

The First Total Syntheses of Ircinol A, Ircinal A, and Manzamines A and D

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SUPPORTING INFORMATION

Procedures for the preparation of compounds **1**, **11**, **14**, and **16-28** with spectral data and copies of NMR spectra for pentacyclic compounds (20 pages).

Vinylogous amide 11:

A solution of the azocine **9** (2.72 g, 8.88 mmol) in CH_2Cl_2 (30 mL) was added dropwise to a 0° C soltuion of the ynone **10** (2.60 g, 9.3 mmol) in CH_2Cl_2 (50 mL). After addition the mixture was allowed to warm to room temperature with stirring over 4 hours. Removal of volatiles under reduced pressure and purification of the residue by flash chromatography (50% EtOAc/petroleum ether) afforded the vinylogous amide **11** as a thick light yellow syrup (5.12 g, 99%).

^{1}H NMR (500 MHz, $CDCl_3$, * denotes minor rotamer signals): δ 7.45,7.61* (bs, 1H); 5,76 (bs, 1H); 5.51 (bs, 1H); 5.31-5.37 (m, 2H); 5.23 (bs, 1H); 5.09 (brd, J = 12.2 Hz, 1H); 4.10, *4.23 (m, 1H); 3.72 (bs, 2H); 3.60 (t, J = 6.5 Hz, 2H); 3.40-3.45 (m, 1H); 3.17-3.28 (m, 2H); 2.30 (m, 2H); 2.20 (bs, 3H); 1.89-2.10 (m, 7H); 1.74 (bs, 1H); 1.59-1.66 (m, 2H); 1.51-1.57 (m, 3H); 1.39 (s, 9H); 1.23-1.47 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.8; 154.8; 150.9(br); 134.1; 131.1(br); 130.0; 129.7; 127.6(br); 124.5(br); 96.7; 79.6; 63.6(br); 62.7; 62.6; 46.1(br); 45.6; 40.7(br); 39.2; 32.3; 28.4; 27.0; 26.9; 26.8; 25.7; 25.6; 25.0; 23.6. IR (thin film, cm^{-1}): 3413; 1695; 1555. HRMS calculated for $C_{30}H_{48}N_2O_4$ (M + H): 501.3692, found: 501.3684. [α] +51.6° (c=0.88, $CHCl_3$).

Ketone 16:

The vinylogous amide **11** (3.40 g, 6.79 mmol) was irradiated with a Hanovia 450W medium pressure mercury lamp in dry degassed CH_3CN (500 mL) in a 500 mL Pyrex photoreactor with a constant purge of argon and with water cooling (15° C) until the starting material was consumed (~6 hours). The solvent was then evaporated and the aminal was redissolved in CH_3CN (500 mL). Pyridine (1.65 mL, 20.4 mmol) was added followed by acetic acid (0.82 mL, 14.3 mmol) and the resulting solution was heated to reflux under argon for 4 hours. The solvent was evaporated and then toluene (100 mL) was added and evaporated (2 x) to remove residual pyridine and acetic acid. Purification by flash chromatography (20% EtOAc/petroleum ether) provided the tetracycle **16** as a yellow oil (678 mg, 20%).

^1H NMR (500 MHz, $CDCl_3$, * denotes minor rotamer signals): δ 5.83-5.89 (m, 1H); 5.25-5.50 (m, 3H); 4.17 (bs, 1H); 3.96*, 3.75 (bs, 1H); 3.59-3.66 (m, 3H); 2.85-2.93 (m, 1H); 2.72-2.77 (m, 1H); 2.58-2.67 (m, 1H); 2.42-2.48 (m, 2H); 2.29-2.40 (m, 2H); 2.06-2.25 (m, 3H); 1.68-2.05 (m, 9H); 1.50-1.65 (m, 4H); 1.43 (s, 9H); 1.36-1.46 (m, 4H); 1.21-1.33 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, * denotes minor rotamer signals): δ 214.4; 154.7; 133.3(br); *131.2; 130.7; *129.5; 128.8; 128.7; 104.5; 79.9(br); 68.5(br); 62.8; *62.6; 55.5; 52.5(br); *48.5; 47.9; 45.0; 40.2; 38.2(br); 37.1; 32.4; 32.2; *31.6; 28.4; 27.5; 27.1; 26.9; 26.4; 26.4; 26.3; 26.0; 25.7; 25.5; *24.6; 20.8. IR (thin film, cm^{-1}): 3453; 1694; 1431; 1153. HRMS calculated for $C_{30}H_{48}N_2O_4$ (M + H): 501.3692, found: 501.3681. [α] -32.3° (c=1.1, $CHCl_3$).

