Catalyzed Asymmetric Diels-Alder Reaction of Benzoquinone. Total Synthesis of (–)-Ibogamine

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SUPPORTING INFORMATION

- Preparative procedures and characterization data for **2, 5-17, 19-21,** and (–)-**1**
- Copies of ^{1}H and ^{13}C NMR spectra of all compounds
- X-ray crystallographic summary data for **12**

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Diene 2

Into a flame dried pressure bottle cooled -78 °C was condensed 1-butyne (3.25 g, 60.1 mmol) under argon. A 1M solution of catecholborane-THF complex (60 mL, 60 mmol) was injected into the stirred mixture, and the solution was heated at 70 °C for 24 h. After the solution had cooled to room temperature, the mixture was distilled at reduced pressure to give 8.57 g (82%) of (*E*)-1-butenyl-1,3,2-benzodioxaborole as a colorless oil: bp 77-78 °C (2.5 Torr); IR (neat) 742, 1246, 1643, 2959, 3199 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (t, J = 7.4 Hz, CH_3), 2.33 (ddq, J = 1.7, 7.5, 7.5 Hz, 2H), 5.83 (dt, J = 1.7, 18.0 Hz, 1H), 7.01-7.28 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2, 28.8, 106.1, 112.2, 122.5, 148.2, 159.2; MS (CI) m/z 174 (M^+), 159, 146, 134, 120, 115, 101, 93, 69; HRMS (CI) m/z 174.0852 (calcd for $C_{10}H_{11}O_2{}^{11}B$: 174.0852).

To a solution of 1.04 g (3 mol%) of $Pd(PPh_3)_4$ in THF (80 mL) was added a solution of **3** (7.53 g, 30.0 mmol) in THF (10 mL), and the mixture was stirred for 1 h at room temperature. To this mixture was added a solution of (*E*)-1-butenyl-1, 3, 2-benzodioxaborole (5.80 g, 33.3 mmol) in THF (10 mL) followed by 66.6 mmol (2 eq) of NaOEt, and the resultant mixture was heated under reflux for 7h. The mixture was allowed to cool to room temperature during 1h, and the residual borane was treated with an aqueous solution of NaOH (3M, 1 mL) and H_2O_2 (30%, 1 mL) for 1h at room temperature. The mixture was extracted with hexane (3x 30 mL), and the extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica gel (ether-pentane, 1:30) gave 4.55 g (67%) of **2** as a colorless oil: R_f 0.4 (hexanes); IR (neat) 1110, 1253, 2337, 2359, 2883, 2957 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.92 (s, 9H), 1.02 (t, J = 7.4 Hz, CH_3), 2.11 (m, 2H), 4.32 (m, 2H), 4.98 (s, 1H), 5.19 (m, 1H), 5.70 (dt, J = 6.5, 16.1 Hz, 1H), 6.06 (d, J = 16.1, Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4 (2C), 13.5, 18.3, 25.9 (3C), 26.1, 63.0, 112.1, 128.7, 131.4, 144.8; MS (CI) m/z 227 (M^++H), 211, 195, 193, 169, 139, 137, 95, 83, 75; HRMS (CI) m/z 227.1815 (calcd for $C_{13}H_{27}OSi$: 227.1831).

Diketone 5

To a solution of BINOL-Ti complex **4** (1M solution, 1.7 mL) and 1,4-benzoquinone (603 mg, 5.58 mmol) in toluene (3 mL) at room temperature was added a solution of **2** (1.47 g, 6.49 mmol) in toluene (2 mL), and the mixture was stirred for 30 min at room temperature. The mixture was concentrated under reduced pressure, and the residue was used for the next reaction without purification due to the instability of **5**.

Hydroxy Ketone 6

To a solution of **5** obtained above in MeOH (5 mL) at 0 °C was added $NaBH_4$ (211 mg, 5.58 mmol) and $CeCl_3.7H_2O$ (2.08 g, 5.58 mmol), and the mixture was stirred for 1 h at 0 °C. The mixture was diluted with Et_2O (30 mL) and was washed with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Chromatography of the residue on silica gel (EtOAc-hexanes, 1:3) gave **6** (1.23 g, 65% from **2**) as a colorless oil: R_f 0.34 (EtOAc-hexanes, 1: 3); $[\alpha]_D$ -35.3 (*c* 1.45, $CHCl_3$); IR (neat) 777, 836, 1073, 1254, 1673, 1685, 2853, 2926, 2953, 3370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.4 Hz, 3H), 1.80-2.27 (m, 5H), 2.73 (m, 2H), 3.98 (m, 2H), 4.92 (m, 1H), 5.62 (s, 1H), 5.83 (dd, *J* = 2, 7, 10.3 Hz), 6.57 (ddd, *J* = 2, 3.5, 10.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3, -5.2, 12.5, 18.4, 22.2, 25.6, 25.9 (3C), 41.3, 43.7, 48.2, 67.0, 70.7, 125.7, 129.6, 134.1, 147.4, 199.7 ; MS (CI) m/z 335(M^+-H), 321, 279, 261, 205, 187, 159, 75; HRMS (CI) m/z 335.2047 (calcd for $C_{19}H_{31}O_3Si$: 335.2043).

Mandelate 7

To a solution of **6** (45 mg, 0.13 mmol), (*R*)-*O*-methylmandelic acid (24 mg, 0.15 mmol), and DCC (30 mg, 0.15 mmol) in CH_2Cl_2 (4 mL) at room temperature was added DMAP (8 mg, 0.07 mmol). After 30 min, the reaction mixture was passed through a plug of cotton which was rinsed with hexanes. The eluant was diluted with saturated aqueous $NaHCO_3$ (1 mL), washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Chromatography of the residue on silica gel (EtOAc-hexanes, 1:7) afforded 53 mg

(82%) of **7** as a colorless oil: R_f 0.25 (EtOAc-hexanes, 1:7), $[\alpha]_D$ -67.1 (*c* 1.2, $CHCl_3$). Integrations in two regions were performed in the crude ^1H NMR spectrum; they are labeled a and b in the following NMR data: IR (neat) 1168, 1252, 1689, 1751, 2852, 2920, 2950 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6 H), 0.91 (s, 9 H), 0.92 (t, *J* = 7.4 Hz, 3H), 1.72-2.09 (m, 4H), 2.15 (m, 1H), 2.79 (t, *J* = 3.9 Hz, 1H), 2.89 (m, 1H), 3.42 (s, 3H), 3.88-4.01[a] (m, 2H), 4.81 (s, 1H), 5.58 (m, 1H), 5.83 (dd, *J* = 2.5, 10.4 Hz, 1H), 5.93 (dt, *J* = 2.4, 5.3 Hz, 1H), 6.24[b] (ddd, *J* = 2.1, 4.0, 10.4 Hz, 1H), 7.31–7.52 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3, -5.2, 12.4, 18.4, 22.8, 25.5, 25.9 (3C), 40.9, 41.0, 47.9, 57.4, 66.9, 73.3, 82.4, 125.5, 127.0 (2C), 128.9, 131.0, 133.9, 135.8, 142.4, 170.0, 198.7; MS (CI) m/z 483 (M^+- H), 469, 427, 353, 319, 261, 187, 121; MS (CI) m/z 483 (M^+- H), 469, 427, 353, 319, 261, 187, 121; HRMS (CI) m/z 483.2567 (calcd for $C_{28}H_{39}O_5Si$: 483.2559).

Mandelate 8

To a solution of **7** (14 mg, 0.04 mmol), (*S*)-*O*-methylmandelic acid (11 mg, 0.06 mmol), and DCC (13 mg, 0.06 mmol) in CH_2Cl_2 (3 mL) at room temperature was added DMAP (3 mg, 0.02 mmol). After 30 min, the reaction mixture was passed through a plug of cotton which was rinsed with hexanes. The mixture was diluted with saturated aqueous $NaHCO_3$ (1 mL), washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Chromatography of the residue on silica gel (EtOAc-hexanes, 1:5) gave 17 mg (82%) of **8** as a colorless oil: R_f 0.22 (EtOAc-hexanes, 1:5); $[\alpha]_D$ -29.0 (*c* 1.53, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6 H), 0.89 (s, 9 H), 0.91 (t, *J* = 7.7 Hz, 3H), 1.36 (m, 1H), 1.71-1.97 (m, 3H), 2.09 (m, 1H), 2.64-2.78 (m, 2H), 3.42 (s, 3H), 3.70 (d, *J* = 12.9 Hz, 1H), 3.78 (d, *J* = 12.9 Hz, 1H), 4.81 (s, 1H), 5.52 (m, 1H), 5.87 (dd, *J* = 2.7, 10.3 Hz, 1H), 5.94 (dt, *J* = 2.5, 5.1 Hz, 1H), 6.45 (ddd, *J* = 1.7, 3.8, 10.3 Hz, 1H), 7.31-7.49 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3 (2C), 12.4, 18.3, 22.4, 25.5, 25.9 (3C), 40.7, 40.9, 47.9, 57.3, 66.4, 73.2, 82.3, 124.5, 127.2 (2C), 128.8 (2C), 129.0, 131.1, 133.7, 136.0, 142.5, 169.9, 198.6

Diol 9

To a solution of **5** obtained above in MeOH (15 mL) at room temperature was added $NaBH_4$ (633 mg, 16.7 mmol) and $CeCl_3.7H_2O$ (6.24 g, 16.7 mmol), and the mixture was stirred for 8 h at room temperature. Workup as for **6** gave diol **9** (1.18 g, 62% from **2**) as a colorless solid: R_f 0.33 (EtOAc-hexanes, 1:3); mp 105-106 °C; $[\alpha]_D$ -129.7 (*c* 1.95, $CHCl_3$); IR (neat) 776, 834, 1005, 1254, 2858, 2881, 2928, 2956, 3387 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.91 (s, 9H), 1.04 (t, *J* = 7.4 Hz, 3H), 1.69 (m, 2H), 1.89-2.11 (m, 4H), 2.14 (d, *J* = 6 Hz, 1H), 2.23-2.35 (m, 2H), 4.01 (m, 2H), 4.15 (m, 1H), 4.44 (m, 1H), 5.65 (d, *J* = 10.2 Hz, 1H), 5.76-5.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3 (2C) 12.4, 18.3, 23.1, 24.2, 25.9 (3C), 37.0, 37.3, 40.9, 64.4, 66.7, 70.3, 127.2, 128.4, 130.3, 137.5; MS (CI) m/z 337 (M^+- H), 321, 303, 262, 205, 189, 171, 161; HRMS (CI) m/z 337.2202 (calcd for $C_{19}H_{33}O_3Si$: 337.2199).

Bromoketones 12 and 13

To a stirred solution of **9** (28 mg, 0.08 mmol) in THF (4 mL) was added N-bromosuccinimide (16 mg, 0.09 mmol), and the mixture was stirred for 1h at room temperature. The mixture was passed through a short pad of silica gel, with EtOAc-hexanes (1:5) as eluent, and the concentrated eluent was purified by column chromatography (EtOAc-hexanes, 1:5) to give 31 mg (91%) of inseparable **10** and **11** as a colorless oil. The mixture of **10** and **11** was dissolved in CH_2Cl_2 (2 mL), and the solution was added dropwise to a suspension of PDC (68 mg, 0.18 mmol) and NaOAc (15 mg, 0.18 mmol) in CH_2Cl_2 (4 mL). The resulting mixture was stirred for 2h at room temperature, then filtered through Florisil, and the filtrate was concentrated under reduced pressure. Flash chromatography (EtOAc:hexanes, 1:20 to 1:10) of the residue afforded 22 mg (73%) of a mixture of **12** and **13**. A homogeneous sample of **12** was obtained as a colorless solid by repeated chromatography: R_f 0.24 (EtOAc-hexanes, 1:5), mp 106-107 °C; $[\alpha]_D$ -29.2 (*c* 0.36, $CHCl_3$); IR (neat) 1689 cm^{-1};^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.91 (s, 9H), 1.01 (t, *J* = 7.4 Hz, 3H), 1.33-1.62 (m, 2H), 1.99 (dd, *J* = 10.3, 16.1, 1H), 2.25 (dd, *J* = 8.1, 16.1 Hz, 1H), 2.50 (t, *J* = 3.8 Hz, 1H), 2.72 (t, *J* = 7.5 Hz, 1H), 2.85 (ddd, *J* = 3.8, 8.1, 11.0

Hz, 1H), 3.64 (d, J = 10.7 Hz, 1H), 3.75 (d, J = 10.7 Hz, 1H), 4.23 (s, 1H), 4.47 (t, J = 4.4 Hz, 1H), 5.96 (d, J = 9.9 Hz, 1H), 6.84 (dd, J = 5.0, 9.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, 11.4, 18.3, 22.6, 25.8, 35.6, 43.1, 44.5, 46.5, 69.9, 70.8, 71.6, 82.9, 128.8, 141.5, 201.6; MS (CI) m/z 415 (M^+), 359, 335, 277, 259, 203, 175, 161, 105. HRMS (CI) m/z 413.1142 (calcd for $C_{19}H_{30}O_3SiBr$: 413.1148). The data for **13** was determined from the mixture: R_f 0.22 (EtOAc-hexanes, 1:5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (t, J = 7.4 Hz, 3H), 1.61 (m, 1H), 1.70 (m, 1H), 1.76 (m, 1H), 2.13-2.21 (m, 2H), 2.37 (dd, J = 12.1, 14.5 Hz, 1H), 2.68 (m, 1H), 3.59 (s, 2H), 3.93 (m, 1H), 4.38 (m, 1H), 5.96 (d, J = 9.9 Hz, 1H), 7.01 (dd, J = 5.7, 9.9 Hz, 1H); ^{13}C NMR (75 MHz,$CDCl_3$) δ -5.3 (2C), 11.7, 23.7, 25.9 (3C), 36.1, 42.1, 49.5, 51.4, 63.5, 66.9, 106,0, 127.2, 147.0, 201.6.

Dione 14

To a solution of **9** (913 mg, 2.70 mmol) in EtOAc (10 mL) was added 5% Rh on Al_2O_3 (1.40 g), and the mixture was placed under a balloon filled with H_2. After 24h, the mixture was filtered through a pad of Celite with EtOAc (10 mL) as eluant, and the filtrate was concentrated under reduced pressure. Chromatography (EtOAc-hexanes, 1:3) of the residue on silica gel produced the saturated diol (871 mg, 94%) as a colorless oil: R_f 0.22 (EtOAc-hexanes, 1:3); mp 123-124 °C; $[\alpha]_D$ -3.4 (*c* 2.3, $CHCl_3$); IR (neat) 836, 1079, 1104, 1254, 1462, 1500, 2856, 2928, 2952, 3439 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.89 (s, 9H), 0.93 (t, J = 7.1 Hz, 3H), 1.06 (br s, 1H), 1.23-1.91 (m, 15H), 3.44 (dd, J = 6.4, 9.9 Hz, 1H), 3.49 (dd, J = 4.5, 9.9 Hz, 1H), 3.74 (ddd, J = 4.5, 9.4, 11.5 Hz, 1H), 4.09 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.3 (2C), 12.3, 18.4, 24.3, 24.7, 26.0 (3C), 26.5, 32.9, 33.3, 39.9, 41.3, 41.9, 43.1, 66.7, 69.0, 73.2.; MS (CI) m/z 343 (M^++H), 325, 283, 267, 209, 193, 175; HRMS (CI) m/z 343.2674 (calcd for $C_{19}H_{39}O_3Si$: 343.2669).

To a solution of pyridinium dichromate (1.20 g, 3.20 mmol) in CH_2Cl_2 (10 mL) at room temperature was added a solution of the diol prepared above (730 mg, 2.13 mmol) in CH_2Cl_2 (3 mL), and the mixture was stirred for 4h at room temperature. The mixture was diluted with Et_2O

(30 mL) and the solution was filtered through a Celite pad. The filtrate was concentrated, and the residue was chromatographed on silica gel (EtOAc-hexanes, 1:3) yielded 635 mg (88%) of **14** as a colorless oil: R_f 0.16 (EtOAc-hexanes, 1:5); $[\alpha]_D$ +88.5 (*c* 1.42, $CHCl_3$); IR (neat) 837, 1098, 1250,1713, 2852, 2925, 2959 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.86 (s, 9H), 0.87 (overlapping m, 1H), 0.88 (t, *J* = 7.4 Hz, 3H), 1.21-1.35 (m, 2H), 1.53-1.76 (m, 4H), 2.00 (m, 1H), 2.35-2.49 (m, 1H), 2.59 (dt, *J* = 4.5, 13.6 Hz, 1H), 2.65-2.74 (m, 2H), 2.83 (m, 1H), 3.09 (m, 1H), 3.34 (dd, *J* = 6.4, 9.9 Hz, 1H), 3.43 (dd, *J* = 5.4, 9.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.5 (2C), 12.3, 18.2, 25.8 (3C), 26.2, 29.6, 30.6, 37.0 (2C), 40.4, 40.6, 49.3, 51.8, 67.7, 208.9, 210.9 ; MS (CI) m/z 339 (M^++H), 323, 281, 263, 207, 189, 147, 75; HRMS (CI) m/z 339.2352 (calcd for $C_{19}H_{35}O_3Si$: 339.2356).

