Total Synthesis of (±)-Isoschizogamine.
Supporting Information

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Experimental Section

General. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. Methylene chloride (CH_2Cl_2) and toluene were distilled from CaH_2 immediately prior to use. Pyridine was dried and stored over KOH. All reactions involving air or moisture-sensitive compounds were performed under a dry nitrogen atmosphere. Column chromatography was carried out with ICN SiliTech 32-63 D 60 Å silica gel.[1] TLC was performed on Merck silica gel 60 F-254 glass plates. Unless otherwise noted, extracts were dried over $MgSO_4$ and solvents were removed with a rotary evaporator at aspirator pressure. IR spectra were obtained using thin films on NaCl plates and NMR spectra were measured in $CDCl_3$. Coupling constants for ^1H NMR spectra are given in Hertz. In some cases Distortionless Enhancement by Polarization Transfer (DEPT) was used to assign ^{13}C NMR resonances as CH_3, CH_2, CH, or C. When ^{13}C resonances overlapped, no special notation was used. Elemental analyses were performed at the University of California, Berkeley microanalysis facility.

Aminals 8 and 9. A solution of 250 mg (0.813 mmol) of lactam **5** in 7.5 mL of THF was treated with 309 mg (8.13 mmol) of $LiAH_4$. The mixture was heated at reflux for 20 h then cooled to room temperature and quenched by sequential addition of 0.3 mL of water, 0.3 mL of 15% aqueous NaOH, and 0.9 mL of water.[2] Approximately 1 g of $MgSO_4$ was added and the resulting slurry was filtered

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[1] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
[2] Feiser, L. F.; Feiser, M. "Reagents for Organic Synthesis," Vol 1, Wiley: New York, 1967, p 584.

through a glass frit and concentrated to give a red oil, which was purified by column chromatography on silica gel which had been washed with 10% triethylamine in hexanes. Elution with 1:9 isopropyl alcohol:hexanes gave 109 mg (47%) of less polar colorless oil **9** and 79 mg (34%) of more polar white solid **8**.

Equilibration of the Aminal Diastereomers. Pure diastereomer **8** or **9** (15 mg) was added to 1 mL of acetic acid at room temperature. The solution was stirred for 2 h then poured into 10 mL of saturated $NaHCO_3$ and extracted with 10 mL of CH_2Cl_2. The extract was dried and the solvent was evaporated to give a crude oil. ^{1}H NMR integration indicated an 85:15 ratio of **8** to **9**.

Desired Diastereomer (8). Mp 122-125 °C. IR: 3384 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.88 (t, 3, J = 7.4), 1.06-1.14 (m, 1), 1.19-1.24 (m, 1), 1.30-1.57 (m, 6), 1.63 (qt, 1, J = 13.6, 4.1), 1.77-1.79 (m, 1), 1.82-1.90 (m, 1), 2.14 (tt, 1, J = 13.2, 4.2), 2.42 (dd, 1, J = 14.5, 3.4), 2.70-2.74 (m, 1), 2.81-2.85 (m, 1), 2.99 (td, 1, J = 13.4, 5.0), 3.03-3.04 (m, 1), 3.14 (td, 1, J = 14.1, 3.6), 4.13 (br s, 1), 6.46 (d, 1, J = 7.9), 6.60 (td, 1, J = 7.3, 1.1), 6.94 (dd, 1, J = 7.3, 1.3), 7.02 (td, 1, J = 7.3, 1.0). ^{13}C NMR (125 MHz): δ 9.30, 22.01, 22.61, 23.49, 27.96, 30.40, 33.83, 34.75, 37.73, 45.10, 45.89, 48.86, 76.02, 111.91, 116.79, 122.39, 127.35, 129.00, 144.72. Anal. Calcd. for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92. Found: C, 81.05; H, 9.56; N, 9.90.