Silyl ether 17:

To a solution of the alcohol **16** (565 mg, 1.13 mmol) and imidazole (231 mg, 3.39 mmol) in CH_2Cl_2 (8 mL) at 0°C was added TBSCl (238 mg, 1.60 mmol). After stirring for 1 hour the mixture was diluted with ether (30 mL) and washed with water, brine and dried ($MgSO_4$). Purification of the crude product by flash chromatography (40% ether/petroleum ether) afforded **17** as a yellow oil (605 mg, 87%).

^{1}H NMR (500 MHz, $CDCl_3$, * denotes minor rotamer signals): δ 5.88 (bs, 1H); 5.40-5.49 (m, 1H); 5.32-5.38 (m, 1H); 5.26-5.31 (m, 1H); 4.18 (bs, 1H); 3.97,*3.80 (bs, 1H); 3.66 (bd, J = 13.8 Hz, 1H); 3.56 (t, J = 6.5 Hz, 2H); 2.95,*2.85 (bs, 1H); 2.73 (d, J = 13.8 Hz, 1H); 2.66 (m, 1H); 2.43-2.54 (m, 2H); 2.06-2.40 (m, 5H); 1.76-2.04 (m, 10H); 1.56-1.65 (m, 1H); 1.43 (s, 9H); 1.41-1.52 (m, 4H); 1.19-1.39 (m, 4H); 0.86 (s, 9H); 0.01 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 214.1; 154.7; 133.3(br); 130.9; 128.7; 128.6; 79.9(br); 68.6; 63.1; 55.5(br); 52.7(br); 48.5; 47.9; 45.0; 40.2; 37.9(br); 37.1; 32.5; 32.4; 31.6(br); 28.4(br); 27.5; 27.2; 27.0; 26.6; 26.5; 26.0; 25.9; 25.7; 18.3; -5.3. IR (thin film, cm^{-1}): 1695. HRMS calculated for $C_{36}H_{62}N_2O_4Si$ (ESI, M + Na): 637.4377, found: 637.4364. [α] -28.3° (c=1.05, $CHCl_3$).

Ketoester 18: A solution of the ketone **17** (454 mg, 0.74 mmol) in THF (4 mL + 1 mL wash) was added dropwise to a -78°C solution of 1.0 M LHMDS (Aldrich, 0.89 mL, 0.89 mmol) in THF (2 mL). After stirring for 30 minutes at -78°C, HMPA (0.16 mL, 0.89 mmol) was added followed by methyl cyanoformate (0.082 mL, 1.03 mmol) and the resulting mixture was then stirred an additional 30 minutes at -78°C and then poured into cold water (20 mL). The aqueous layer was extracted with ether (3 x 20 mL) and the combined ethereal extracts were dried ($MgSO_4$) and evaporated to give the ketoester **18** as a pale yellow syrup (450 mg, 90%) which was used without further purification.

Esters 19 and 20: The ketoester **18** (450 mg, 0.67 mmol) was dissolved in methanol (10 mL) and was cooled to 0°C. $NaBH_4$ (31 mg, 0.80 mmol) was added and the reaction was stirred at 0°C for 1 hour. Saturated NH_4Cl (20 mL) was added and the mixture was extracted with ether (3 x 20 mL). The combined ethereal extracts were dried ($MgSO_4$) evaporated and the residue chromatographed (30% EtOAc/petroleum ether) to afford the hyroxy ester as a colorless foam (420 mg, 93%).

^{1}H NMR (500 MHz, $CDCl_3$, * denotes minor rotamer signals): δ 5.80-6.06 (m, 1H); 5.26-5.43 (m, 2H); 5.11 (bs, 1H); 4.24-4.28 (m, 1H); 4.16,*4.14 (bs, 1H); 4.01,*3.85 (bs, 1H); 3.71 (s, 3H);