Ketal 15

A solution of **14** (570 mg, 1.68 mmol) and PPTS (43 mg, 0.17 mmol) in MeOH (10 mL) was heated at 55 °C for 3h, after which the mixture was allowed to cool to room temperature. The solution was diluted with saturated aqueous $NaHCO_3$ (3 mL) and was extracted with Et_2O (20 mL). The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica gel (EtOAc-hexanes, 1:2) gave 404 mg (89%) of **15** as a colorless oil: R_f 0.16 (EtOAc-hexanes, 1:2); $[\alpha]_D$ +15.7 (*c* 0.21, $CHCl_3$); IR (neat) 1097, 1123, 1461, 1712, 2831, 2867, 2923, 2958, 3419 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.66 (ddd, *J* = 12.7, 12.7, 12.7 Hz, 1H), 0.84 (t, *J* = 7.5 Hz, 3H), 1.18 (m, 1H), 1.31 (ddd, *J* = 12.3, 12.3, 12.3 Hz, 1H), 1.49-1.67 (m, 4H), 1.76 (m, 1H), 1.79 (dt, *J* = 5.0, 14.3 Hz, 1H), 1.89 (br s, 1H, *OH*), 2.08 (ddd, *J* = 2.1, 5.0, 14.3 Hz, 1H), 2.13 (ddt, *J* = 2.5, 9, 14.3 Hz, 1H), 2.22 (ddt, *J* = 2.6, 4.6, 13.1 Hz, 1H), 2.41 (dt, 6.8, 14.3 Hz, 1H), 2.91 (m, 1H), 3.19 (s, 3H), 3.29 (s, 3H), 3.44 (dd, *J* = 6.0, 10.6 Hz, 1H), 3.46 (dd, *J* = 6.4, 10.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.4, 26.3, 28.1, 28.2, 30.1, 38.6, 40.5, 41.7, 45.7, 47.2, 47.9, 48.2, 68.1, 100.5, 211.6; MS (CI) m/z 270 (M^+), 253, 239, 221, 207, 189, 125, 101, 84; HRMS (CI) m/z 270.1830 (calcd for $C_{15}H_{26}O_4$: 270.1831).

Oxime 16

To a solution of TIPSCl (332 mg, 1.72 mmol) and imidazole (117 mg, 1.72 mmol) in DMF (5 mL) at room temperature was added a solution of **15** (310 mg, 1.15 mmol) in DMF (1 mL, 1.15 mmol), and the mixture was stirred for 2h at room temperature. The mixture was diluted with pentane (20 mL), and the solution was washed with H_2O (3x 10 mL) and saturated NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:5) furnished 456 mg (93%) of the TIPS ether as a colorless oil: R_f 0.23 (EtOAc-hexanes, 1:10); $[\alpha]_D$ +6.6 (*c* 1.16, $CHCl_3$); IR (neat) 1055, 1097, 1116, 1719, 2361, 2864, 2942, 2956 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.64 (ddd, *J* = 13.1,13.1, 13.1 Hz, 1H), 0.85 (t, *J* = 7.5 Hz, 3H), 1.03-1.07 (m, 21H), 1.19 (m, 1H), 1.28 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 1.49-1.69 (m, 4H), 1.73.1.87 (m, 2H), 2.08 (ddd, *J* = 2.1, 4.8, 11.3 Hz, 1H), 2.21 (ddt, *J* = 2.8, 5.3, 13.1 Hz, 1H), 2.40 (dt, *J* = 6.1, 13.5 Hz, 1H), 2.92 (m, 1H), 3.19 (s, 3H), 3.30 (s, 3H), 3.45 (dd, *J* = 6.8, 9.5 Hz, 1H), 3.53 (dd, *J* = 5.8, 9.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 12.4, 17.9, 26.3, 28.0, 28.4, 30.3, 38.6, 41.0, 41.8, 45.9, 47.7, 47.8, 48.4, 68.5, 100.6, 211.5; MS (CI) m/z 426 (M^+), 409, 383, 351, 221, 184, 171, 147, 101; HRMS (CI) m/z 426.3162 (calcd for $C_{24}H_{46}O_4Si$: 426.3165).

A suspension of the ketone prepared above (312 mg, 0.73 mmol), hydroxylamine hydrochloride (508 mg, 2.31 mmol), and NaOAc (600 mg, 7.31 mmol) in MeOH (3 mL) was heated gently at reflux for 3h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. Chromatography of the residue on silica gel (MeOH-CH_2Cl_2, 1:60) gave 261 mg (81%) of **16** as a colorless oil: R_f 0.21 (EtOAc-hexanes, 1:5); $[\alpha]_D$ +20.1 (*c* 1.05, $CHCl_3$); IR (neat) 881, 1056, 1099, 1120, 1462, 2864, 2941, 2956, 3404 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (brs, 1H), 3.46-3.57 (m, 2H), 3.33 (m, 1H), 3.23 (s, 3H), 3.18 (s, 3H), 2.77 (t, *J* = 3.4 Hz, 1H), 2.02 (m, 1H), 1.93 (m, 1H), 1.3-1.7 (m, 9H), 1.07 (m, 21H), 0.88 (m, 1H), 0.87 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 12.5, 17.9, 20.1, 26.6, 26.7, 26.8, 30.2, 41.4, 41.7, 43.1, 45.5, 47.3, 47.5, 68.7, 101.2, 158.2.

Lactam 17

To a mixture of *p*-toluenesulfonyl chloride (203 mg, 1.07 mmol), triethylamine (0.15 mL, 1.07 mmol), and a catalytic amount of DMAP in dichloromethane (3 mL) was added a solution of **16** (186 mg, 0.43 mmol), and the mixture was stirred for 3h at room temperature. The mixture was diluted with dichloromethane (10 mL), and the solution was washed with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica gel (EtOAc-hexanes, 1:3, to MeOH-CH_2Cl_2, 1:15) afforded 138 mg (74%) of **17** as a colorless oil: R_f 0.12 (EtOAc-hexanes, 1:3); $[\alpha]_D$ -8.4 (*c* 2.38, $CHCl_3$); IR (neat) 882, 1055, 1106, 1461, 1663, 2864, 2941, 2956 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (ddd, *J* = 12.8, 12.8, 12.8 Hz, 1H), 0.92 (t, *J* = 7.4 Hz, 3H), 0.96-1.13 (m, 22H), 1.31 (dq, *J* = 7.4, 7.4 Hz, 1H), 1.49-1.83 (m, 6H) 1H, 1.91 (ddt, *J* = 1.7, 7.5, 13.6 Hz, 1H), 2.19-2.28 (m, 1H), 2.47 (dt, *J* = 1.2, 13.1 Hz, 1H), 3.15 (s, 3H), 3.18 (s, 3H), 3.50 (br d, *J* = 6.0, 2H), 3.79 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4, 11.8, 17.9, 23.3, 25.3, 25.8, 29.65, 29.70, 40.6, 42.8, 46.8, 47.2, 47.3, 49.6, 68.2, 102.0, 176.5; MS (CI) m/z 442 (M^++H), 410, 398, 378, 366; HRMS (CI) m/z 442.3353(calcd for $C_{24}H_{48}NO_4Si$: 442.3353).

Tosylate 19

To a solution of **17** (125 mg, 0.28 mmol) in THF (3 mL) at room temperature under argon was added a 1M solution of TBAF (0.4 mL, 0.4 mmol), and the mixture was stirred for 1h at room temperature. The mixture was diluted with dichloromethane (10 mL), and the solution was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica gel (MeOH-CH_2Cl_2, 1:15) gave 79 mg (99%) of an alcohol as a colorless oil: R_f 0.1 (MeOH-CH_2Cl_2, 1:15); $[\alpha]_D$ -31.7 (*c* 1.1, $CHCl_3$); IR (neat) 1054, 1104, 1452, 1655, 2872, 2929, 2956, 3385 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (ddd, *J* = 12.3, 12.3, 12.3 Hz, 1H), 0.94 (t, *J* = 7.3 Hz, 3H), 1.09 (ddd, *J* = 12.4, 12.4, 12.4 Hz, 1H), 1.33 (dq, *J* = 7.2, 7.2 Hz, 2H), 1.51-1.87 (m, 7H), 1.93 (ddt, *J* = 2.3, 7.6, 15.2 Hz, 1H), 2.26 (m, 1H), 2.48 (dt, *J* = 1.4, 13.7 Hz, 1H), 3.16 (s, 3H), 3.18 (s, 3H), 3.49 (m, 2H), 3.79

(m, 1H), 5.25 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4, 23.2, 25.3, 25.7, 29.4, 29.7, 40.0, 42.8, 46.6, 47.3, 47.4, 49.6, 67.7, 101.9, 176.8; MS (CI) m/z (M^+) 286, 268, 254, 222, 204, 146, 114, 101; HRMS (CI) m/z 286.2013 (calcd for $C_{15}H_{28}NO_4$: 286.2019).

To a mixture of *p*-toluenesulfonyl chloride (21 mg, 0.11 mmol), triethylamine (31 uL, 0.23 mmol), and a catalytic amount of DMAP in dichloromethane (3 mL) was added the alcohol obtained above (21 mg, 0.08 mmol), and the mixture was stirred for 3h at room temperature. The mixture was diluted with dichloromethane (10 mL), and the solution was washed with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica gel (MeOH-CH_2Cl_2, 1:15) produced 33 mg (100%) of **19** as a colorless oil: R_f 0.29 (MeOH-CH_2Cl_2, 1:15); $[\alpha]_D$ - 27.2 (*c* 1.2, $CHCl_3$); IR (neat) 1052, 1104, 1176, 1188, 1357, 1456, 1660, 2956 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74 (ddd, *J* = 12.8, 12.8, 12.8 Hz, 1H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.96 (ddd, *J* = 12.7, 12.7, 12.7 Hz, 1H), 1.31 (dq, *J* = 7.3, 7.3 Hz, 2H), 1.41-1.58 (m, 3H), 1.68 (dt, *J* = 3.5, 13.6 Hz, 1H), 1.71-1.95 (m, 3H), 2.15-2.27 (m, 1H), 2.37-2.49 (overlapping m, 1H), 2.47 (s, 3H), 3.11 (s, 3H), 3.15 (s, 3H), 3.72-3.80 (overlapping m, 2H), 3.82 (dd, *J* = 6.6, 9.6 Hz, 1H), 4.97 (br s, exchangeable, 1H); 7.36 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4, 21.6, 22.9, 25.3, 25.6, 29.0, 29.7, 37.0, 42.5, 46.3, 47.36, 47.44, 49.1, 74.2, 101.7, 127.9, 129.9, 132.7, 144.9, 176.6; MS (CI) m/z (M^+-OMe) 408, 376, 285, 204, 173; HRMS (CI) m/z 439.2029 (calcd for $C_{22}H_{33}NO_6S$: 439.2028).

Lactam 20

To a solution of NaH (3 mg, 0.11 mmol) in THF (3 mL) at 0°C under argon was added a solution of **19** (16 mg, 0.04 mmol) in THF (1 mL), and the mixture was stirred for 30 min at room temperature and then refluxed for 1 h. The mixture was diluted with saturated aqueous NH_4Cl (0.5 mL), and the solution was extracted with dichloromethane. The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica gel (MeOH-CH_2Cl_2, 1:15) yielded 6.6 mg

(71%) of **20** as a colorless oil: R_f 0.1 (MeOH-CH_2Cl_2, 1:15); $[\alpha]_D$ -21.2 (*c* 1.1, $CHCl_3$); IR (neat) 1051, 1064, 1102, 1404, 1454, 1634, 1658, 2358, 2930 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.12 (ddt, *J* = 2.4, 9.2, 13.6 Hz, 1H), 1.30-1.81 (m, 7H), 1.92-2.13 (m, 3H), 2.27 (ddd, *J* = 1.0, 7.4, 13.2 Hz, 1H), 2.72 (dt, J = 0.9, 13.3 Hz, 1H), 3.09 (m, 1H), 3.17 (s, 3H), 3.19 (s, 3H), 3.60 (br d, *J* = 2.8 Hz, 1H), 3.75(ddd, *J* = 2.6, 4.3, 11.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2, 25.8, 27.2, 27,4 28.3, 30.0, 31.4, 40.5, 42.8, 47.7 (2C), 50.1, 50.7, 103.1, 179.2; MS (CI) m/z (M^+) 267, 252, 236, 220, 204, 138, 101; HRMS (CI) m/z 267.1835 (calcd for $C_{15}H_{25}NO_3$: 267.1834).

Oxoibogamine 21

To a solution of *p*-toluenesulfonic acid monohydrate (11 mg, 0.06 mmol) in acetone (3 mL) at 0°C under argon was added a solution of **20** (15 mg, 0.06 mmol) in acetone (1 mL), and the mixture was stirred for 12h at room temperature. The mixture was diluted with saturated aqueous $NaHCO_3$ (0.5 mL) and was extracted with $CHCl_3$. The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give 11 mg of the keto lactam (86%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.3 Hz, 3H, CH_3), 1.33-1.60 (m, 4H), 1.69-1.87 (m, 2H), 1.89-2.06 (m, 2H), 2.54 (ddd, *J* = 4.9, 9.7, 13.8 Hz, 1H), 2.62-2.74 (m, 3H), 3.02 (ddd, *J* = 7.4, 10.1, 13.6 Hz, 1H) 3.17 (d, J = 11.8 Hz, 1H), 3.84-3.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0, 26.0, 27.1, 28.6, 30.2, 31.5, 37.1, 38.4, 49.6, 49.9, 52.1, 175.8, 210.5.

To a solution of the keto lactam (7 mg, 0.03 mmol) in AcOH (1 mL) at room temperature was added a solution of phenylhydrazine (5 mg, 0.05 mmol) in AcOH (1 mL), and the mixture was stirred for 1h at 50°C. The mixture was allowed to cool to room temperature during 1h, after which boron trifluoride etherate (9 mg, 0.06 mmol) was added. The resulting yellow solution was stirred for 12h at 80 °C. After the mixture had cooled to room temperature, it was diluted with CH_2Cl_2, and the solution was washed with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on

silica gel (MeOH-CH_2Cl_2, 1:30) gave 7 mg (77%) of **21** as a pale yellow solid: R_f 0.23 (MeOH-CH_2Cl_2, 1:30); mp 230-232 °C; $[\alpha]_D$ +27.9 (*c* 0.7, $CHCl_3$); IR (neat) 1631, 3429 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.4 Hz, 3H), 1.48-2.19 (m, 8H), 3.03 (m, 1H), 3.18 (d, *J* = 11.8 Hz, 1H), 3.74 (d, J = 15.7 Hz, 1H), 3.81 (m, 1H), 3.97 (dd , *J* = 1.7, 15.7 Hz, 1H), 4.15 (s, 1H) 7.06-7.18 (m, 2H), 7.25 (m, 1H), 7.50 (m, 1H), 7.89 (br s, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1, 27.5, 28.6, 30.7, 32.1, 32.8, 35.9, 38.9, 49.3, 51.5, 102.6, 110.3, 118.2, 119.7, 121.7, 127.8, 135.0, 138.8, 175.8 ; MS (CI) m/z (M^++H) 295, 279, 135, 122, 91, 73; HRMS (CI) m/z 294.1731 (calcd for $C_{19}H_{22}N_2O$: 294.1732).