Undesired Diastereomer (9). IR: 3414 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.80 (t, 3, J = 7.5), 1.12 (td, 1, J = 13.7, 5.1), 1.28-1.35 (m, 1), 1.36-1.40 (m, 2), 1.47-1.51 (m, 1), 1.60-1.62 (m, 2), 1.70 (dt, 1, J = 14.2, 2.0), 1.81 (qt, 1, J = 13.0, 4.8), 2.05-2.17 (m, 2), 2.23-2.51 (m, 6), 2.94 (d, 1, J = 3.2), 4.53 (br s, 1), 6.54 (d, 1, J = 7.9), 6.57 (td, 1, J = 7.4, 1.1), 6.92 (dd, 1, J = 8.4, 1.4), 6.98 (td, 1, J = 7.6, 1.5). ^{13}C NMR (125 MHz): δ 10.36 (CH_3), 22.90 (CH_2), 23.58 (CH_2), 29.32 (CH_2), 29.59 (CH_2), 30.39 (CH_2), 30.96 (CH_2), 36.74 (CH), 42.46 (CH), 47.39 (C), 47.66 (CH_2), 49.34 (CH_2), 75.56 (C), 111.36 (CH), 115.31 (CH), 125.79 (CH), 126.13 (C), 127.43 (CH), 145.29 (C). Anal. Calcd. for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92. Found: C, 80.53; H, 9.40; N, 9.68.

Aldols 14 and 15. An approximately 1 M solution of KHMDS in THF was prepared as follows: KH (1.50 g, 37.5 mmol; 35% mineral oil dispersion) in a conical flask was washed with pentane (3 x 5 mL). THF (25 mL) was added followed by slow addition of hexamethyldisilizane (4.04 g, 25 mmol). A 0.500 mL aliquot of the solution was added to 2:1 isopropyl alcohol:water and titrated with 0.100 M HCl with phenolphthalein as an indicator immediately prior to use.

Procedure A. KHMDS (6.94 mL of a 1.04 M solution in THF, 7.22 mmol) was added with a syringe pump over 2 h to a solution of ketone **13** (1.18 g, 6.56 mmol) in 20 mL of THF at room temperature. The flask was immersed in an ice water bath, stirred for 5 min, and 2.85 g (32.8 mmol) of LiBr was added (exothermic). The mixture was stirred for 20 min then cooled to –78 °C. Freshly prepared 3-azidopropanal[3] (812 mg, 8.20 mmol) was added as a solution in 5 mL of THF over 5 min and the solution was allowed to stir for 1 h. The reaction was quenched by addition of 10 mL of saturated NH_4Cl, allowed to return to room temperature, and diluted with 50 mL of water. The mixture was extracted with ether (3 x 50 mL), the combined extracts were washed with 50 mL of brine, the solution was dried, and the solvent was evaporated to give an oil. The crude aldol adducts were purified by column chromatography with 1:19 acetone:CH_2Cl_2 to afford 691 mg (40%) of less polar syn diastereomer **14** and 462 mg (27%) of more polar anti diastereomer **15**.

Procedure B. KHMDS (4.67 mL of a 0.90 M solution in THF, 4.20 mmol) was added with a syringe pump to a solution of ketone **13** (681 mg, 4.00 mmol) in 10 mL of THF over 2 h. The flask was cooled to –78 °C and dibutylboron triflate (1.06 mL, 4.20 mmol) was added as a solution in 3 mL of THF. After the reaction was stirred for 30 min, 728 mg (8.00 mmol) of freshly prepared 3-azidopropanal was added as a solution in 2 mL of THF. The solution was stirred for 1 h at -78 °C and then 1 h at 0 °C. The reaction was quenched by pouring into 50 mL of a pH 7 phosphate buffer, and the aqueous solution was extracted with Et_2O (3 x 50 mL). The combined extracts were washed with 50 mL of brine, dried and concentrated. The residue was dissolved in 12 mL of methanol and cooled to 0 °C, then 4 mL of 30% H_2O_2 was added. The solution was allowed to warm to room temperature and stirred for 1 h. Water (40 mL) was added to the flask and most of the methanol was removed under reduced pressure. The water was then extracted with ether (3 x 50 mL), and the combined ether extracts were washed with 50 mL of brine and dried. The solvent was removed to give a crude oil that showed no

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[3] Davies, A. J.; Donald, A. S. R.; Marks, R. E. *J. Chem. Soc. (C)* **1967**, 2109.

evidence of containing anti diastereomer **15** (TLC and ^{1}H NMR analysis). The oil was purified by column chromatography with 1:19 acetone:CH_2Cl_2 to give 531 mg (49%) of aldol **14**.