3.56-3.60 (m, 3H); 3.02 (bs, 1H); 2.78 (dd, J = 12.0, 9.0 Hz, 1H); 2.66 (dd, J = 13.0, 2.1 Hz, 1H); 2.61 (bs, 2H); 2.52 (bdd, J = 12.6, 3.5 Hz, 1H); 2.36 (bdd, J = 12.6, 7.8 Hz, 1H); 1.91-2.12 (m, 7H); 1.68-1.88 (m, 2H); 1.46-1.56 (m, 11H); 1.43 (s, 9H); 1.33-1.40 (m, 3H); 1.23-1.30 (m, 2H); 0.87 (s, 9H); 0.03 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.2; 154.6(br); 136.2; 129.3; 128.7; 79.6; 72.7; 69.4; 63.1; 54.5; 51.2; 49.7(br); 48.7; 45.0; 44.8; 43.4; 40.3; 39.6(br); 32.5; 31.5; 30.5; 30.2; 28.4; 28.3; 27.1; 26.1; 26.0; 25.8; 25.7; 24.3; 18.4. IR (thin film, cm^{-1}): 3307; 1743; 1695. HRMS calculated for $C_{38}H_{66}N_2O_6Si$ (ESI, M + H): 675.4768, found: 675.4760. [α] -38.5° (c=0.47, $CHCl_3$).

The hydroxyester (291 mg, 0.43 mmol) and TEA (90 μL, 0.65 mmol) were dissolved in CH_2Cl_2 (5 mL) and cooled to 0°C with stirring. Methanesulfonyl chloride (41 μL, 0.52 mmol) was added dropwise and the mixture was allowed to stir at 0°C for 30 minutes. Ether (25 mL) was added and the resulting mixture was washed with saturated $NaHCO_3$ and the organic layer then dried (MgSO4). Purification of the crude product by chromatography (60% ether/petroleum ether) provided the mesylate as a faint yellow syrup (308 mg, 95%).

^1H NMR (500 MHz, $CDCl_3$, * denotes minor rotamer signals): δ 5.87-5.92 (m, 1H); 5.36-5.42 (m, 1H); 5.23-5.34 (m, 1H); 5.13 (bs, 1H); 4.09 (bs (1H); 4.02,*3.85 (bs, 1H); 3.70 (s, 3H); 3.65-3.74 (m, 1H); 3.58 (t, J = 6.5 Hz, 2H); 3.00 (m, 1H); 2.96 (s, 3H); 2.92-2.96 (m, 1H); 2.67 (bs, 2H); 2.53 (bd, J = 12.0 Hz, 1H); 2.44 (bs, 1H); 2.38 (m, 1H); 1.80-2.21 (m, 9H); 1.70 (bs, 2H); 1.54-1.60 (m, 2H); 1.47-1.53 (m, 3H); 1.42 (s, 9H); 1.33-1.39 (m, 2H); 1.17-1.32 (m, 3H); 0.86 (s, 9H); 0.02 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8; 154.4(br); 133.6; 131.0; 129.8; 128.6; 79.7; *77.2; 77.6; 66.3(br); 63.1; 52.9(br); 52.1; 49.3(br); 47.5; 46.4(br); 44.6; 41.4(br); 38.7; 32.5; 32.4; 32.3; 29.7; 28.9(br); 28.4; 27.7; 27.3; 27.1; 26.0; 25.7; 23.9; 18.3; -5.3. IR (thin film, cm^{-1}): 1741; 1694. HRMS calculated for $C_{39}H_{68}N_2O_8SSi$ (ESI, M + H): 753.4543, found: 753.4565. [α] -38.9 (c=0.44, $CHCl_3$).

To a solution of the above mesylate (300 mg, 0.40 mmol) in benzene (10 mL) was added DBU (0.12 mL, 0.80 mmol) and the mixture was refluxed for 12 hours. After cooling to room temperature the mixture was washed with saturated $NaHCO_3$, brine and the organic layer then dried ($MgSO_4$). Purification of the crude product by flash chromatography (30-50% ether/petroleum ether) afford the conjugated ester **19** (149 mg, 57%) as a yellow oil (mix of C12 epimers) followed by the nonconjugated ester **20** (86 mg, 33%) as a yellow oil.