(–)-Ibogamine (1)

To a solution of **21** (4.2 mg, 0.014 mmol) in dry THF (3 mL) was added $NaBH_4$ (28 mg, 0.74 mmol) in one portion. The mixture was cooled to 0 °C, and $BF_3.OEt_2$ (160 mg, 1.13 mmol) was syringed into the mixture dropwise at 0 °C. The resulting yellow suspension was stirred at room temperature for 3h under argon. The solvent was evaporated, and MeOH (2 mL), H_2O (0.4 mL), and 10% HCl (0.2 mL) were added. This acidic solution was stirred at room temperature for 4h, after which the MeOH was evaporated and the residue was taken up into CH_2Cl_2 (10 ml). The solution was neutralized (pH 8) with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2. The organic extract was dried over $MgSO_4$ and was concentrated to give a yellow solid. Column chromatography of this material (MeOH: CH_2Cl_2 = 1:30) afforded ibogamine (**1**, 3.1 mg, 78%) as a pale yellow crystalline solid; R_f 0.23 (MeOH-CH_2Cl_2, 1:15); mp 156-157 °C; $[\alpha]_D$ -45.8 (*c* 0.2, EtOH; IR (neat) 3400 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 0.91 (t, *J* = 7.1 Hz, 3H), 1.24 (m, 1H), 1.43-1.62 (m, 3H), 1.66 (ddd, *J* = 3.4, 6.4, 13.2 Hz, 3H), 1.77-1.90 (m, 2H), 2.06 (m, 1H), 2.72 (m, 1H), 2.91 (s, 1H), 2.96 (ddd, *J* = 1.6, 3.8, 11.7 Hz, 1H), 3.02-3.11 (m, 2H), 3.17 (m, 1H), 3.33 (ddd, *J* = 4.4, 12.3, 16.6 Hz, 1H), 3.42 (m, 1H), 7.06-7.31 (m, 3H), 7.48 (d, 7.1 Hz, 1H), 7.67 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 20.5, 26.3, 27.7, 31.9, 34.0, 41.1, 41.9, 49.9, 54.3, 57.7, 109.1, 110.1, 117.9, 119.2, 121.1, 129.6, 134.7,

141.5; MS (CI) m/z (M^++H) 281, 195, 149, 136, 97, 69 HRMS (CI) m/z 280.1938 (calcd for $C_{19}H_{24}N_2$: 280.1940).

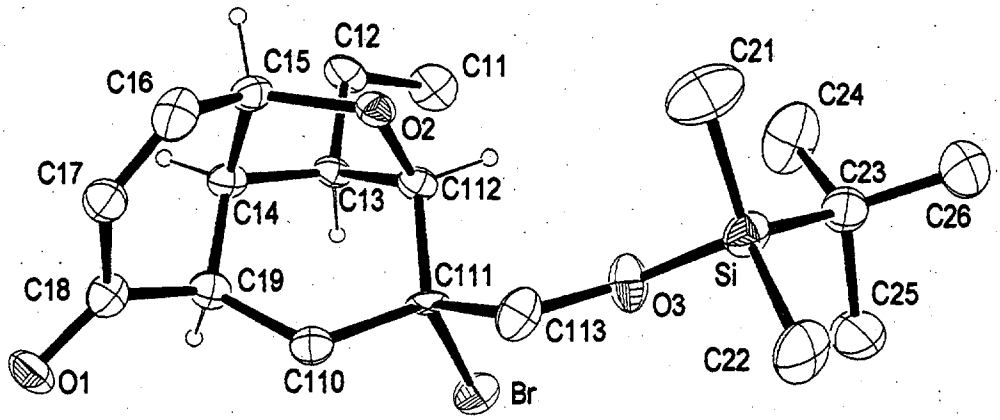
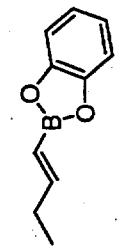
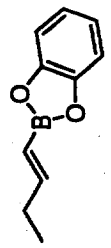


Table 1. Crystal data and structure refinement for choi.

Identification code	choi	
Empirical formula	C19 H31 Br O3 Si	
Formula weight	415.44	
Temperature	298(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 12.019(3) Å	α= 90°.
	b = 6.524(5) Å	β= 105.64(2)°.
	c = 14.017(5) Å	γ = 90°.
Volume	1058.4(9) $Å^3$	
Z	2	
Density (calculated)	1.304 Mg/m^3	
Absorption coefficient	3.290 mm^{-1}	
F(000)	436	
Crystal size	0.50 x 0.50 x 0.50 mm^3	
Theta range for data collection	3.27 to 57.74°.	
Index ranges	-13<=h<=13, -7<=k<=6, -15<=l<=15	
Reflections collected	3193	
Independent reflections	2755 [R(int) = 0.0654]	
Completeness to theta = 57.74°	97.3 %	
Max. and min. transmission	0.2900 and 0.2900	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2755 / 1 / 219	
Goodness-of-fit on F^2	2.841	
Final R indices [I>2sigma(I)]	R1 = 0.0428, wR2 = 0.0970	
R indices (all data)	R1 = 0.0444, wR2 = 0.0995	
Absolute structure parameter	0.05(5)	
Extinction coefficient	0.007(3)	
Largest diff. peak and hole	1.263 and -1.354 e.$Å^{-3}$	

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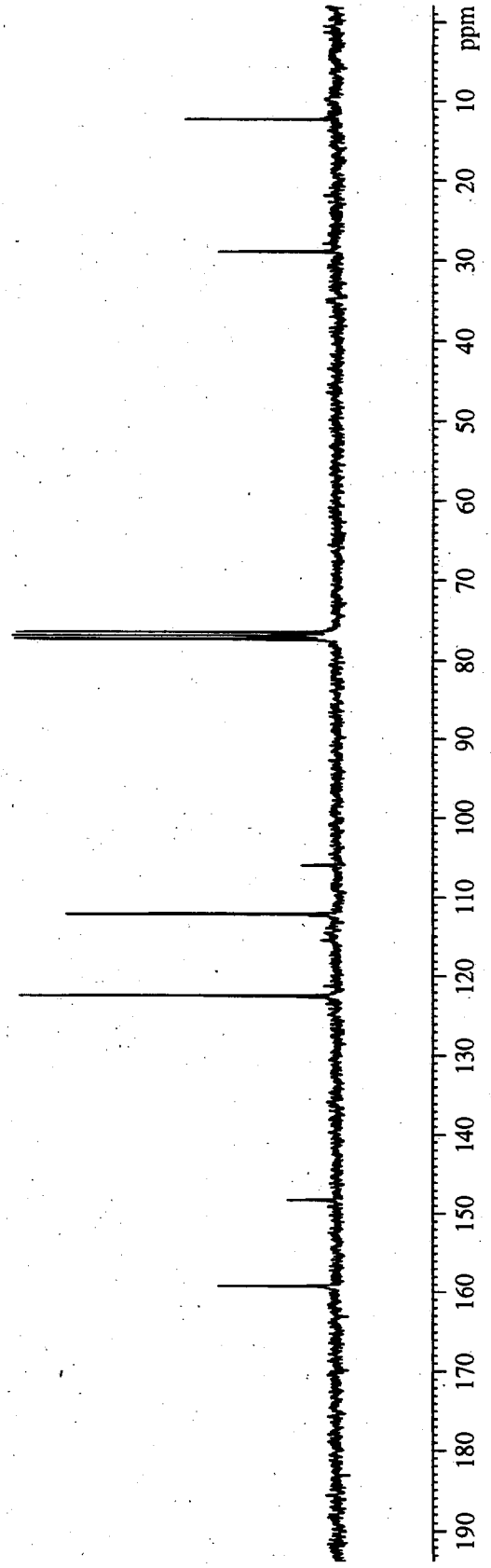
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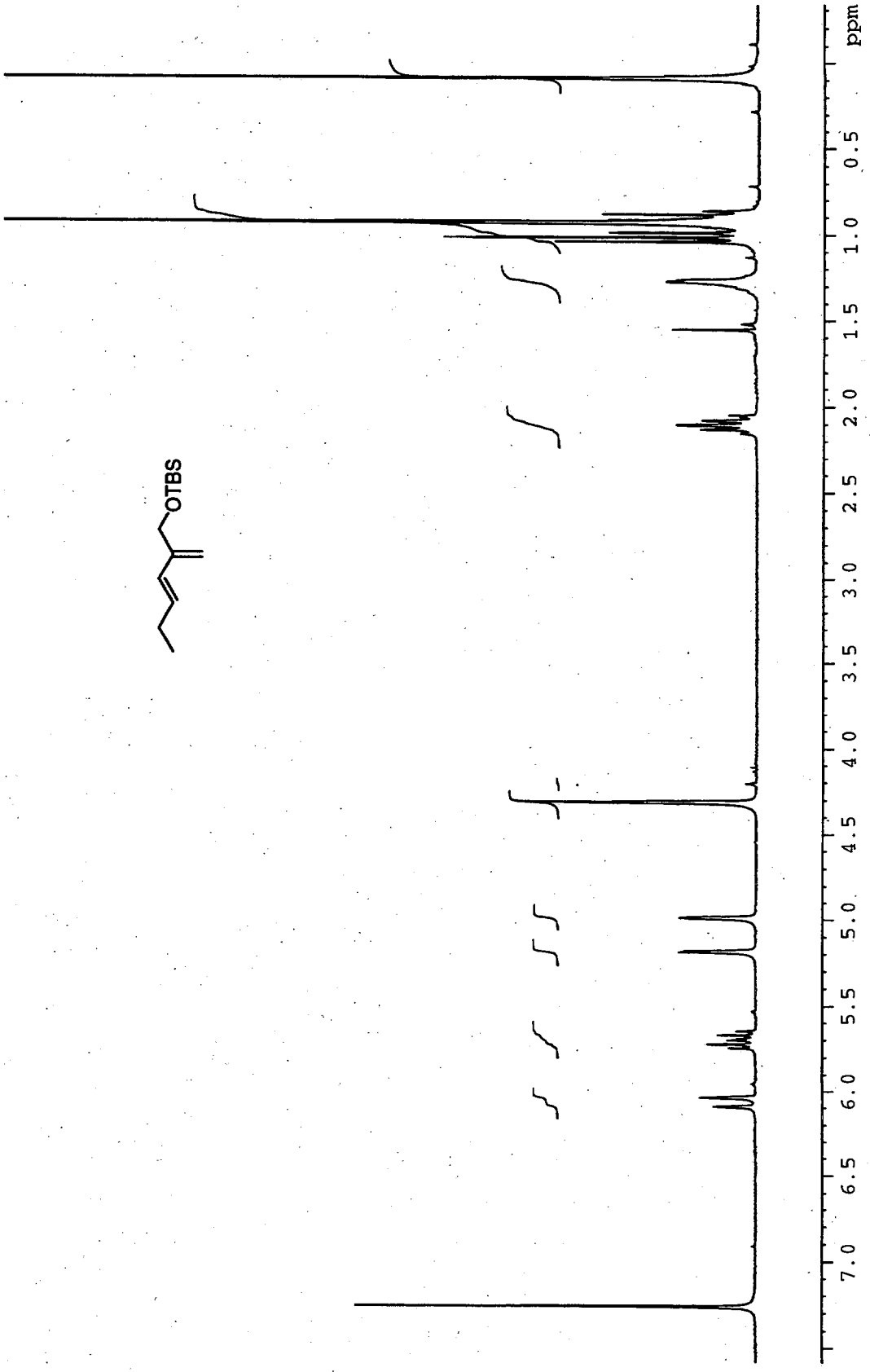

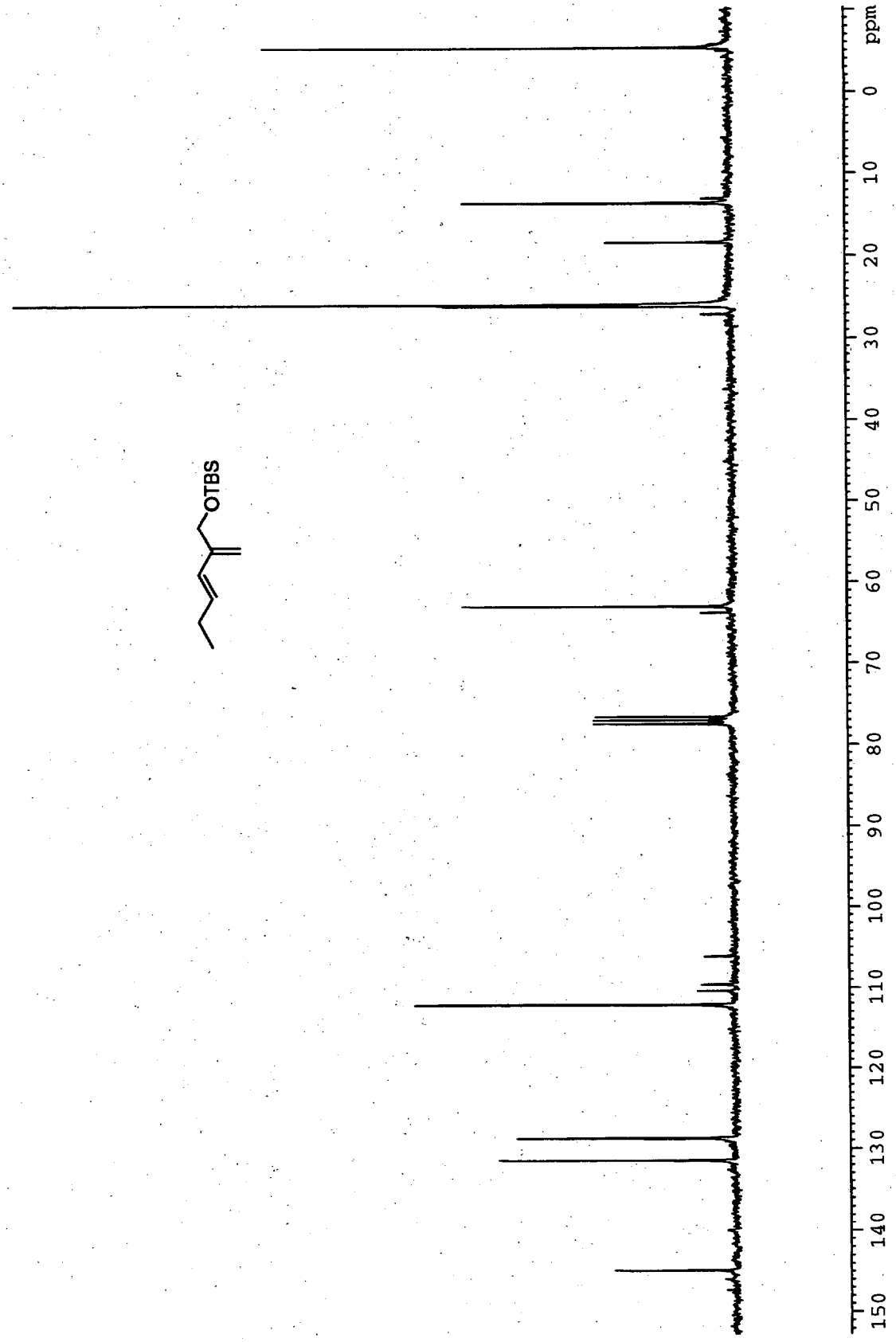
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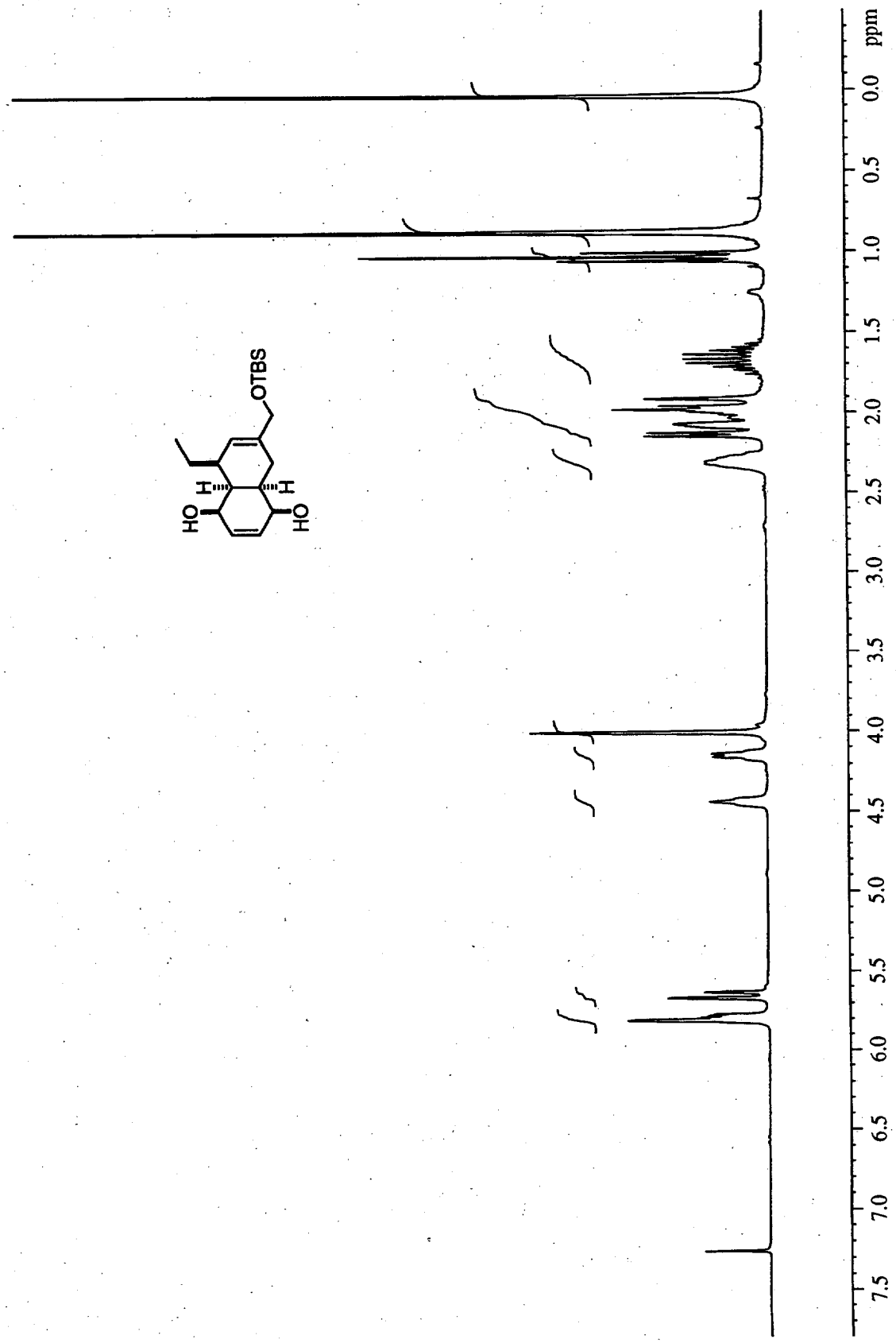

