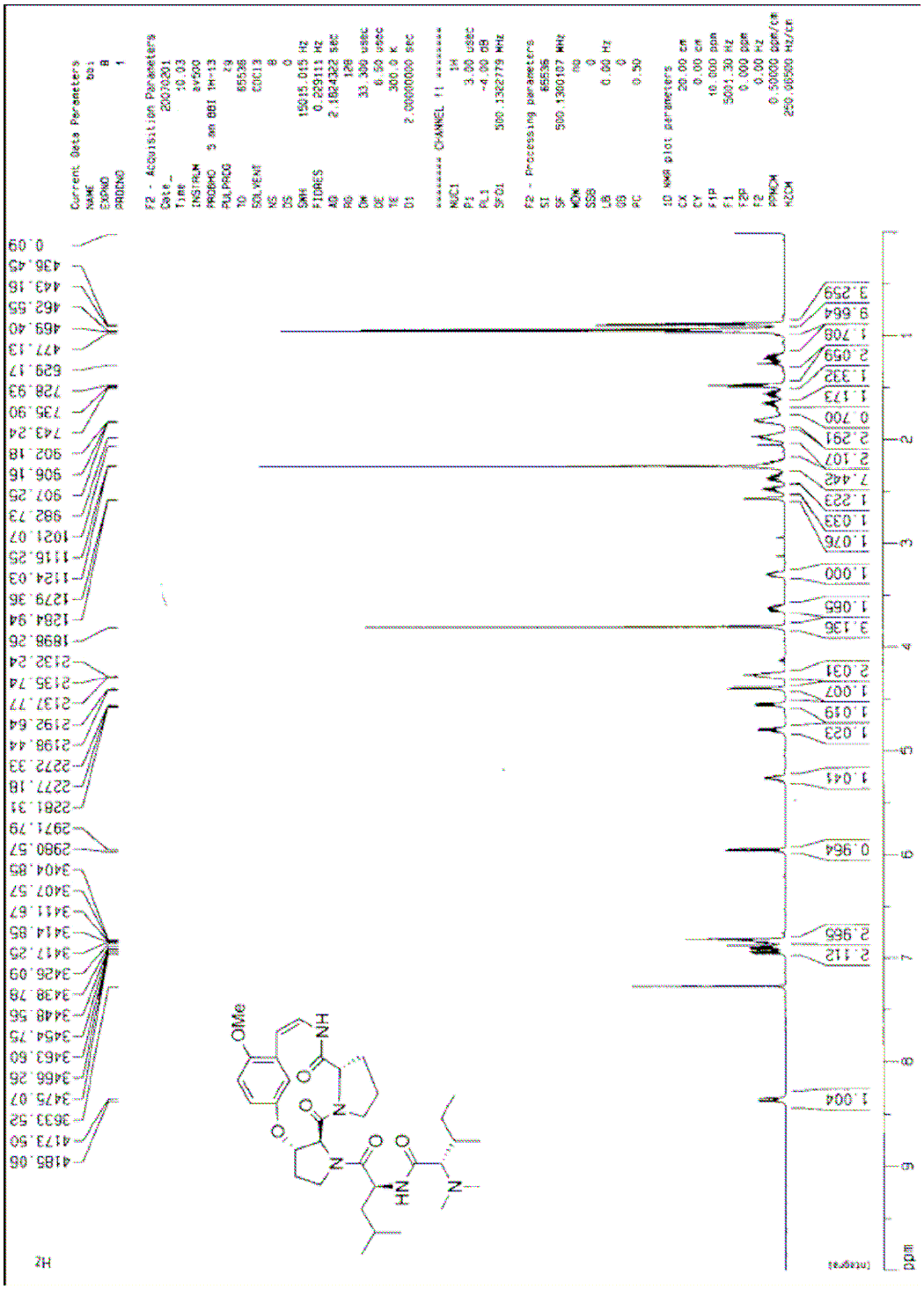
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