Nonconjugated ester **20**: ^1H NMR (500 MHz, $CDCl_3$, * denotes minor rotamer/conformer signals): δ 5.82 (ddd, J = 8.1, 8.1, 8.12 Hz, 1H); 5.58,*5.56 (d, J = 3.3 Hz, 1H); 5.27-5.37 (m, 3H); 3.97 (m, 1H); 3.88,*3.83 (bs, 1H); 3.69 (s, 3H); 3.54-3.60 (m, 2H); 3.45 (bs, 1H); 3.18 (m, 1H); 2.91 (bt, J = 12.0 Hz, 1H); 2.81 (m, 1H); 2.69,*2.68 (s, 1H); 2.47 (m, 1H); 2.35 (m, 1H); 2.25 (m, 1H); 2.09-2.17 (m, 4H); 1.94-2.08 (m, 4H); 1.88 (m, 1H); 1.77 (m, 3H); 1.68 (m, 1H); 1.46-1.55 (m, 3H); 1.43 (s, 9H); 1.18-1.40 (m, 5H); 0.87 (s, 9H); 0.02 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.3; 154.8; 138.2(br); 132.2; 130.6; 128.9; 121.6; 79.4; 64.7; 63.1; 55.3(br); 52.1; 49.5(br); 44.2; 40.8; 40.1(br); 39.3(br); 36.7; 33.9; 32.5; 32.3; 29.7; 28.5; 28.0; 27.1; 26.9; 26.0; 25.9; 25.7; 24.8; 18.3; -5.3. IR (thin film, cm^{-1}): 1742; 1694; 1164. HRMS calculated for $C_{38}H_{64}N_2O_5Si$ (ESI, M + H): 657.4663, found: 657.4682. [α] -62.7° (c=0.45, $CHCl_3$).

Selenide 21: To a solution of 2,2,5,5-tetramethylpiperidine (48 μL, 0.283 mmol) in THF (1 mL) at 0°C was added dropwise 1.56 M nBuLi/hexane (0.18 mL, 0.283 mmol). After stirring 15 minutes the solution was cooled to -78°C and a solution of the ester **20** (124 mg, 0.189 mmol) in THF (2 mL + 1 mL wash) was added dropwise over 10 minutes. The mixture was allowed to slowly warm to 0°C and stir for 30 minutes. After recooling to -78°C, a solution of PhSeCl (54 mg, 0.283 mmol) in THF (1 mL) was added dropwise and stirring was then continued for 30 minutes. The reaction was quenched with saturated $NaHCO_3$ (5 mL) and extracted with ether (2 x 10 mL). The combined ethereal extracts were dried ($MgSO_4$) evaporated and the crude product chromatographed (30% ether/petroleum ether) to afford the selenide **21** as a yellow syrup (119 mg, 78%).

^{1}H NMR (500 MHz, $CDCl_3$,* denotes minor rotamer/conformer signals): δ 7.60 (m, 2H); 7.25-7.4 (m, 3H); 5.96,*5.57 (bs, 1H); 5.80,*5.65 (m, 1H); 5.30-5.40,*5.19 (m, 3H); 4.11 (bs, 1H); 3.78 (m, 1H); 3.52-3.66 (m, 4H); 3.18-3.36 (m, 3H); 2.82-3.11 (m, 4H); 2.75 (dd, J = 11.2, 5.7 Hz, 1H); 2.68 (m, 1H); 2.53 (m, 1H); 2.38 (m, 1H); 2.14-2.26 (m, 3H); 1.91-2.12 (m, 3H); 1.71-1.78 (m, 2H); 1.47-1.61 (m, 4H); 1.43 (s, 9H); 1.19-1.39 (m, 5H); 0.87 (s, 9H); 0.03 (s, 9H). IR (thin film, cm^{-1}): 1724; 1695; 1434; 1365. HRMS calculated for $C_{44}H_{68}N_2O_5SeSi$ (ESI, M + H): 813.4141, found: 813.4165. [α] -55.4° (c=0.50, $CHCl_3$).

Hydroxyester 22 (via selenoxide): To a solution of the selenide **21** (110 mg, 0.135 mmol) in CH_2Cl_2 (6 mL) at 0°C was added pyridine (33 μL, 0.41 mmol) followed by 15% H_2O_2 (71 μL, 0.297 mmol). After stirring for 30 minutes the reaction was allowed to warm to room temperature with stirring for 1 hour. 10% aq. $NaHSO_3$ (1 mL) was added followed by ether (10 mL). The ethereal layer was then washed with saturated $NaHCO_3$, brine and was then dried ($MgSO_4$). Chromatography of the crude product (30% ether/petroleum ether) provided the tertiary alcohol **22** (44 mg, 48%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$,* denotes minor rotamer signals): δ 6.91 (s, 1H); 6.35 (bs, 1H); 5.90 (m, 1H); 5.26-5.42 (m, 3H); 4.33,*4.03 (bs, 1H); 4.17 (m, 2H); 3.73 (s, 3H); 3.43-3.60 (m, 3H); 2.94 (m, 1H); 2.73 (m, 1H); 2.64 (m, 2H); 2.51 (m, 1H); 2.05-2.25 (m, 4H); 2.02 (m, 2H); 1.81-1.97 (m, 3H); 1.48-1.58 (m, 4H); 1.44 (s, 9H); 1.20-1.41 (m, 5H); 1.11 (m, 2H); 0.87 (s, 9H); 0.02 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.2; 154.7; 145.4; 135.8; 135.4; 130.2; 129.4; 127.0; 79.6; 74.7; 67.5; 63.2; 54.8; 53.3; 51.8; 51.6; 45.9; 45.0; 42.3; 37.4; 32.7; 32.5; 32.3; 30.5; 29.7; 28.5; 28.4; 27.1; 26.0; 25.9; 22.6; 18.4; -5.3. IR (thin film, cm^{-1}): 3395 1713; 1697; 1254. HRMS calculated for $C_{38}H_{64}N_2O_6Si$ (ESI, M + H): 673.4612, found: 673.4607. [α] -28.8° (c=0.65, $CHCl_3$).