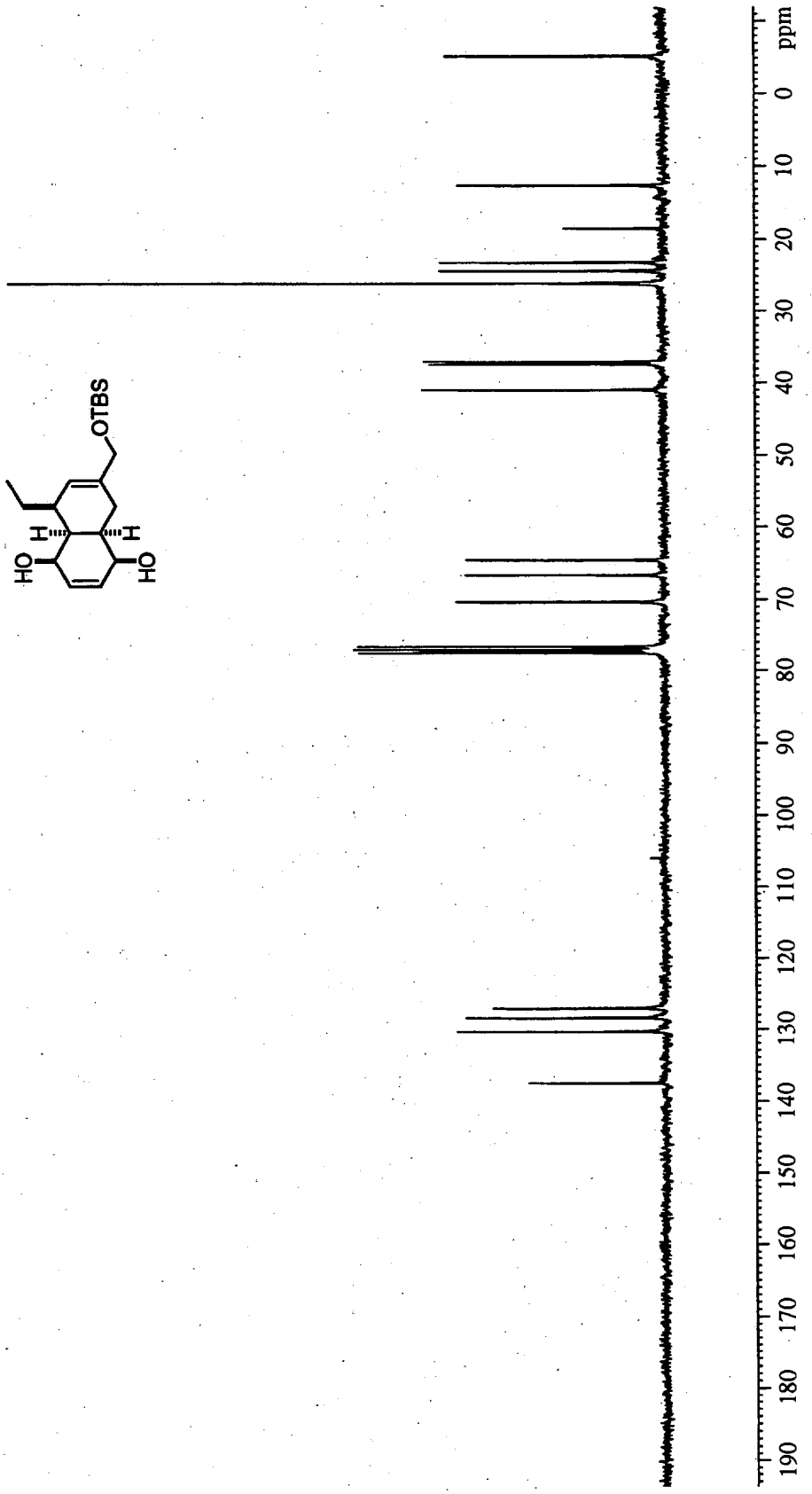
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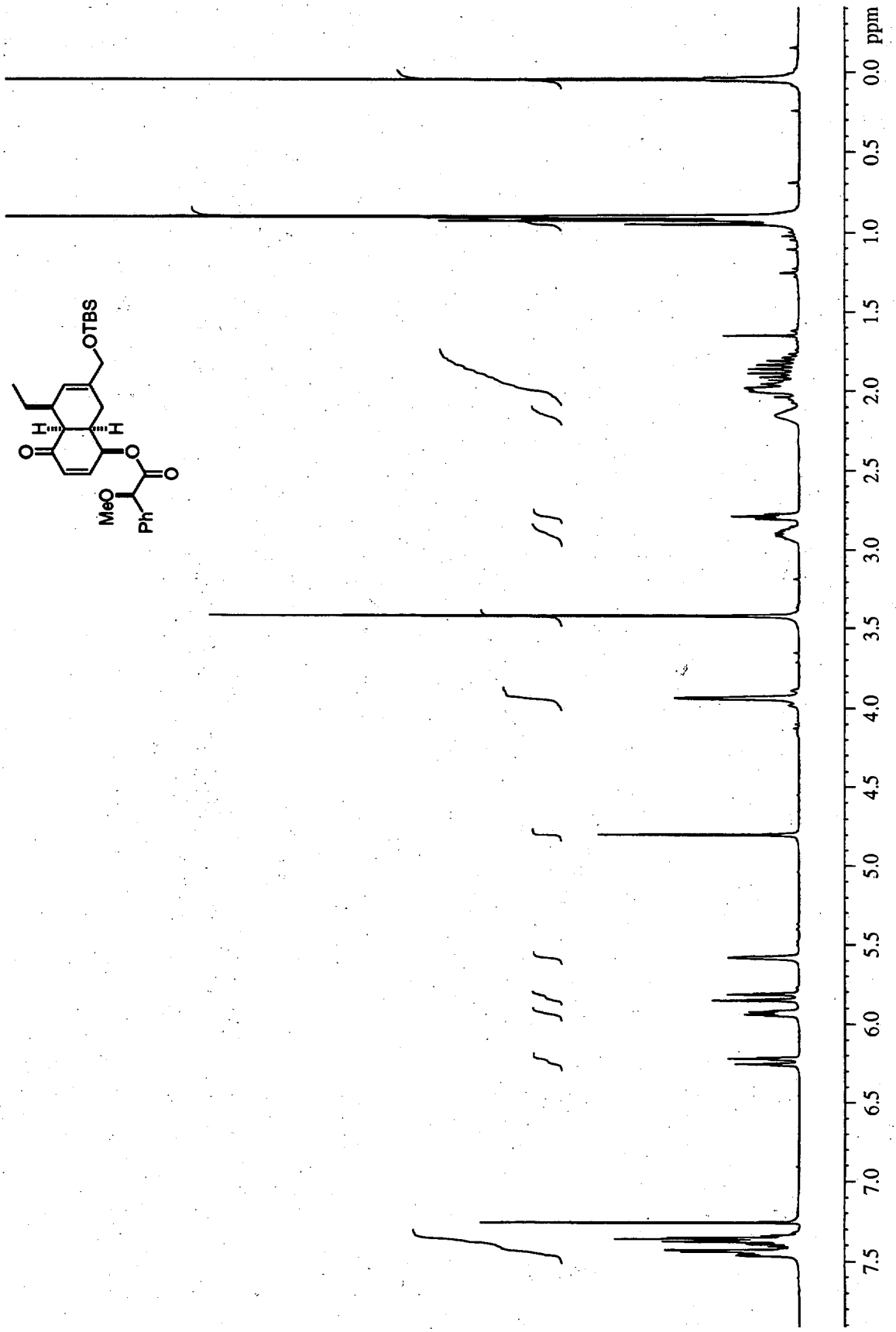
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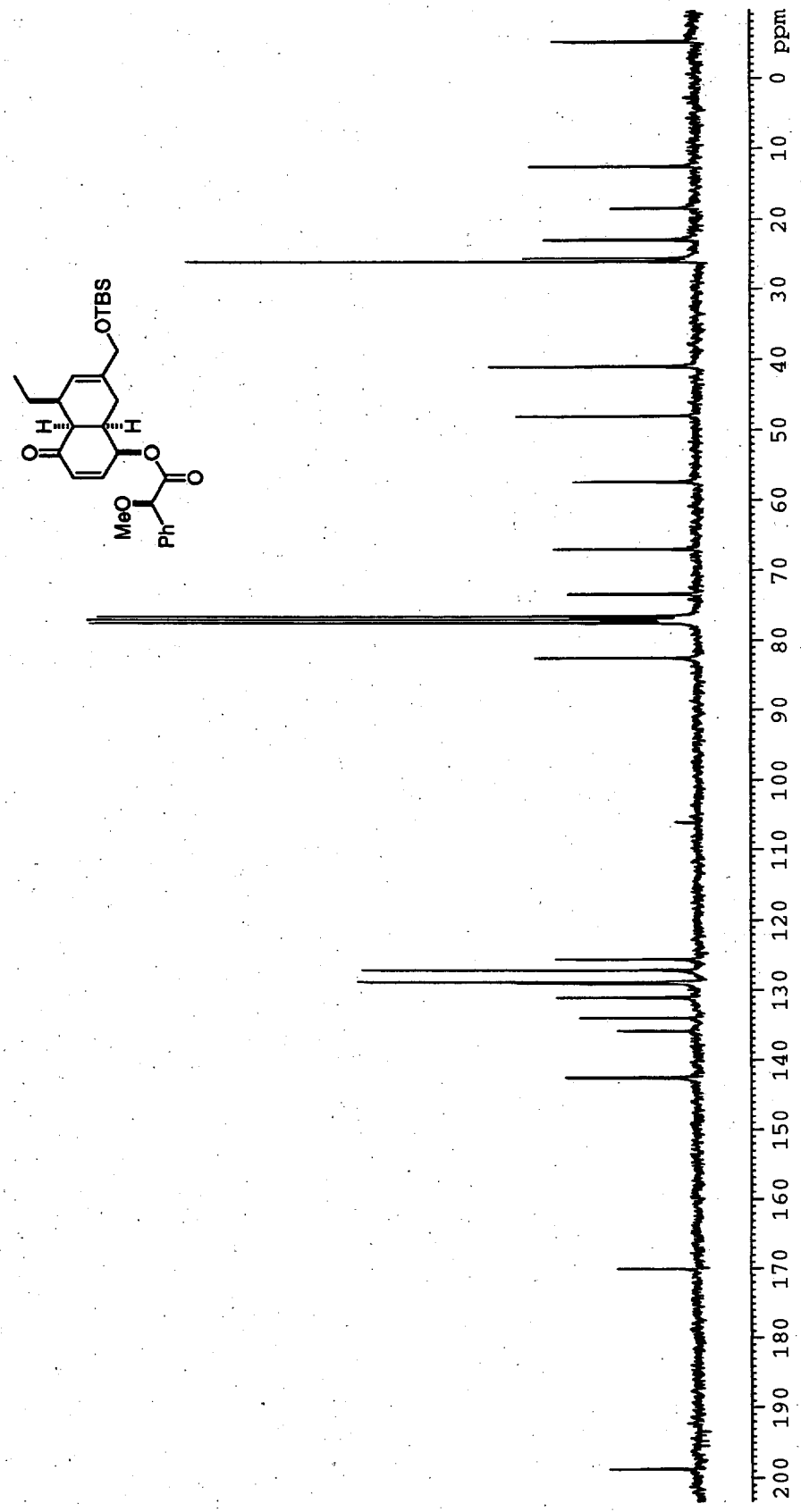
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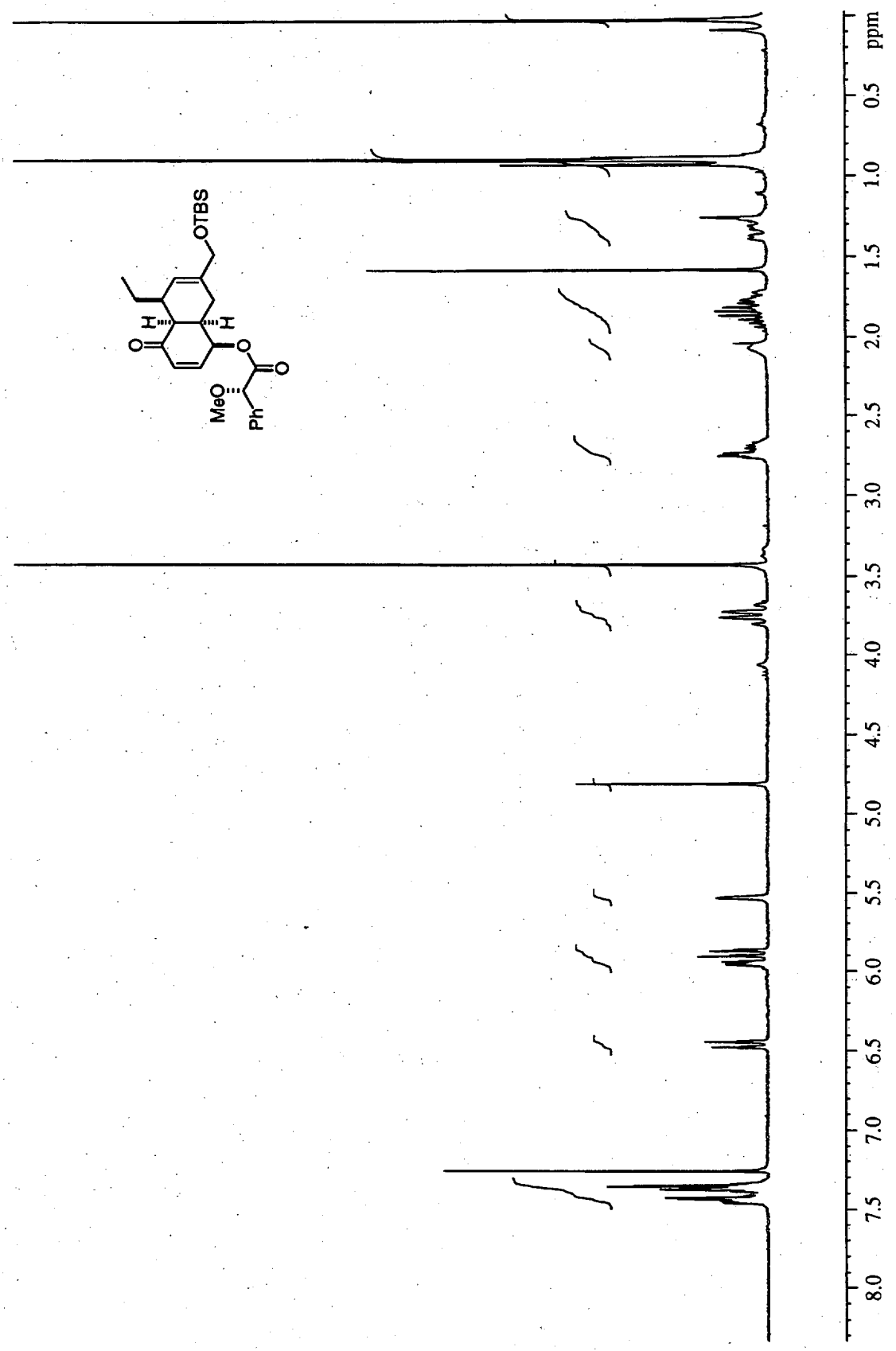