Procedure C. KHMDS (4.95 mL of a 0.848 M solution in THF, 4.20 mmol) was added with a syringe pump to a solution of ketone **13** (678 mg, 3.98 mmol) in 13 mL of THF over 2 h. The flask was cooled to –78 °C and *i*-Bu_2AlCl (742 mg, 4.20 mmol) was added. The reaction was stirred for 30 min and then 728 mg (8.00 mmol) of 3-azidopropanal was added. The solution was stirred for 1 h then quenched with 2 mL of methanol. The flask was warmed to 0 °C with an ice bath and 2 mL of 2 M HCl was added. The mixture was stirred for 10 min and the aluminum salts were filtered. The filtrate was poured into 40 mL of 0.5 M HCl, the aqueous layer was extracted with ether (3 x 40 mL) and the combined ether layers were washed with 50 mL of brine and dried. The solvent was evaporated to give an oil that was purified by column chromatography with 1:19 acetone:CH_2Cl_2 to give 587 mg (55%) of syn diastereomer **14** and 170 mg (16%) of anti diastereomer **15**.

Syn Diastereomer (14). IR: 3477, 2099, 1727 cm^{-1}. ^{1}H NMR (300 MHz): δ 1.45-1.50 (m, 1), 1.63-1.69 (m, 1), 1.77-2.06 (m, 7), 2.18-2.27 (m, 1), 2.36-2.40 (m, 1), 3.38-3.48 (m, 2), 3.60 (t, 1, J = 2.2), 3.73 (dt, 1, J = 11.1, 2.1), 3.77-3.96 (m, 4), 5.01 (dd, 1, J = 6.2, 4.0). ^{13}C NMR (100 MHz): δ 18.86, 30.72, 30.80, 36.31, 38.38, 48.49, 52.83, 64.43, 64.53, 71.36, 101.58, 223.29. Anal. Calcd. for $C_{12}H_{19}N_3O_4$: C, 53.52; H, 7.11; N, 15.60. Found: C, 53.48; H, 7.31; N, 15.65.

Anti Diastereomer (15). IR: 3460, 2099, 1730 cm^{-1}. ^{1}H NMR (300 MHz): δ 1.46-1.57 (m, 1), 1.69-2.37 (m, 9), 2.76 (d, 1, J = 6.8), 3.35-3.52 (m, 3), 3.77-3.86 (m, 2), 4.93 (t, 1, J = 5.2). ^{13}C NMR (100 MHz): δ 18.62, 29.24, 30.49, 36.95, 38.67, 48.59, 54.43, 64.57, 101.61, 222.42. Anal. Calcd. for $C_{12}H_{19}N_3O_4$: C, 53.52; H, 7.11; N, 15.60. Found: C, 53.82; H, 7.26; N, 15.51.

Meldrum's Acid Derivative 16. 2-Nitroveratraldehyde (5.00 g, 23.7 mmol) in 10 mL of pyridine was treated with 5.13 g (35.6 mmol) of Meldrum's acid. The red solution was stirred at room temperature for 8 h then poured into 200 mL of 1 M HCl. The solid was filtered and washed with water. The crude solid was recrystallized from ethyl acetate to give 4.60 g (58%) of a yellow solid, mp 170-172 °C. IR: 1735, 1521, 1277 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.73 (s, 6), 3.91 (s, 3), 3.94 (s, 3), 6.95 (s, 1), 7.69 (s, 1), 8.62 (s, 1). ^{13}C NMR (100 MHz): δ 27.43, 56.34, 56.47, 105.07, 107.12, 112.10, 116.80, 123.29, 139.67, 150.08, 152.84, 155.64, 158.89, 161.66. Anal. Calcd. for $C_{15}H_{15}NO_8$: C, 53.42; H, 4.48; N, 4.15. Found: C, 53.69; H, 4.59; N, 4.07.

Imine 12. Palladium (10% on carbon, 75 mg) was added to a solution of aldol **14** (430 mg, 1.60 mmol) in 5 mL of ethanol. The flask was equipped with a three-way adapter and a hydrogen filled balloon. The vessel was evacuated under aspirator vacuum and purged with hydrogen three times and then stirred under hydrogen for 1 h. The solution was filtered through celite and the solvent was evaporated to give 430 mg of crude imine that was used without purification. An analytically pure sample was obtained by running the reaction as described above on 95 mg of aldol **14** and purifying the product by column chromatography on silica that had been washed with 10% Et_3N/hexanes. Elution with 1:2:7 methanol:acetone:CH_2Cl_2 provided 56.0 mg (71%) of pure imine **12** as a white solid, mp 94-98 °C. IR: 3362, 1683 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.55-1.63 (m, 2), 1.76-1.90 (m, 4), 1.95-2.05 (m, 3), 2.28-2.31 (m, 1), 2.57 (br m, 1), 3.55-3.56 (m, 1), 3,70-3.85 (m, 3), 3.93-3.97 (m, 2), 4.25 (dd, 1, J = 5.4, 3.5), 4.92 (dd, 2, J = 6.0, 3.6). ^{13}C NMR (125 MHz): δ 12.80, 25.38, 29.23, 32.52, 37.58, 45.04, 45.86, 64,47, 64.74, 67.31, 102.13, 180.17. Anal. Calcd. for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.90; H, 8.75; N, 6.11.