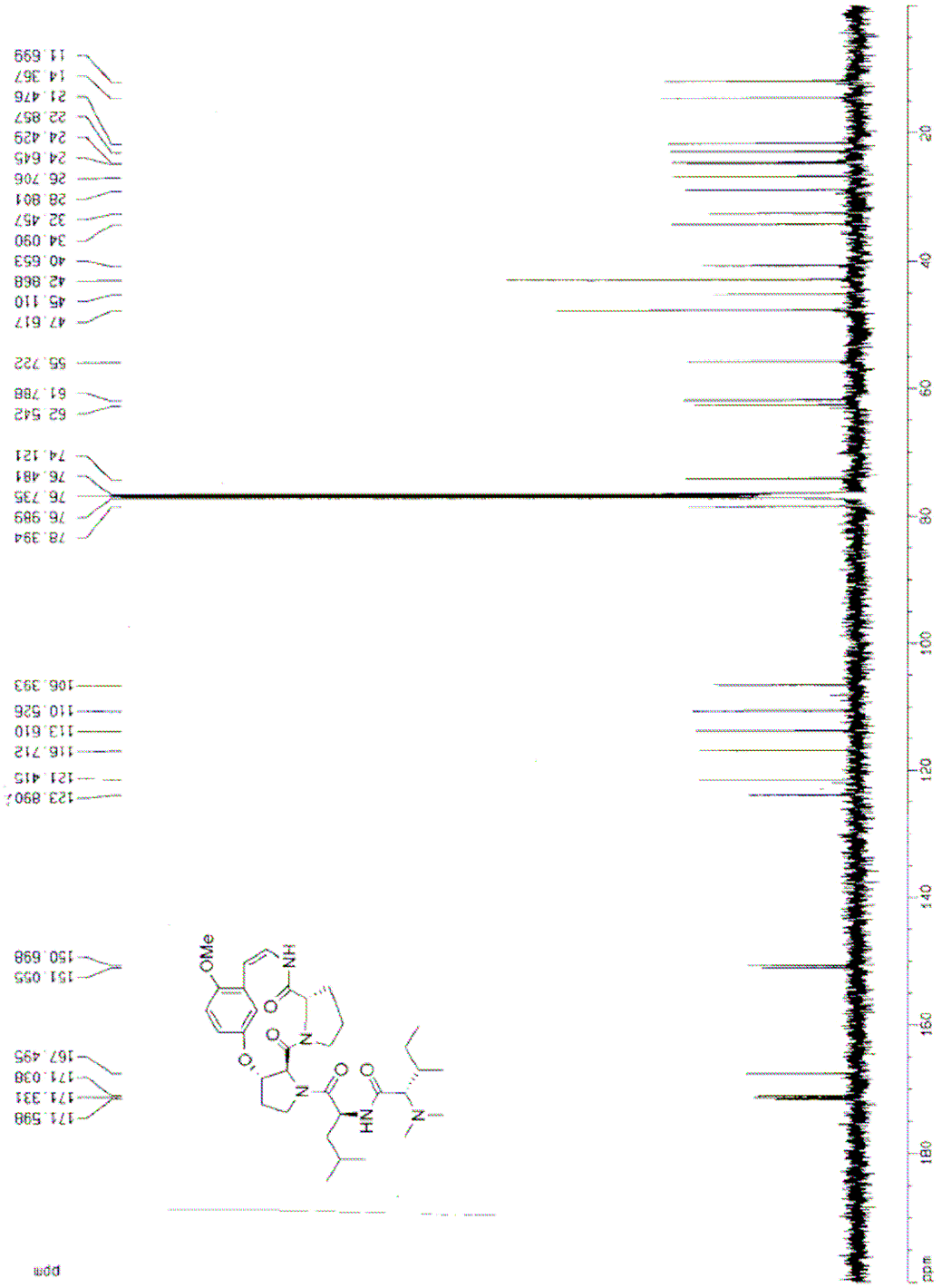
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