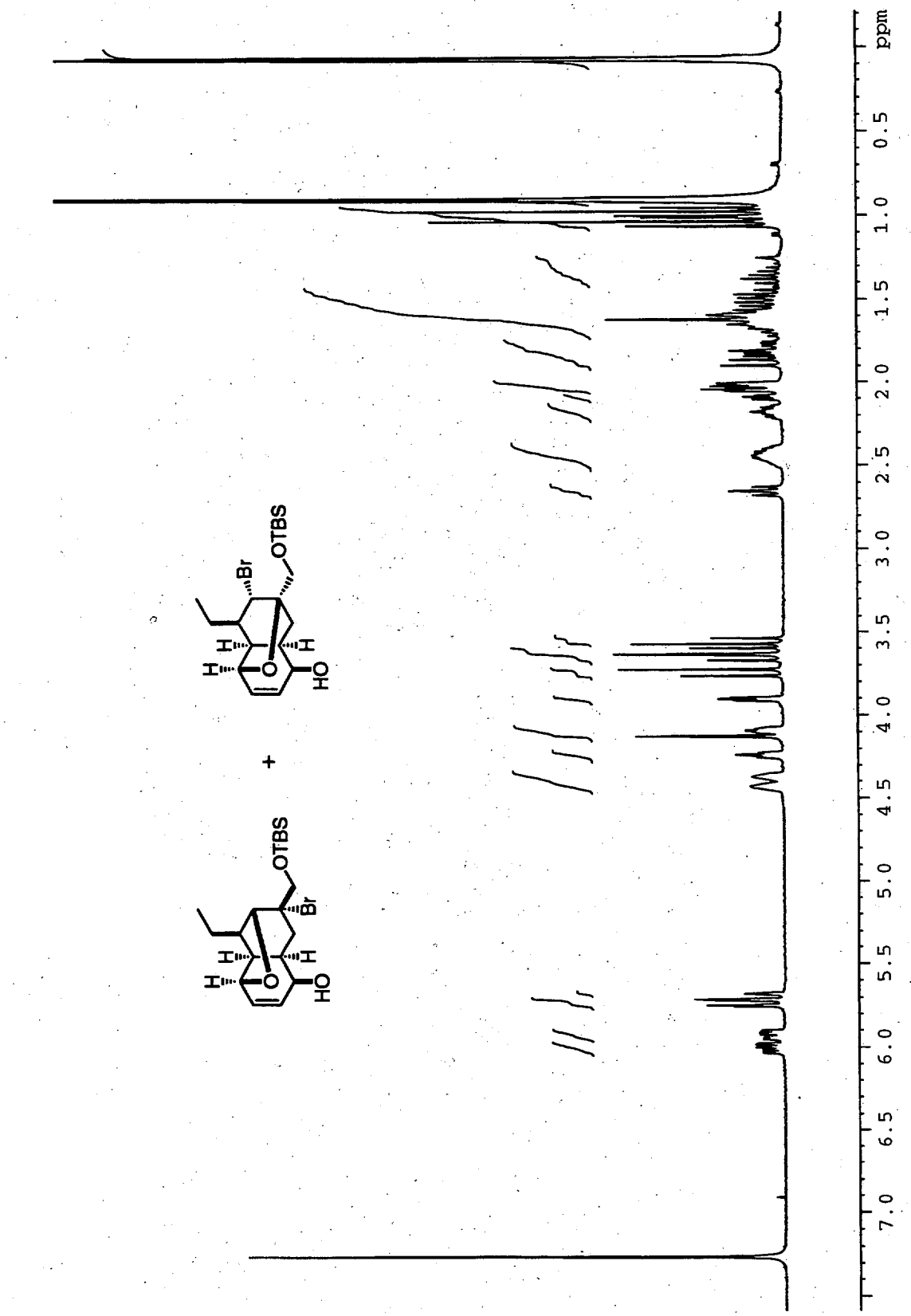

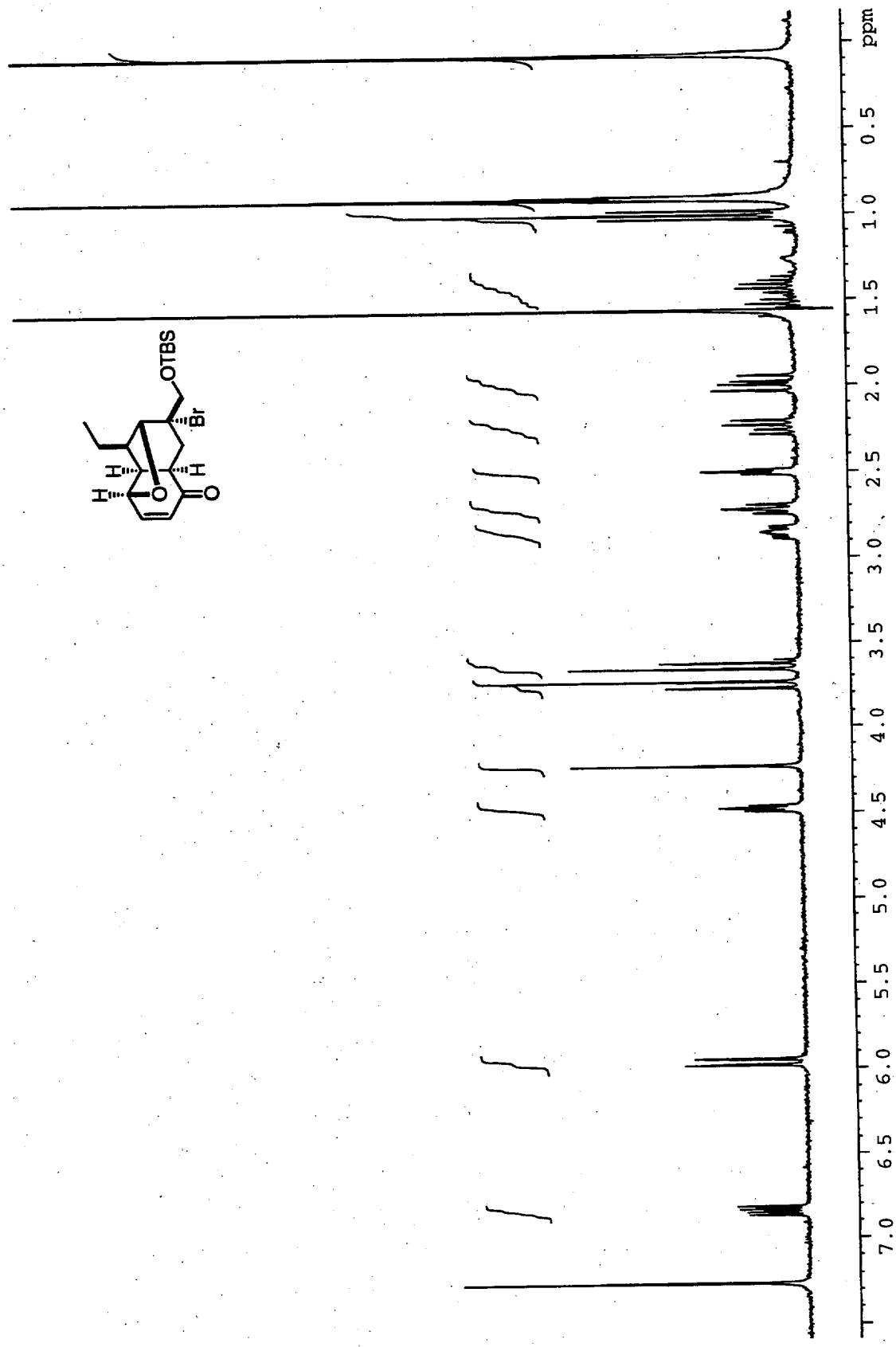

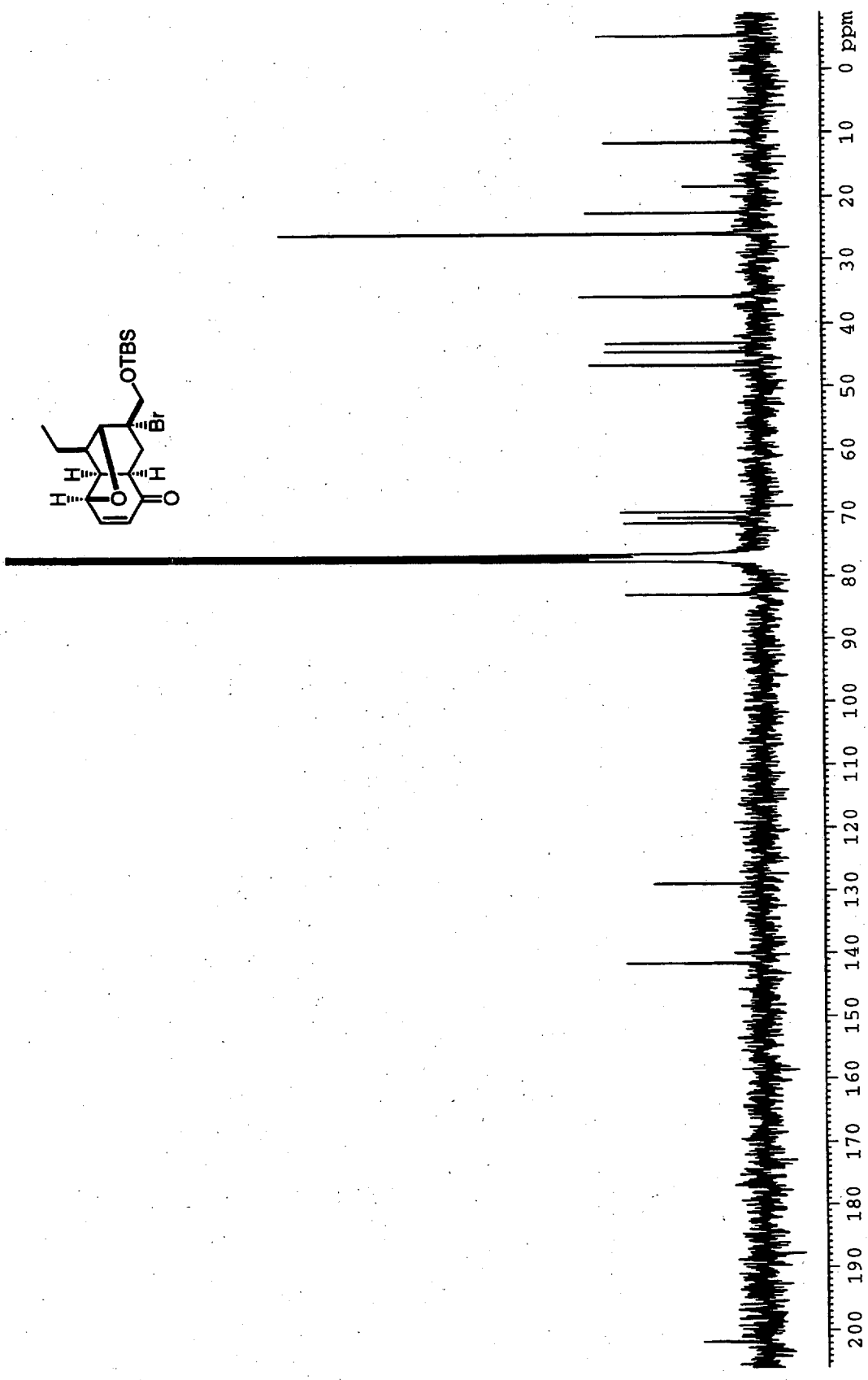

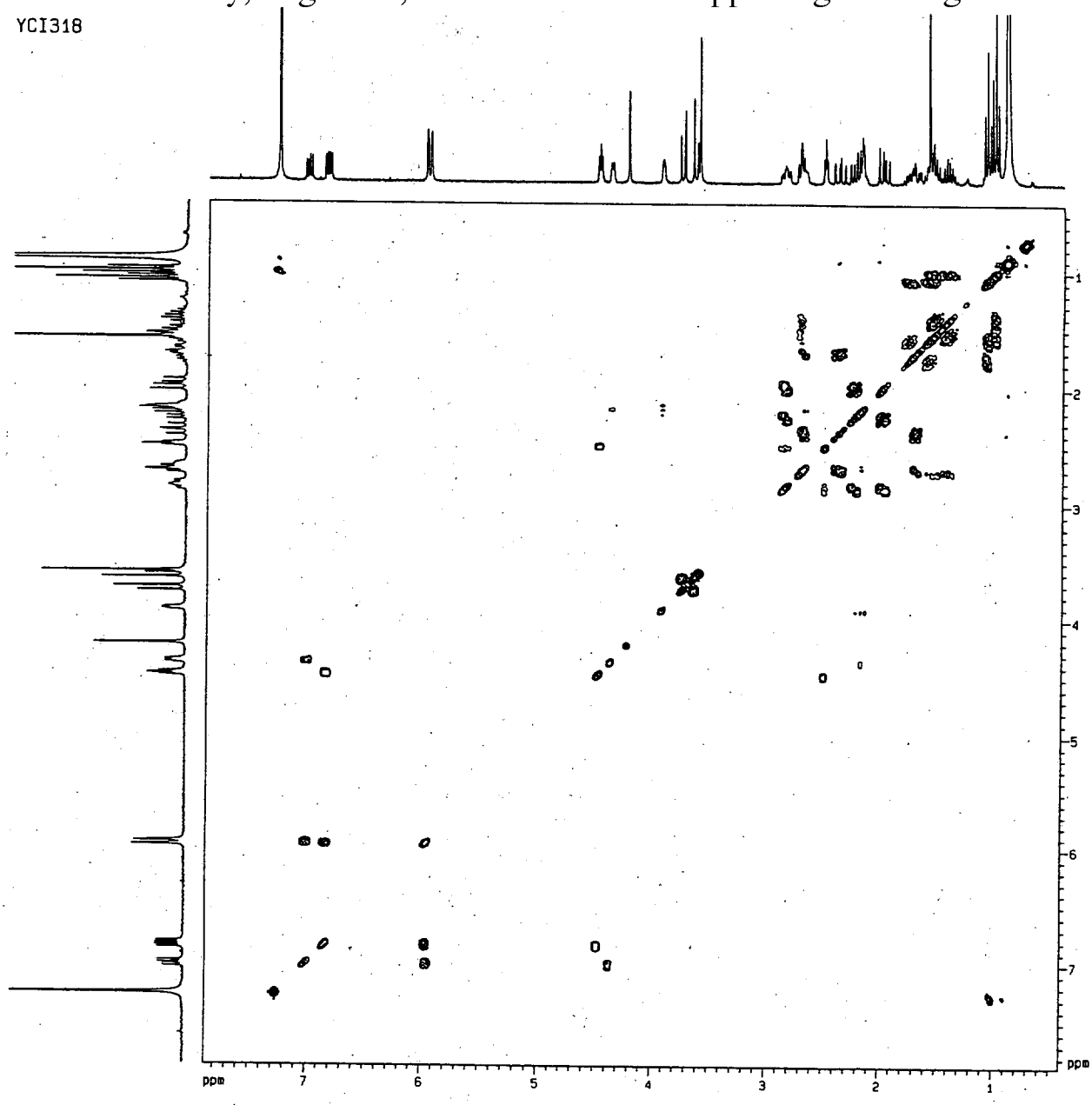

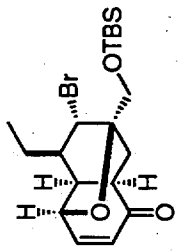

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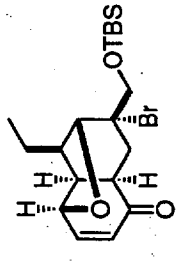