Lactams 17 and 18. A flask containing imine **12** (360 mg, 1.60 mmol) in CH_2Cl_2 (1.6 mL) was cooled to -40 °C. Meldrum's acid derivative **16** (593 mg, 1.76 mmol) was added. The mixture was stirred for 20 h and the formation of a yellow solid was observed. The flask was allowed to warm to room temperature over 3 h and the solvent was removed to give a yellow solid. This yellow solid was suspended in 5 mL of toluene and then heated at reflux for 10 min. The flask was cooled and the solvent was evaporated to give a red oil that was purified by column chromatography with 40% acetone/hexanes to afford 477 mg (65%, 2 steps) of more polar desired diastereomer **17** and 66 mg (9 %) of less polar undesired diastereomer **18** (88:12 diastereomeric ratio).

Desired Diastereomer (17). IR: 3430, 1651, 1519, 1271 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.85-1.94 (m, 5), 2.15-2.33 (m, 4), 2.68 (br t, 1, J = 14.5), 2.93 (dd, 1, J = 15.7, 6.2), 3.35 (td, 1, J = 12.7, 5.4), 3.78-4.00 (m, 11), 4.04 (br s, 1), 4.58 (br dd, 1, J = 13.2, 5.7), 4.99 (t, 1, J = 4.9), 6.73 (s, 1), 7.43 (s, 1). ^{13}C NMR (100 MHz): δ 26.12, 28.17, 28.75, 34.74 (br), 35.81, 40.00, 40.24, 49.42, 56.28, 64.43, 64.87, 66.93, 102.46, 107.73, 110.43 and 111.05 (1 C), 117.44, 131.44, 139.73, 142.09, 147.48, 152.92, 169.68. Anal. Calcd. for $C_{23}H_{28}N_2O_8$: C, 59.99; H, 6.13; N, 6.08. Found: C, 59.75; H, 6.40; N, 5.82.

Undesired Diastereomer (18). IR: 3439,1650, 1518, 1274 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.89-2.01 (m, 6), 2.20-2.42 (m, 3), 2.70 (dd, 1, J = 15.7, 1.1), 3.10 (dd, 1, J = 15.7, 8.9), 3.22 (td, 1, J = 12.9, 5.1), 3.80-3.98 (m, 11), 4.10 (d, 1, J = 2.5), 4.28 (d, 1, J = 8.6), 4.92 (dd, 1, J = 5.6, 1.7), 6.83 (s, 1), 7.59 (s, 1). ^{13}C NMR (100 MHz): δ 26.00, 28.03, 29.05, 33.53, 36.08, 39.04, 39.66, 49.14, 56.31, 56.50, 64.47, 64.92, 66.74, 102.39, 108.76, 110.47, 118.07, 131.13, 140.56, 141.42, 147.57, 153.75, 169.62. Anal. Calcd. for $C_{23}H_{28}N_2O_8$: C, 59.99; H, 6.13; N, 6.08. Found: C, 59.73; H, 6.51; N, 5.72.