Hydroxyester 22 (via epoxide): To a mixture of the nonconjugated ester **20** (96 mg, 0.145 mmol) and solid $NaHCO_3$ (20 mg) in CH_2Cl_2 (2 mL) at 0°C was added dropwise a 0.18 M solution of MCPBA/CH_2Cl_2 (1.71 mL, 0.308 mmol). The mixture was then allowed to slowly warm to 15°C over 3 hours (monitoring disappearance of the starting material N-oxide). The

reaction was then quenched with 10% $NaHSO_3$ (3 mL) and stirred for 10 minutes (to reduce N-oxide). Ether (20 mL) was added and the resulting ethereal layer was washed with saturated $NaHCO_3$ (2 x), dried and evaporated to give the crude epoxide. This material was dissolved in methanol (3 mL) and treated with a catalytic amount of NaOMe (1 drop 25 wt%/methanol) and stirred for 4 hours at room temperature. Saturated $NaHCO_3$ (5 mL) was then added and the resulting mixture was extracted with ether (3 x 10 mL). The combined extracts were dried ($MgSO_4$) evaporated and the crude product chromatographed (30% ether/petroleum ether) to afford the tertiary alcohol **22** (68 mg, 69%) as a pale yellow oil, the spectral data of which was identical to that described above.

Alcohol 23: To a solution of silyl ether **22** (68 mg, 0.10 mmol) in THF (2 mL) was added dropwise 1.0 M TBAF/THF (0.30 mL, 0.30 mmol) and the mixture stirred at room temperature for 3 hours. Saturated NH_4Cl (5 mL) was added and the resulting mixture was extracted with ether (3 x 5 mL). The combined ethereal extracts were dried ($MgSO_4$) evaporated and chromatographed (80% ether/petroleum ether) to afford the alcohol **23** (53 mg, 94%) as a pale yellow oil.

^1H NMR (500 MHz, $CDCl_3$,* denotes minor rotamer signals): δ 6.89 (s, 1H); 6.40 (bs, 1H); 5.89 (m, 1H); 5.32 (m, 2H); 5.23 (m, 1H); 4.29,*4.03 (bs, 1H); 4.16 (m, 2H); 3.72 (s, 3H); 3.60 (m, 2H); 3.45 (m, 1H); 2.95 (s, 1H); 2.52-2.73 (m, 4H); 1.94-2.24 (m, 8H); 1.73-1.91 (m, 3H); 1.48-1.55 (m, 4H); 1.43 (s, 9H); 1.27-1.40 (m, 5H); 1.10 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.1; 154.7; 145.3; 135.6; 129.7; 129.4; 128.4; 125.5; 79.8; 74.3; 67.6; 62.6; 54.7; 53.3; 51.8; 51.4; 45.9; 44.5; 43.0; 42.3; 37.3; 32.6; 32.2; 30.6; 29.7; 28.4; 26.7; 25.5; 25.2; 21.8. IR (thin film, cm^{-1}): 3453; 1713; 1694; 1434. HRMS calculated for $C_{32}H_{50}N_2O_6$ (ESI, M + H): 559.3747, found: 559.3744. [α] -13.3° (c=0.43, $CHCl_3$).

Tosylate 24: To a solution of the primary alcohol **23** (34 mg, 0.061 mmol) and TEA (26 μL, 0.18 mmol) in CH_2Cl_2 (1 mL) was added p-toluenesulfonyl chloride (18 mg, 0.09 mmol) and

mixture was allowed to stir 24 hrs at room temperature. Chromatography of this mixture, eluting with 30% EtOAc/hexanes, afforded the tosylate **24** as a thick oil (42 mg, 96%).