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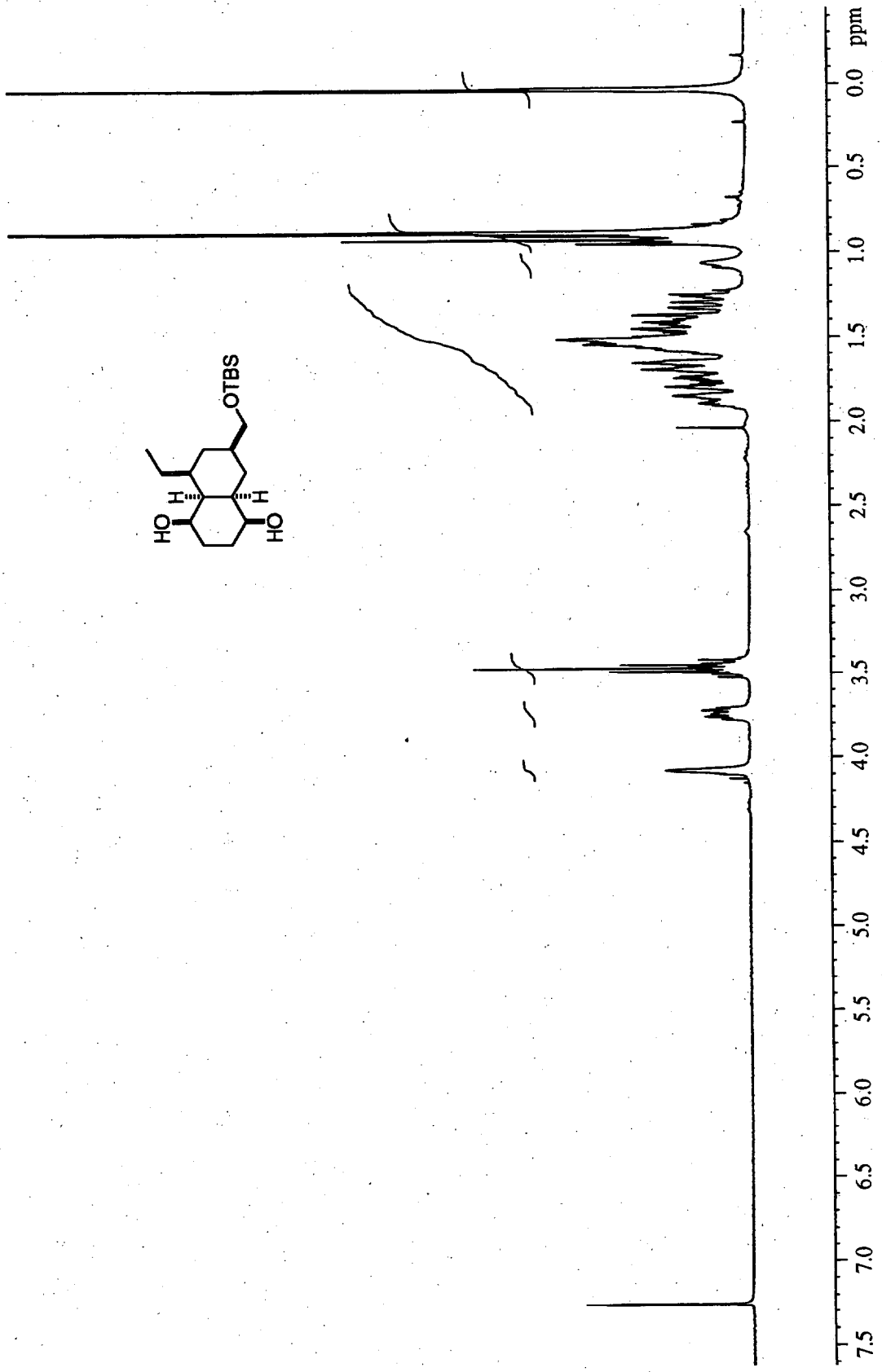
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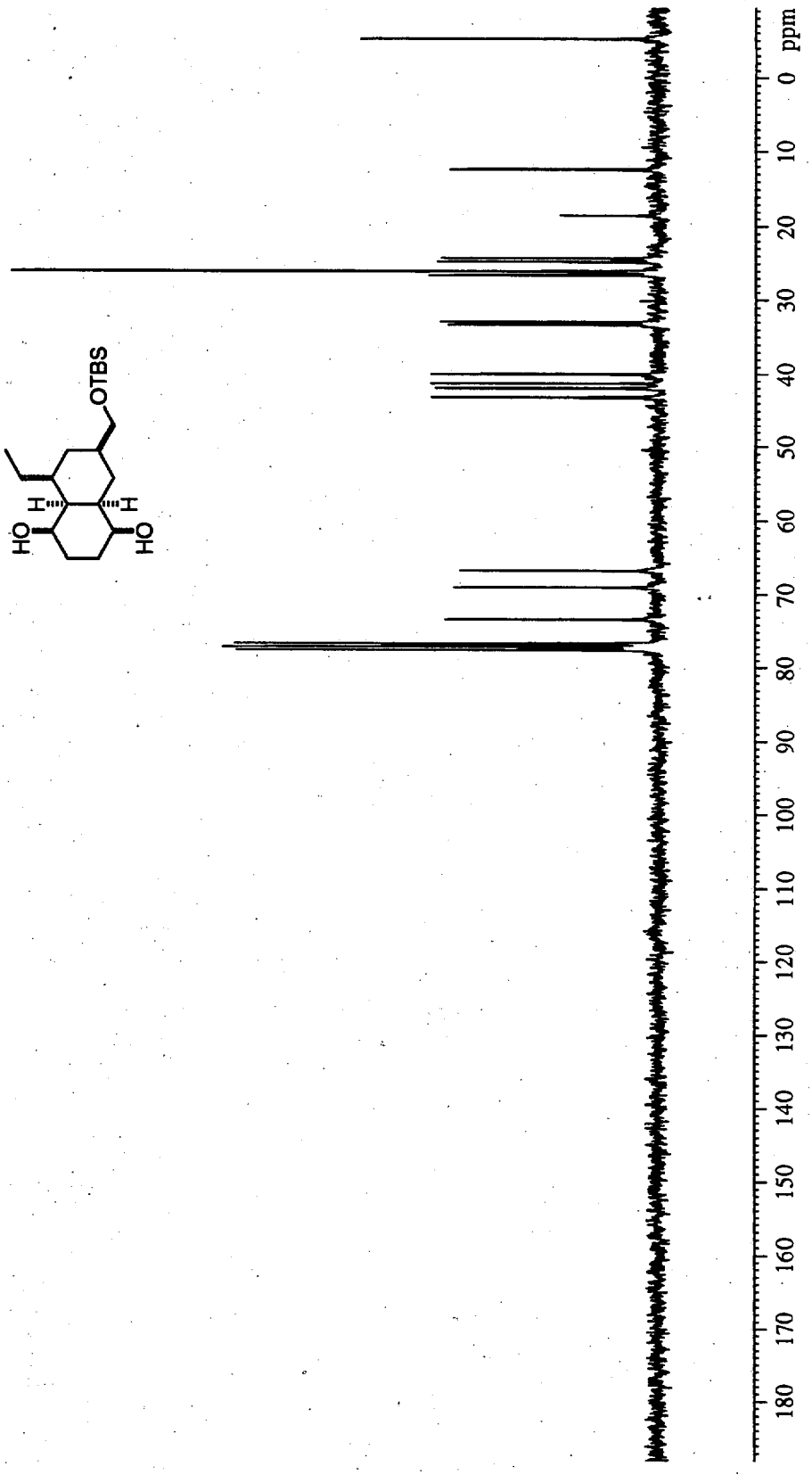
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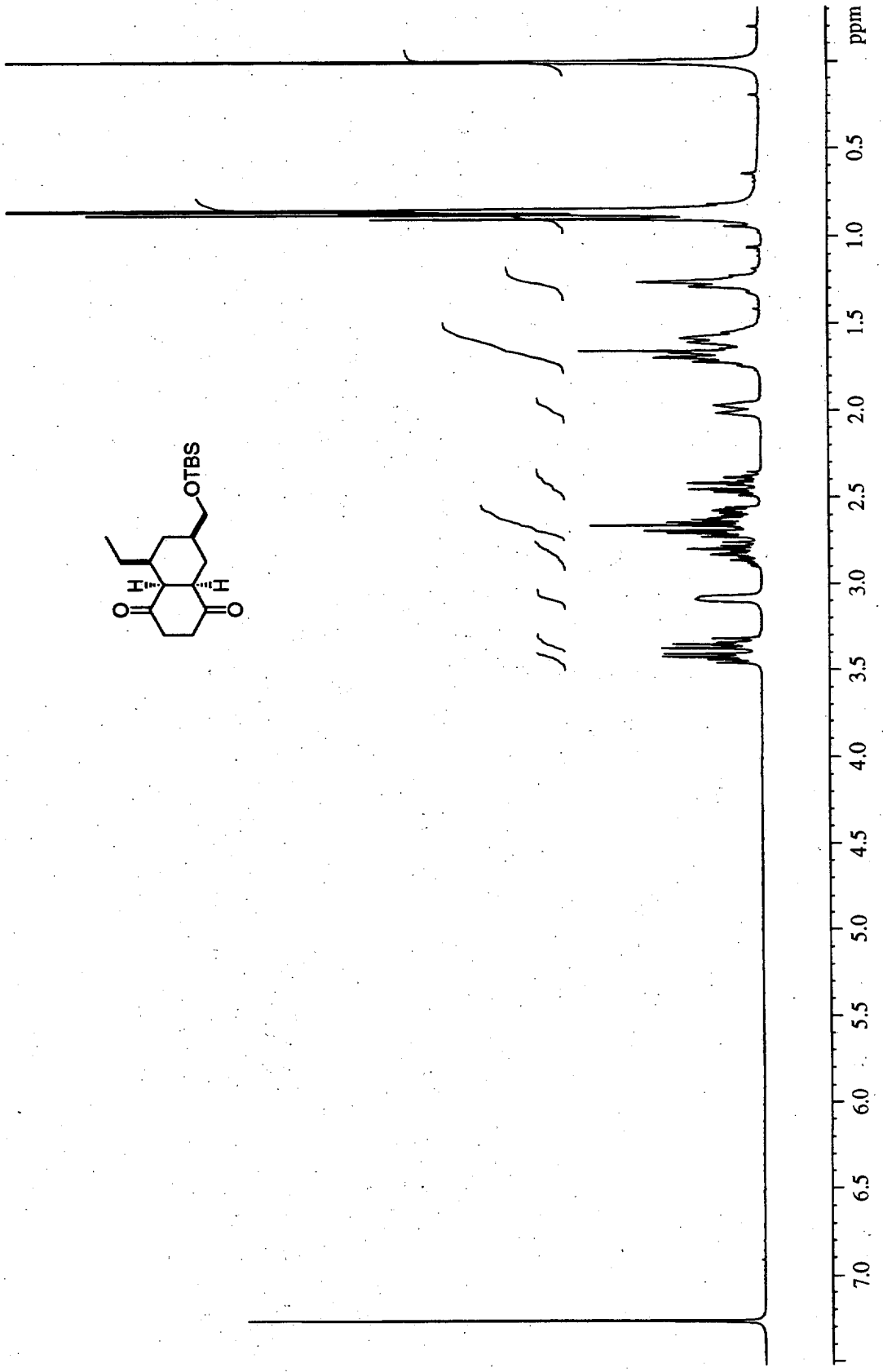