Lactam 19. Lactam **17** (426 mg, 0.925 mmol) was dissolved in 5 mL of CH_2Cl_2 and Martin's sulfurane dehydrating reagent (684 mg, 1.02 mmol) was added. The solution was stirred for 1 h and the solvent was evaporated. The resulting brown oil was purified by column chromatography with 3:1 ethyl acetate:hexanes to give 302 mg (74%) of lactam **19** as a yellow foam. IR: 1668, 1517, 1271 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.77-1.85 (m, 3), 1.91 (dd, 1, J = 13.9, 4.9), 2.11-2.16 (m, 1), 2.21-2.36 (m, 1), 2.65 (br t, 1, J = 13.4), 3.00 (dd, 1, J = 16.2, 6.6), 3.72-3.90 (m, 11), 4.36 (dd, 1, J = 18.9, 5.1), 4.53 (dd, 1, J = 13.0, 6.6), 4.85 (t, 1, J = 4.9), 5.73 (ddd, 1, J = 10.0, 5.0, 1.9), 5.89 (dd, 1, J = 10.0, 1.8), 6.78 (s, 1), 7.41 (s, 1). ^{13}C NMR (100 MHz): δ 28.50, 34.96, 35.13, 40.26, 40.92, 41.87, 45.20, 56.10, 56.17, 64.47, 64.62, 102.28, 107.58, 110.35 and 110.97 (1 C), 112.53, 121.38, 132.02, 132.85, 140.37, 141.77, 147.35, 152.98, 168.09. Anal. Calcd. for $C_{23}H_{26}N_2O_7$: C, 62.43; H, 5.92; N, 6.33. Found: C, 62.12; H, 5.87; N, 6.20.

(±)-Isoschizogamine (1). Cu(acac)$_2$ (18.0 mg, 0.0688 mmol) was suspended in 2 mL of absolute ethanol. $NaBH_4$ (85.0 mg, 2.26 mmol) was added and the dark suspension was allowed to stir for 20 min at which time the solution became colorless and a dark precipitate had formed. Lactam **19** (102 mg, 0.231 mmol) was added as a solution in 2 mL of THF and the solution was stirred for 4.5 h. The solution was poured into 25 mL of saturated aqueous $NaHCO_3$, the aqueous layer was extracted with $CHCl_3$ (3 x 25 ml), and the combined extracts were dried over K_2CO_3. The solvent was evaporated to give a slightly yellow oil. This oil was dissolved in 4.5 mL of THF. $LiAlH_4$ was added and the solution was heated at reflux for 14 h. The solution was cooled to room temperature and the reaction was quenched by sequential addition of 90 μL of H_2O, 90 μL of 15% NaOH, and 270 μL of H_2O.[2] Anhydrous K_2CO_3 (1 g) was added, the salts were filtered and washed with 50 mL $CHCl_3$ and the solvent was evaporated to give a brown oil. This oil was dissolved in 4 mL of 1:1 acetic acid:H_2O and the solution was heated at reflux for 3 h. The solution was cooled and poured into 40 mL of 1 N NaOH, and the aqueous solution was extracted with $CHCl_3$ (3 x 40 mL). The combined extracts were dried over K_2CO_3 and the solvent was evaporated to give a brown oil. This oil was dissolved in CH_2Cl_2 and PDC (113 mg, 0.300 mmol) was added. The solution was stirred for 3.5 h and then 5 mL of saturated aqueous $NaHCO_3$ was added and the resulting mixture was stirred for 15 min. The solution was filtered through celite and 15 mL of additional $NaHCO_3$ solution was added. This mixture was extracted with $CHCl_3$ (3 x 40 mL) and the combined extracts were dried over K_2CO_3. The solvent was evaporated to give a brown oil that was purified by column chromatography on silica that had been washed with a 1:4:5 solution of Et_3N:CH_2Cl_2:ethyl acetate. Elution with 3:1 ethyl acetate:CH_2Cl_2 gave 22.2 mg (27% from **19**) of (±)-isoschizogamine (**1**) as a colorless oil with ^1H and ^{13}C NMR spectral data identical to that reported.[4] IR: 1692 cm^{-1}. ^1H NMR (500 MHz): δ 1.14-1.26 (m, 2), 1.64-1.69 (m, 1), 1.74-1.86 (m, 2), 2.20 (tt, 1, J = 13.2, 3.8), 2.30 (ddd, 1, J = 12.1, 6.9, 2.5), 2.50 (d, 1, J = 16.5), 2.52 (dd, 1, J = 14.6, 4.2), 2.85 (d, 1, J = 16.5), 2.91 (dd, 1, J = 14.7, 3.2), 3.19 (d, 1, J = 2.8), 3.29 (dd, 1, J = 16.3, 3.3), 3.43 (d, 1, J = 17.1), 3.85 (s, 3), 3.91 (s, 3), 5.58 (ddd, 1, J = 10.2, 4.6, 1.7), 5.73 (br d, 1, J = 10.0), 6.59 (s, 1), 8.50 (s, 1). ^{13}C NMR (125 MHz): δ 24.72, 26.66, 34.83, 36.51, 37.66, 44.20, 44.38, 45.97, 47.83, 55.96, 56.02, 84.44, 102.47, 111.13, 117.42, 119.96, 130.88, 131.49, 145.22, 147.52, 173.79.