^{1}H NMR (500 MHz, $CDCl_3$,* denotes minor rotamer signals): δ 7.75 (d, J = 8.3 Hz, 2H); 7.31 (d, J = 8.3 Hz, 2H); 6.89 (s, 1H); 6.34 (bs, 1H); 5.88 (m, 1H); 5.19-5.35 (m, 3H); 4.29,*4.04 (bs, 1H); 4.16 (m, 2H); 3.99 (t, J = 7.6 Hz, 2H); 3.72 (s, 3H); 3.45 (m, 1H); 2.92 (s, 1H); 2.50-2.72 (m, 4H); 2.42 (s, 3H); 2.03-2.24 (m, 4H); 1.97 (m, 2H); 1.73-1.88 (m, 3H); 1.52-1.65 (m, 4H); 1.42 (s, 9H); 1.25-1.36 (M, 4H); 1.08 (M, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.1; 154.6; 145.2; 144.6; 135.6; 133.2; 130.1; 129.8; 129.5; 129.1; 128.4; 127.8; 79.6; 74.7; 70.5; 67.4; 54.7; 53.3; 52.3; 51.8; 51.5; 45.9; 44.9; 44.2; 42.9; 42.3; 37.4; 32.6; 31.7; 30.9; 30.2; 29.6; 28.4; 26.5; 25.3; 21.7. IR (thin film, cm^{-1}): 3416; 1711; 1692; 1433; 1176. HRMS calculated for $C_{39}H_{56}N_2O_8S$ (ESI, M + H): 713.3836, found: 713.3841. [α] -26.5° (c=0.26, $CHCl_3$).

Methyl ircinate 25: A solution of the tosylate **24** (27.0 mg, 0.038 mmol) in CH_2Cl_2 (0.5 mL) was treated with TFA (1 mL) and stirred for 1 hour. The volatiles were evaporated to leave the crude TFA salt which was dissolved in CH_3CN (2 mL) and added over 12 hours (syringe pump) through a reflux condenser to a refluxing solution of diisopropylethylamine (3 mL) in CH_3CN (30 mL). After the addition the mixture was allowed to heat at reflux for an additional 8 hours. The mixture was cooled and evaporated, and the residue was taken up in $CHCl_3$ (3 mL) and washed with saturated $NaHCO_3$ (2 mL) dried ($MgSO_4$) and evaporated. Chromatography (25% EtOAc/hexanes) afforded methyl ircinate **25** (2.1 mg, 12%) as a pale yellow film.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.80 (s, 1H); 5.88 (m, 1H); 5.53 (m, 1H); 5.44 (ddd, J = 10.4, 10.4, 4.9 Hz, 1H); 5.18 (ddd, J = 10.4, 8.5, 1.4 Hz, 1H); 4.07 (dd, J = 8.5, 8.5 Hz, 1H); 3.72 (s, 3H); 3.32 (s, 1H); 2.97 (m, 2H); 2.71 (m, 2H); 2.52 (m, 2H); 2.40 (m, 2H); 2.21 (m, 2H); 2.20 (d, J = 12.0 Hz, 1H); 2.11 (m, 1H); 1.99 (m, 1H); 1.86-1.95 (m, 3H); 1.74-1.85 (m, 3H); 1.67 (m, 2H); 1.54 (d, J = 12.0 Hz, 1H); 1.50 (m, 2H); 1.15-1.41 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5; 147.8; 134.6; 132.1; 131.8; 129.6; 128.5; 74.6; 69.7; 68.3; 54.6; 53.4; 51.7; 50.7; 49.5; 46.9; 44.5; 39.1; 37.1; 32.1; 31.7; 28.1; 26.8; 25.9; 25.7; 25.7; 21.3. IR (thin film, cm^{-1}): 3359;

1713; 1248. HRMS calculated for $C_{27}H_{40}N_2O_3$ (ESI, M + H): 441.3117, found: 441.3121. [α] +25° (c=0.45, $CHCl_3$).

Methyl ircinate 25 (via amine 26): The Boc deprotection and cyclization of the corresponding acetylenic compound (40 mg, 0.056 mmol) were carried out as descibed above for **24**. There was obtained after chromatography (25% EtOAc/hexanes) the pentacyclic acetylene (21.9 mg, 89%) as a pale yellow film.