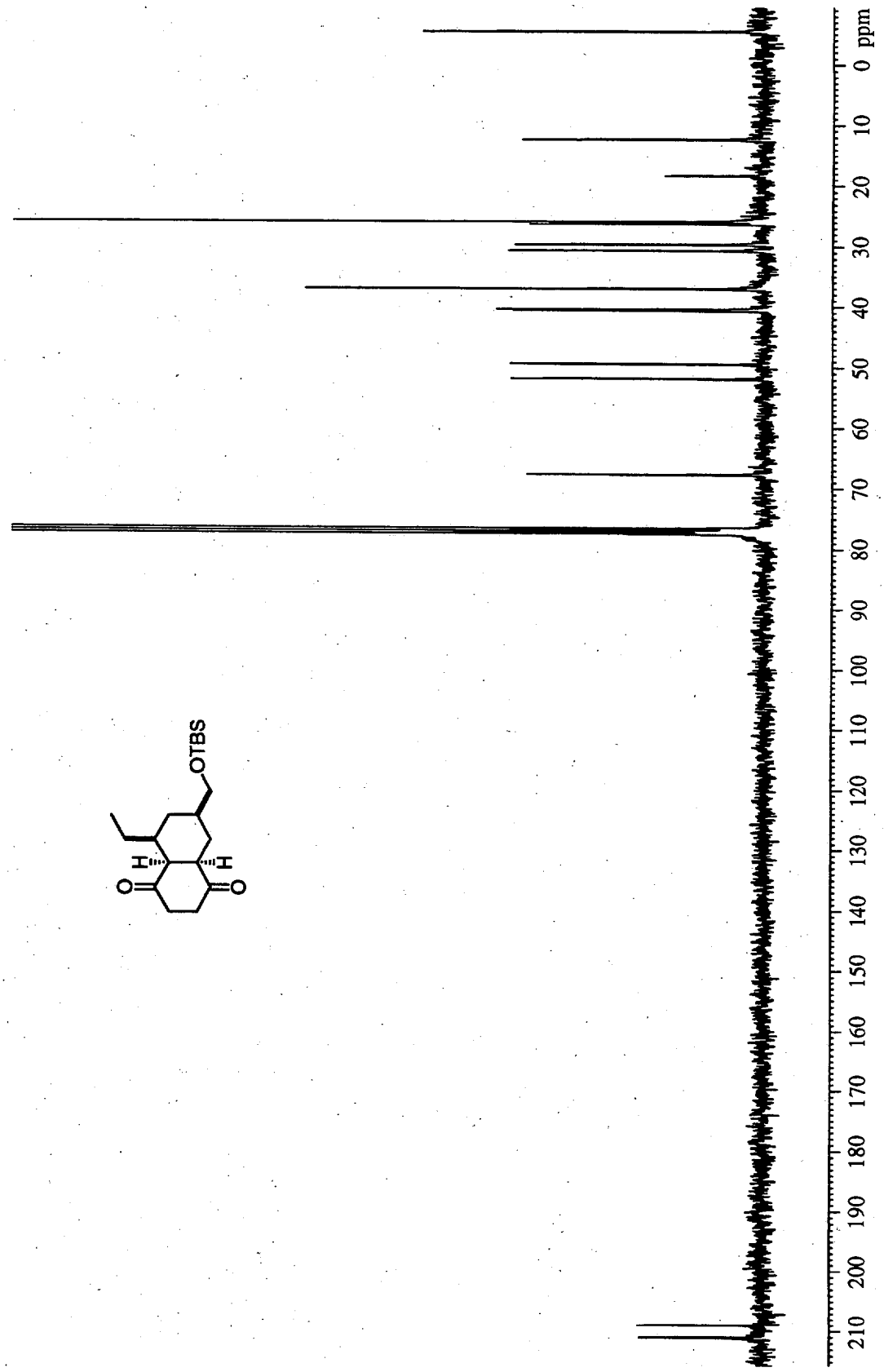
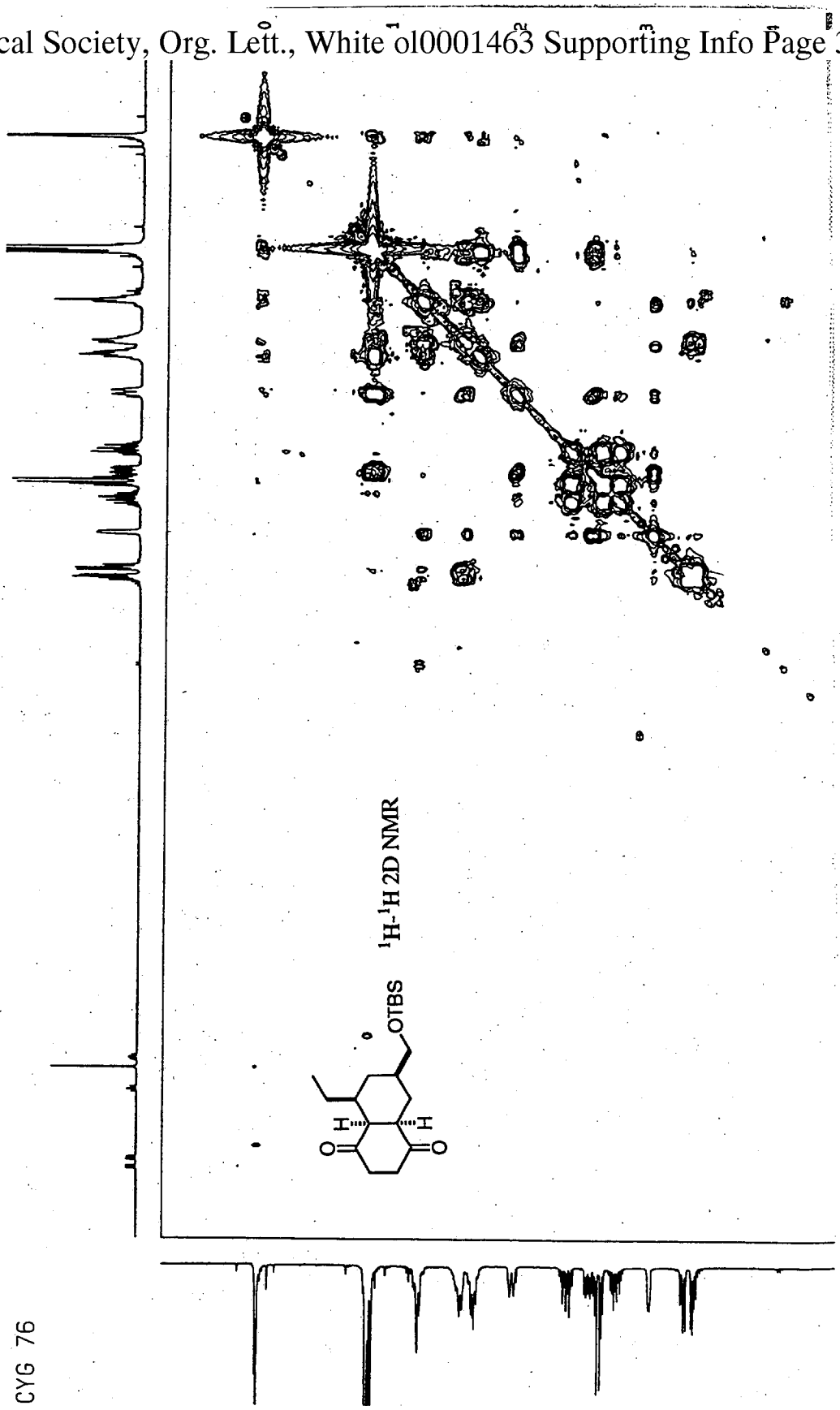
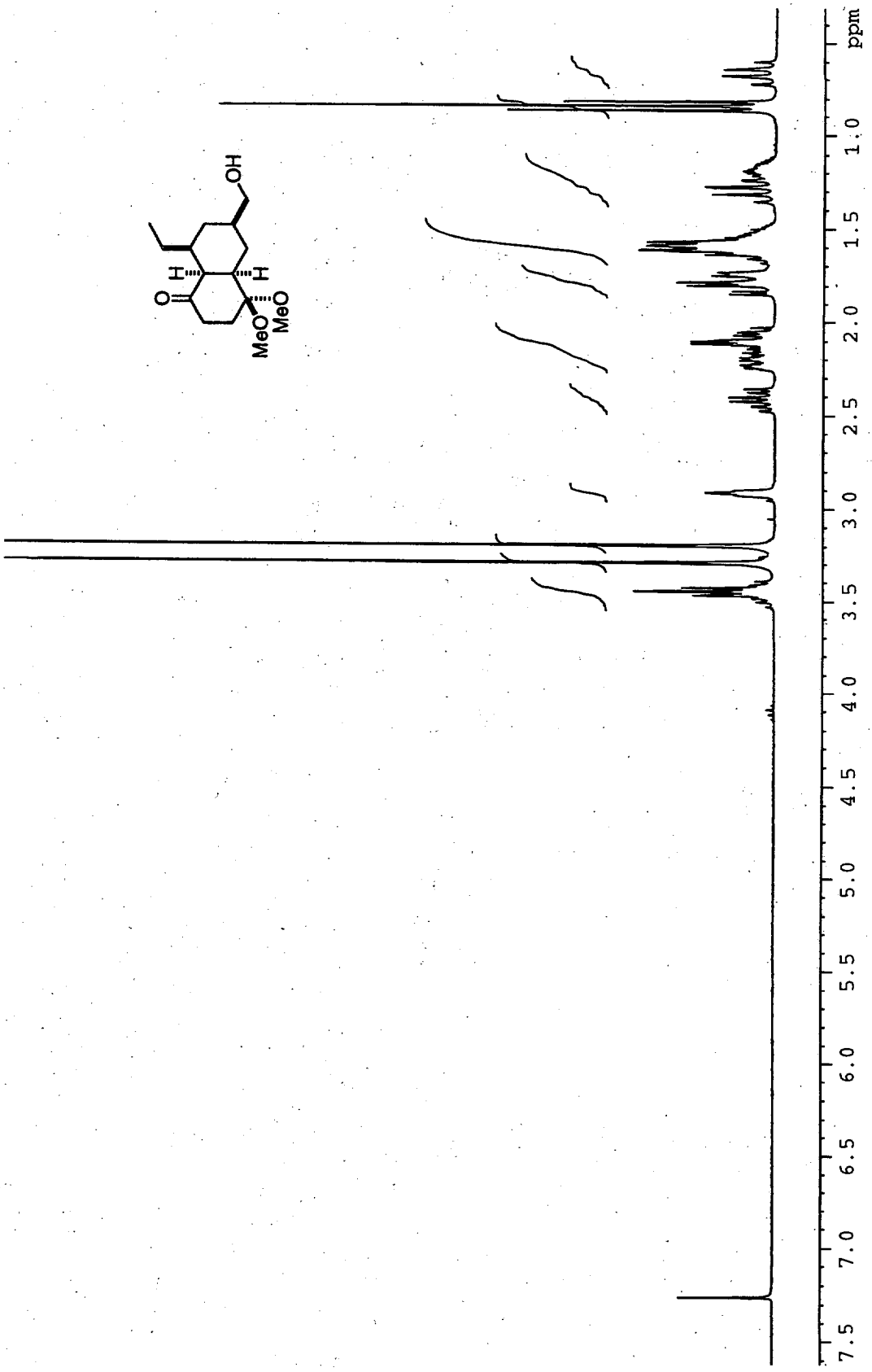
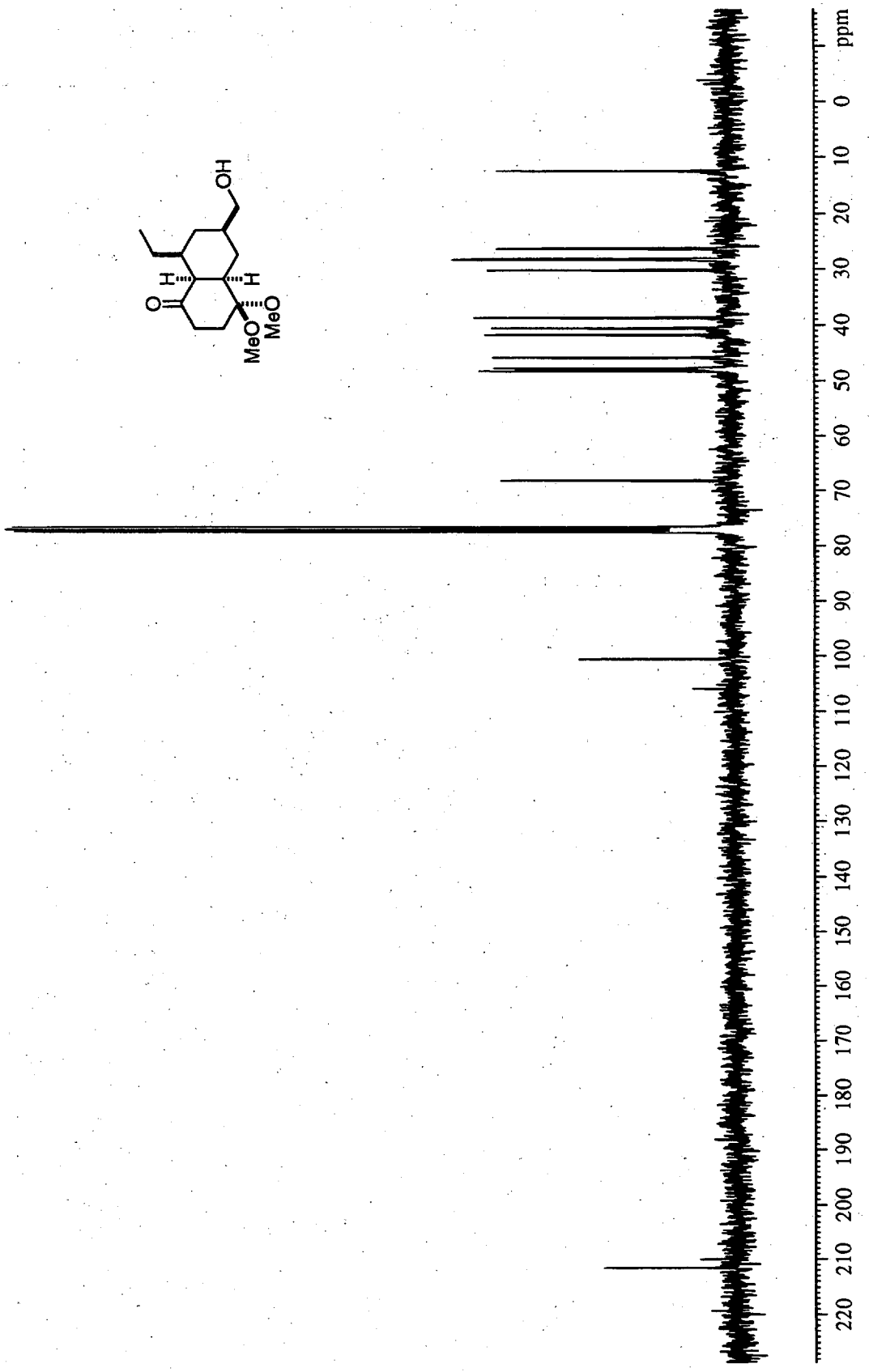
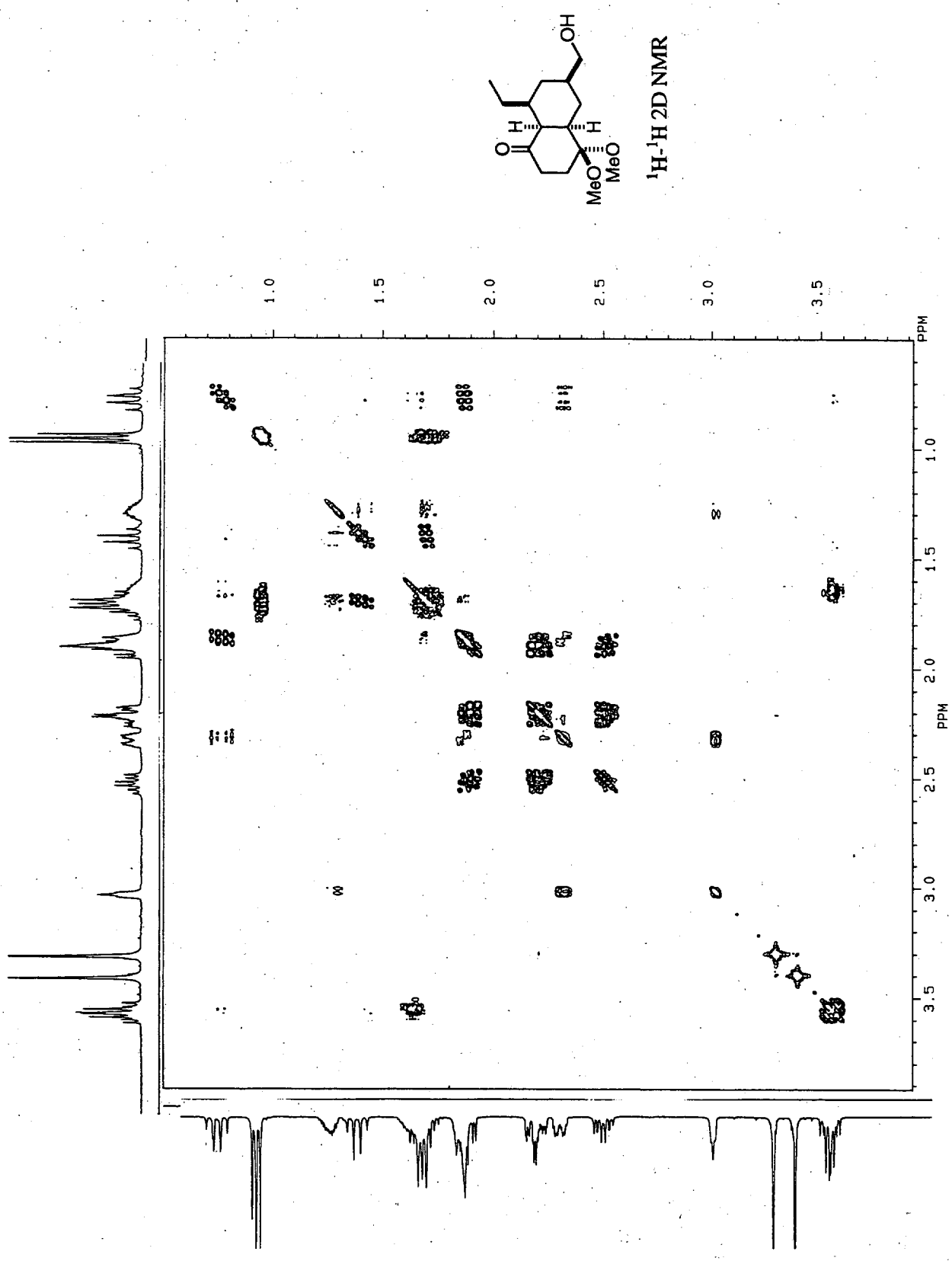