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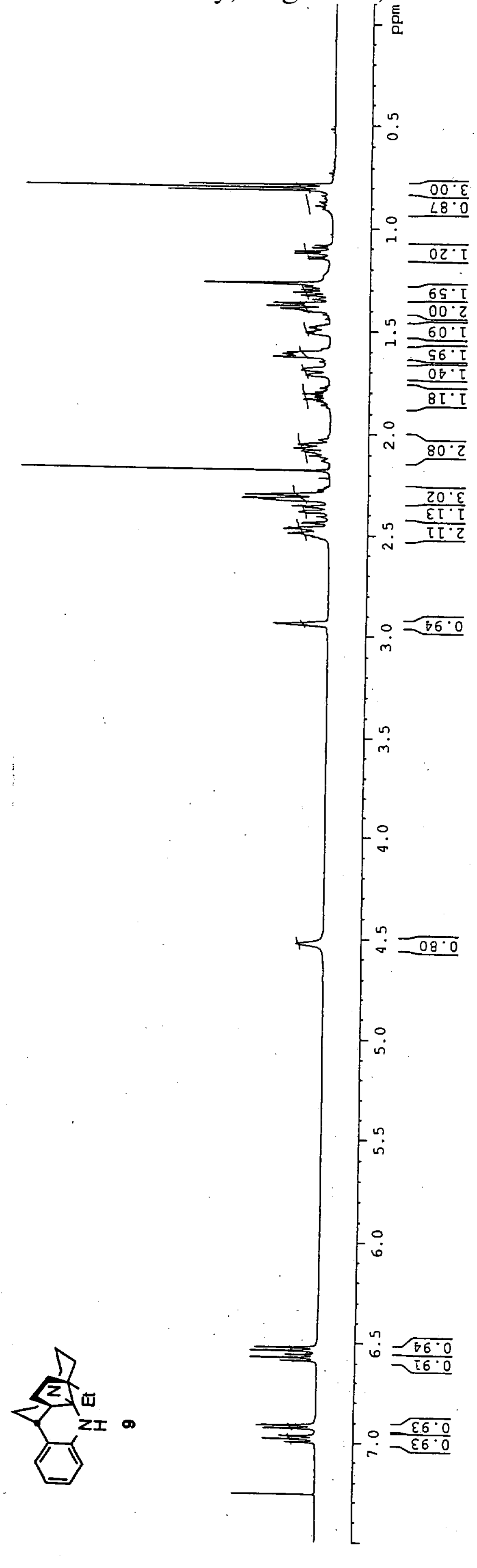
[4] Hajicek, J.; Taimr, J.; Budesinsky, M. *Tetrahedron Lett.* **1998**, *39*, 505.