^1H NMR (500 MHz, $CDCl_3$): δ 6.91 (bs, 1H); 6.77 (s, 1H); 5.88 (m, 1H); 5.20 (dd, J = 8.5, 8.5 Hz, 1H); 4.54 (s, 1H); 4.15 (dd, J = 8.5, 8.5 Hz, 1H); 3.72 (s, 3H), 3.32 (dd, J = 13.7, 9.9 Hz, 1H); 3.19 (dd, J = 13.7, 6.5 Hz, 1H); 2.77 (d, J = 11.5 Hz, 1H); 2.70 (d, J = 10.5 Hz, 1H); 2.19-2.44 (m, 6H); 2.11 (m, 2H); 2.00 (m, 1H); 2.01 (d, J = 11.5 Hz, 1H); 1.87-1.94 (m, 4H); 1.78 (m, 1H); 1.49-1.70 (m, 5H); 1.39 (d, J = 13.2 Hz, 1H); 1.00-1.37 (m, 3H); 0.87 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.6; 146.1; 135.2; 130.3; 129.4; 82.2; 82.1; 70.3; 68.1; 64.2; 56.7; 54.9; 54.8; 51.7; 49.6; 46.8; 42.9; 39.2; 37.0; 33.1; 32.1; 29.7; 28.5; 28.2; 25.2; 18.5; 12.0; . IR (thin film, cm^{-1}): 1712; 1435; 1251. HRMS calculated for $C_{27}H_{38}N_2O_3$ (ESI, M + H): 439.2961, found: 439.2948. [α] +45° (c= 1.00, $CHCl_3$).

This acetylene (20.0 mg, 0.046 mmol) and quinoline (20 μL) were stirred in degassed methanol (4 mL) and Lindlar catalyst (5% $Pd/CaCO_3/Pb$, 5 mg) was added. The mixture was then stirred under a balloon of H_2 for 4 hours. The mixture was then degassed with argon and filtered through Celite and evaporated. Chromatography (25% EtOAc/hexanes) afforded methyl ircinate **25** (18.9 mg, 94%), identical in all respects to material described above.

Ircinol A 27: T o a solution of **25** (8.5 mg, 0.020 mmol) in CH_2Cl_2 (2 mL) at -78°C was added 1.0 M DIBAL/CH_2Cl_2 (80 μL, 0.80 mmol) dropwise and the reaction was allowed to slowly warm to -50°C over 2 hours. Methanol (0.5 mL) was then added and the resulting solution was warmed to room temperature and treated with saturated sodium potassium tartrate (3 mL). The resulting mixture was stirred vigorously until the layers were clear (30 minutes). The organic

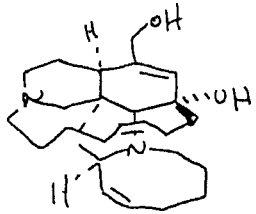
layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 3 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. Chromatography (EtOAc) afforded ircinol A **27** (6.6 mg, 83%) as a colorless film. [α] -18.3° (c=0.30, MeOH). Spectral data were identical to that reported in ref. 8.