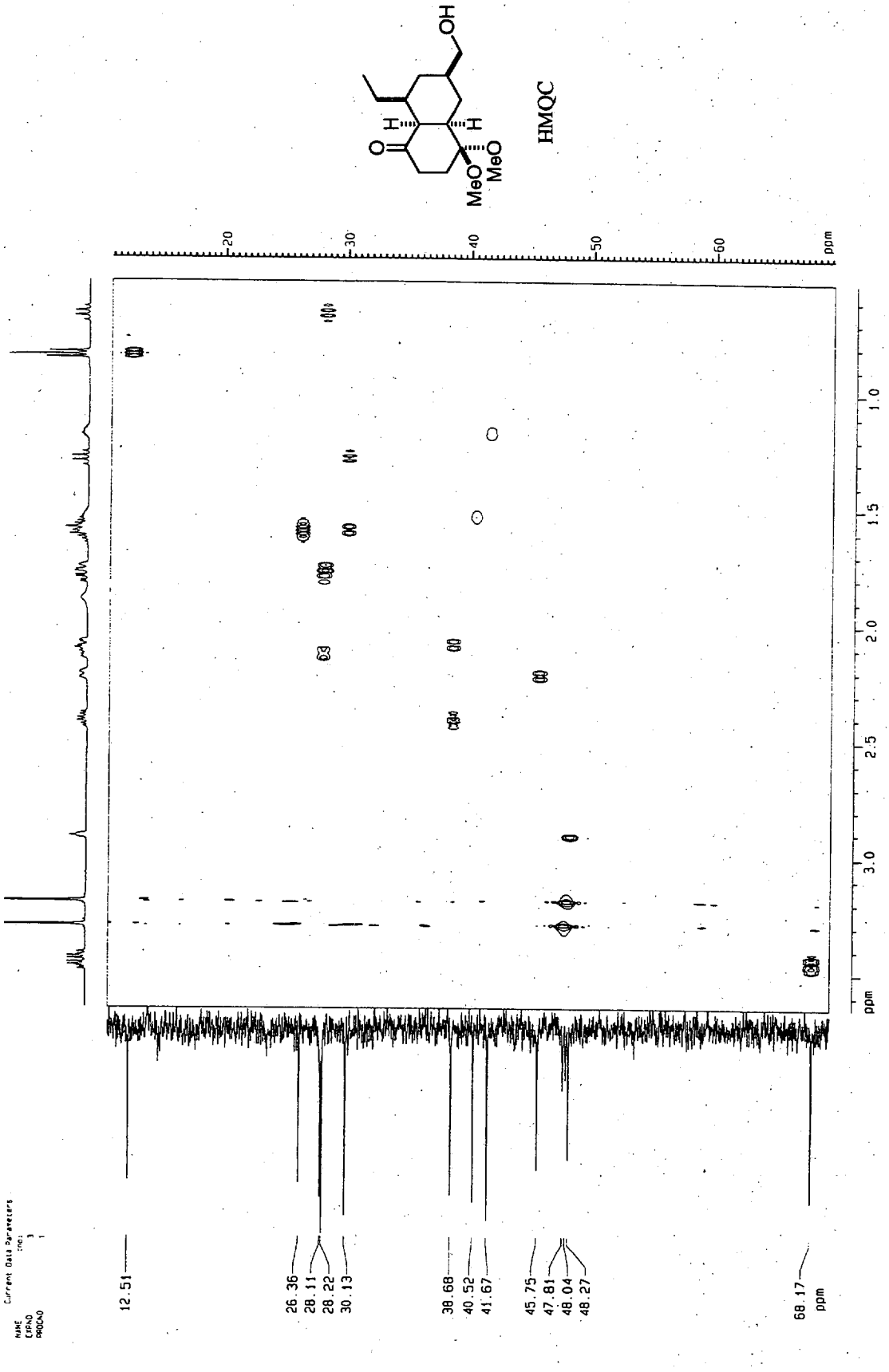

^{1}H-^{1}H 2D NMR
OTBS
H
H
O
O
CYG 76

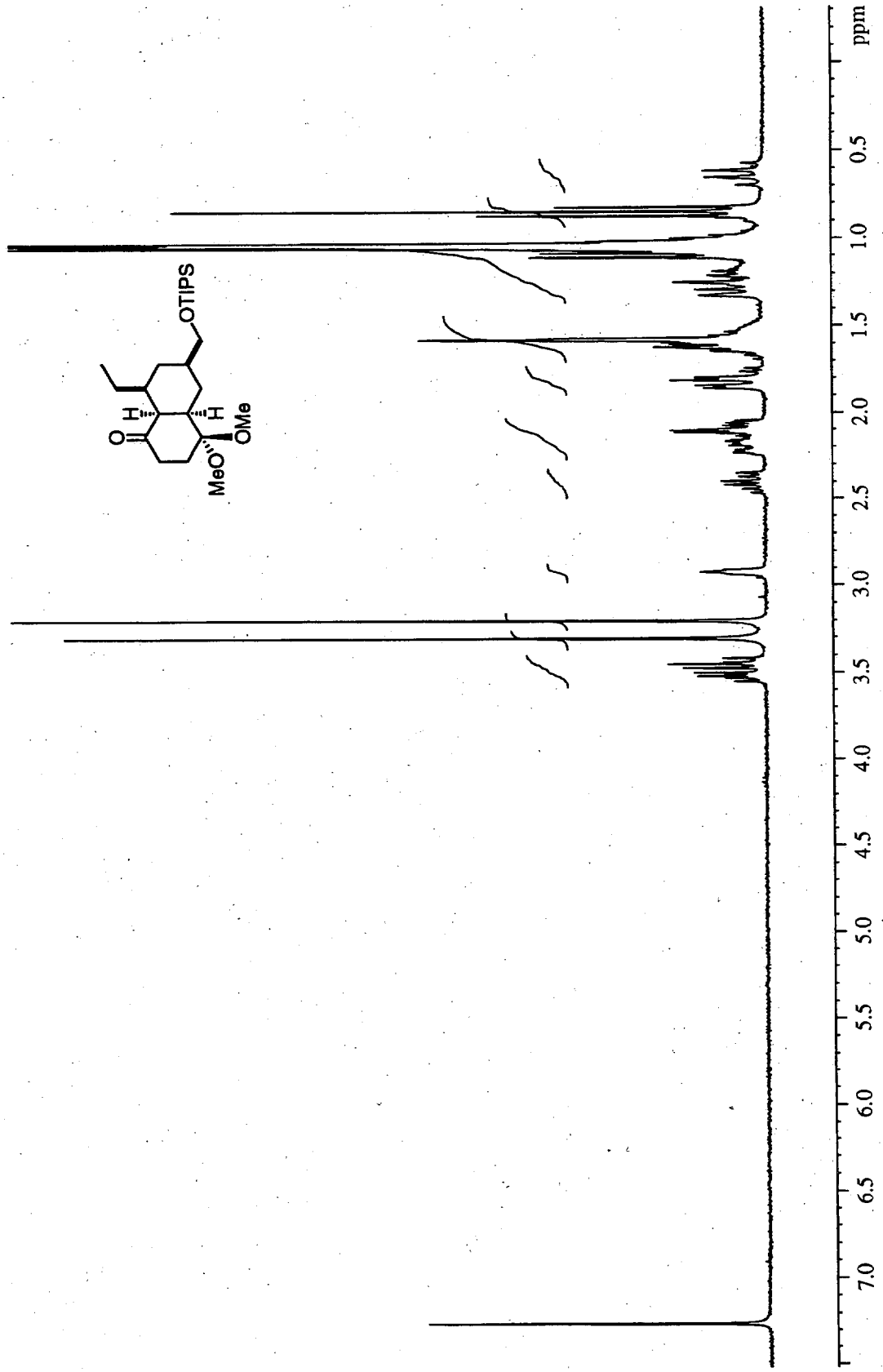


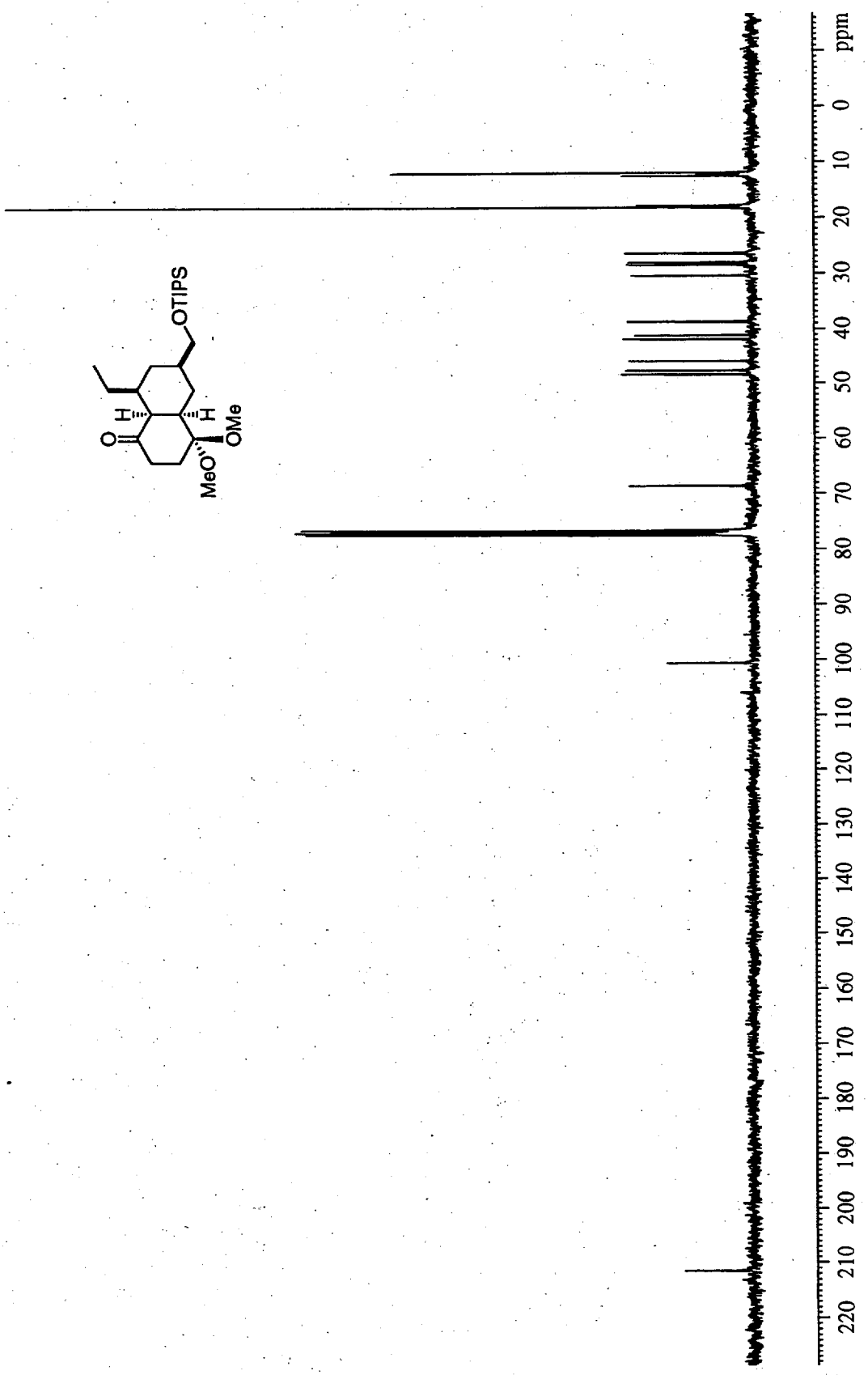


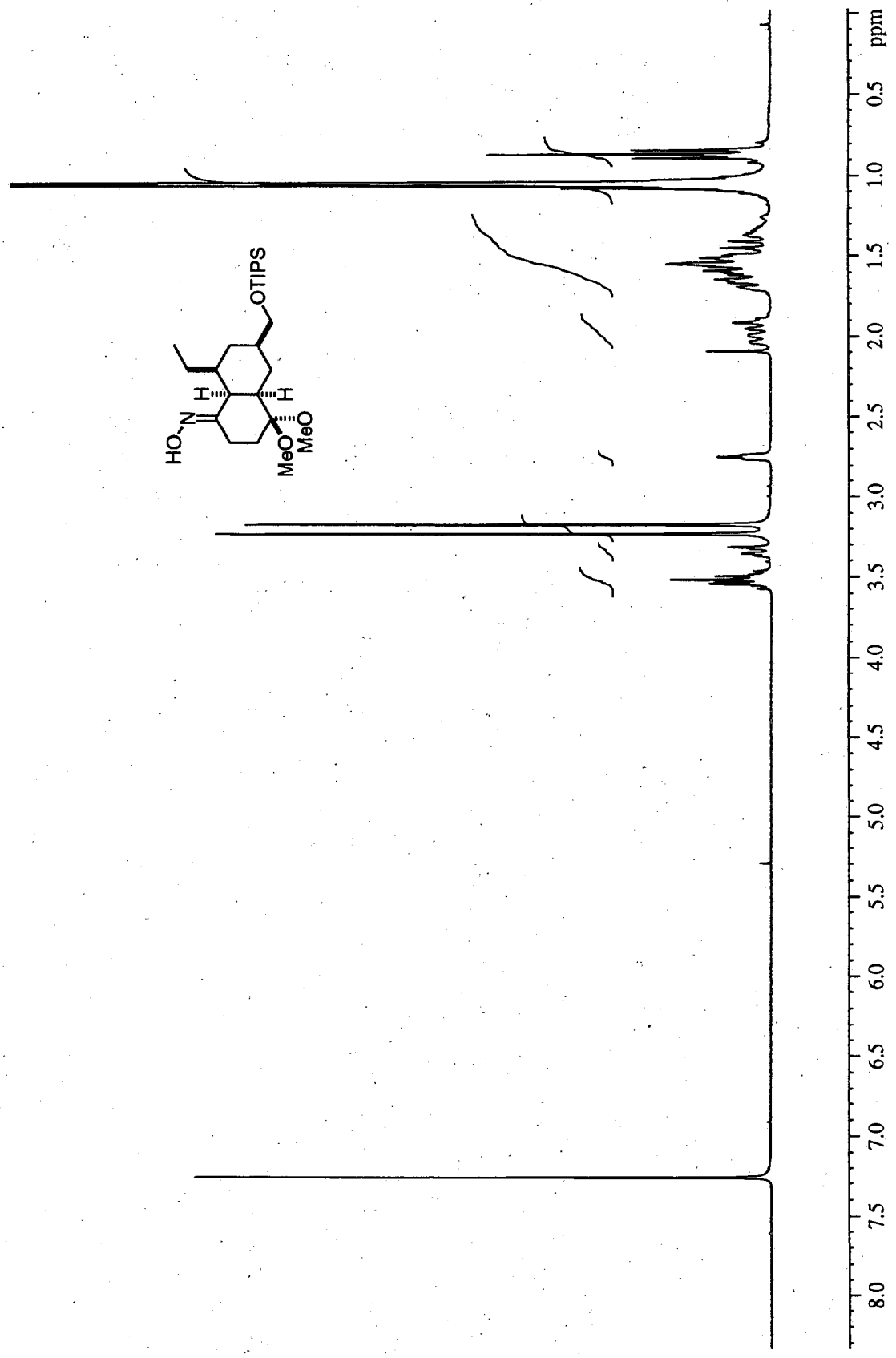


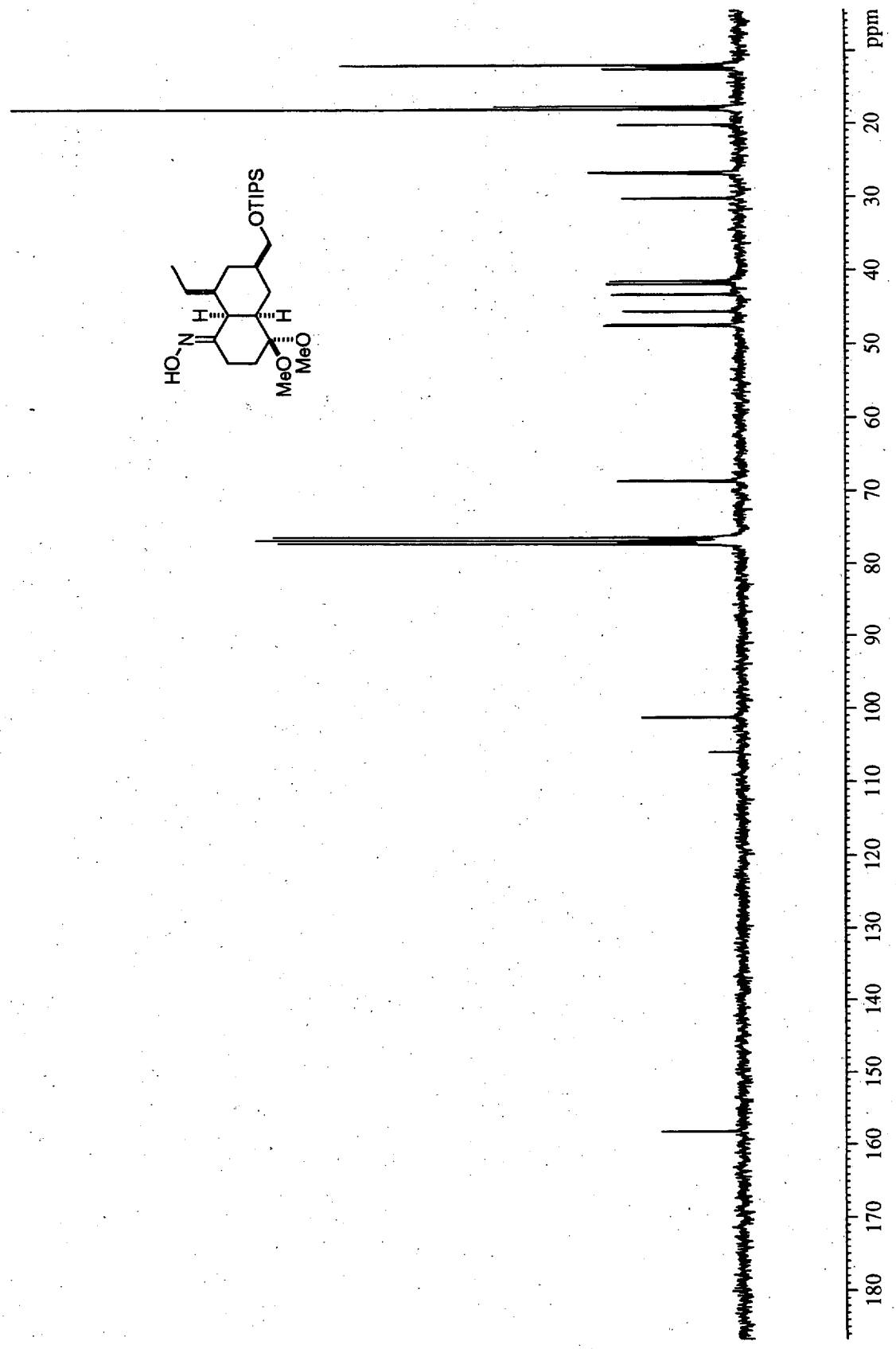
^1H-^1H 2D NMR




OTIPS
O
H
MeO
H
OMe
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0






OTIPS
H
H
HO
N
MeO
MeO
ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180