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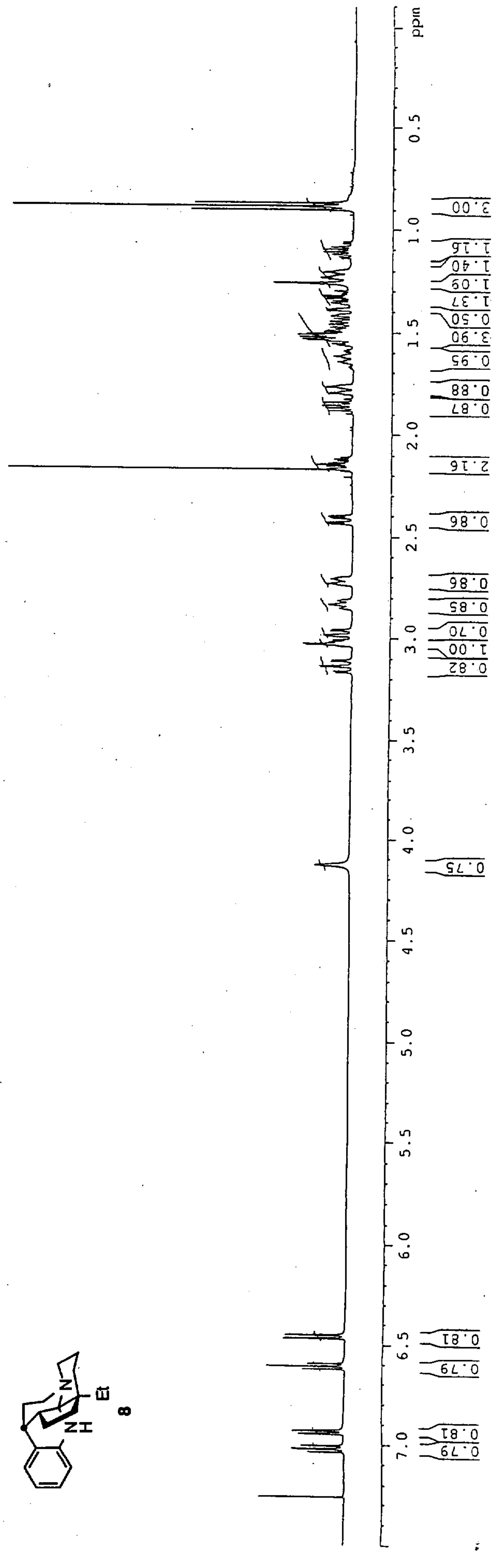
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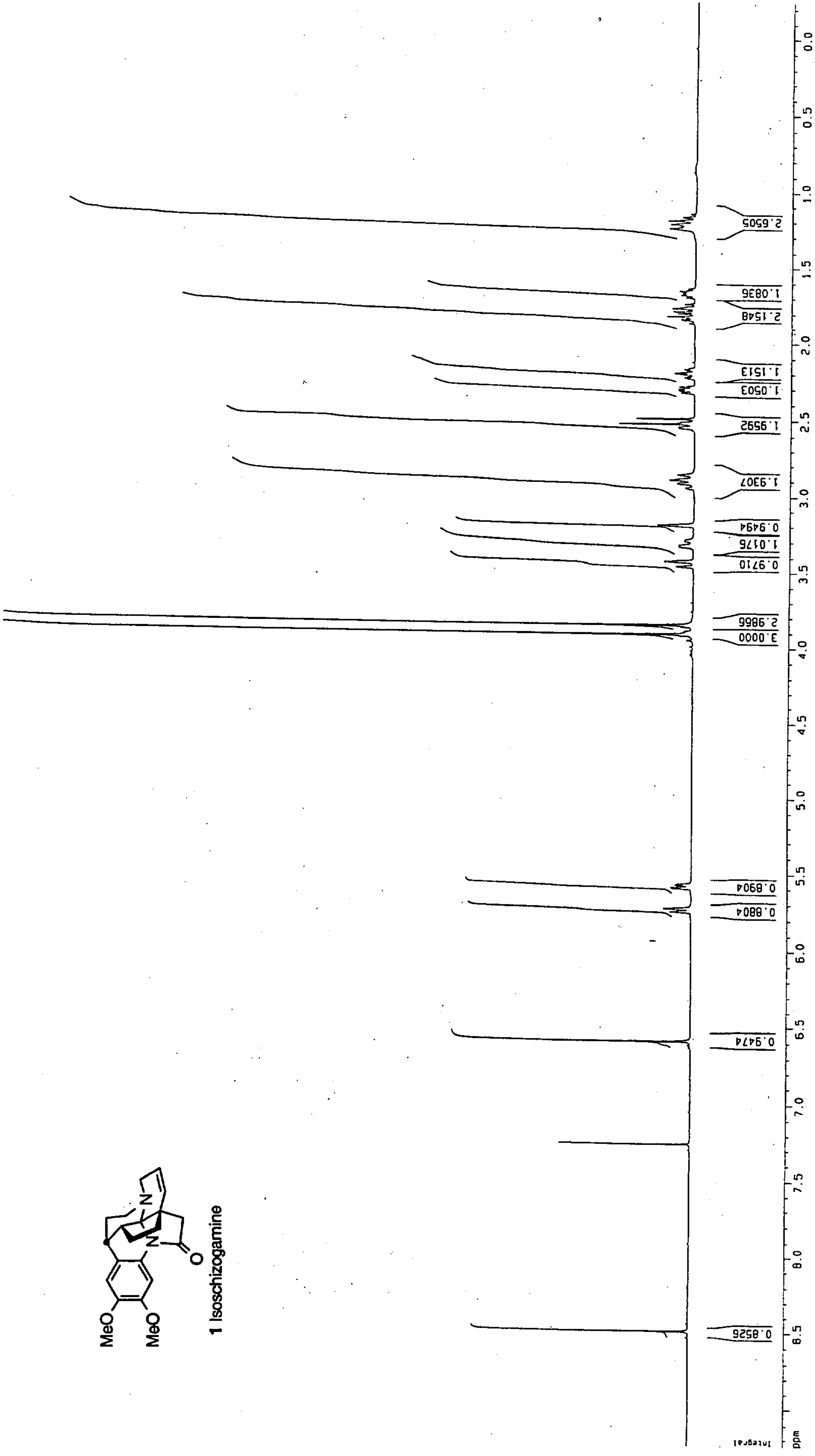

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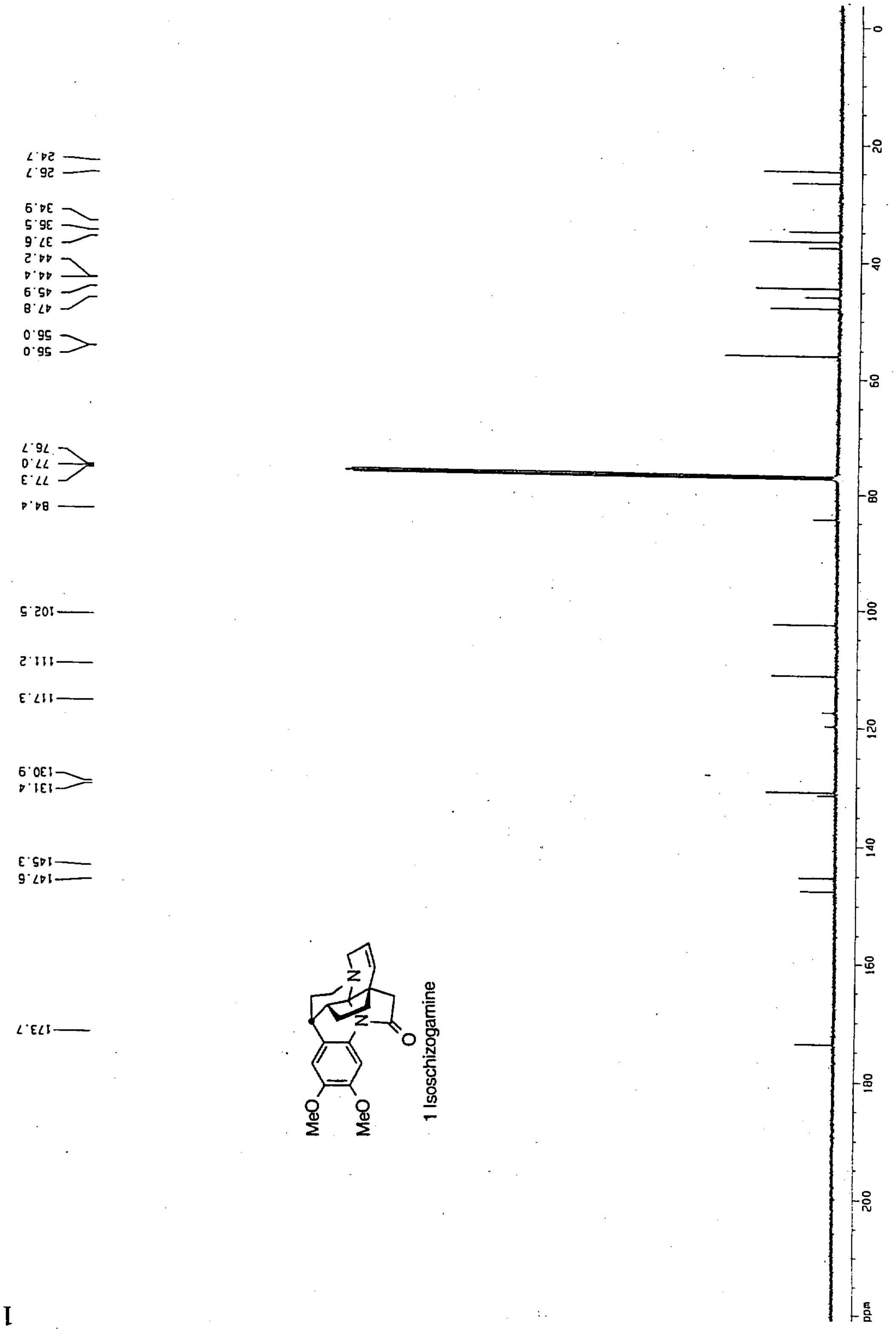

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