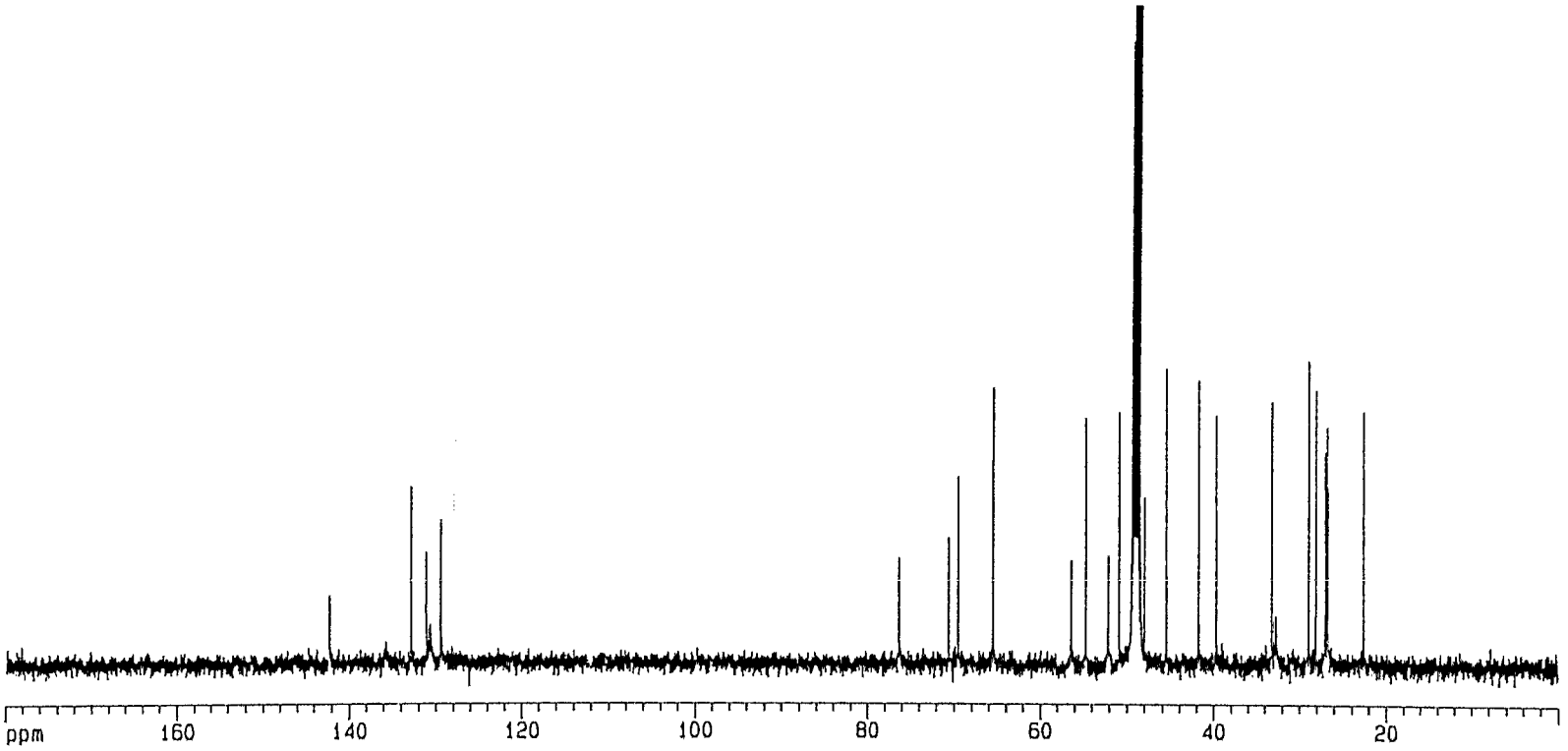
Ircinal A 4: A solution of ircinol A **27** (6.0 mg, 0.015 mmol) in CH_2Cl_2 (2 mL) at 0°C was treated with Dess-Martin periodinane (10 mg, 0.022 mmol) and stirred for 15 minutes. CH_2Cl_2 (5 mL) and 10% $NaHSO_3$ (1 mL) were then added followed by saturated $NaHCO_3$ (5 mL). The layers were shaken and separated and the aqueous layer was extracted with CH_2Cl_2 (2 mL). The combined organic layers were dried ($MgSO_4$) evaporated and chromatographed (15% acetone/hexanes) to give ircinal A **4** (5.3 mg, 90%) as a pale yellow film. [α] +46.2° (c=0.23, $CHCl_3$). Spectral data were identical to that reported in ref. 6.

Manzamine D 28: A solution of ircinal A (4.5 mg, 0.011 mmol) and tryptamine (2.5 mg, 0.015 mmol) in $CHCl_3$ (1 mL) was treated with TFA (10 μL) and powdered 4A molecular sieves (25 mg). After stirring 18 hours the solution was diluted with $CHCl_3$ (3 mL) filtered, washed with saturated $NaHCO_3$ (3 mL), dried ($MgSO_4$) and evaporated. Chromatography (5% MeOH/$CHCl_3$) afforded manzamine D **28** (3.5 mg, 58%) as a white film. Spectral data was identical to that reported in ref. 6.

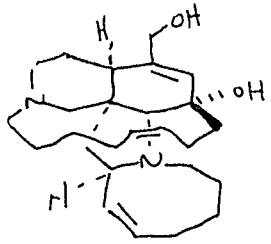
Manzamine A 1: A solution of manzamine D **28** (1.0 mg, 0.002 mmol) in 0.5 mL benzene was treated with DDQ (1.0 mg, 0.004 mmol) and stirred for 1 h. The reaction mixture was diluted with ethyl acetate (2 mL), washed with 0.1 M NaOH (1 mL), water, brine and the organic layers dried. Evaporation and chromatography yielded 0.5 mg manzamine A **1** (50 %) as a white film.

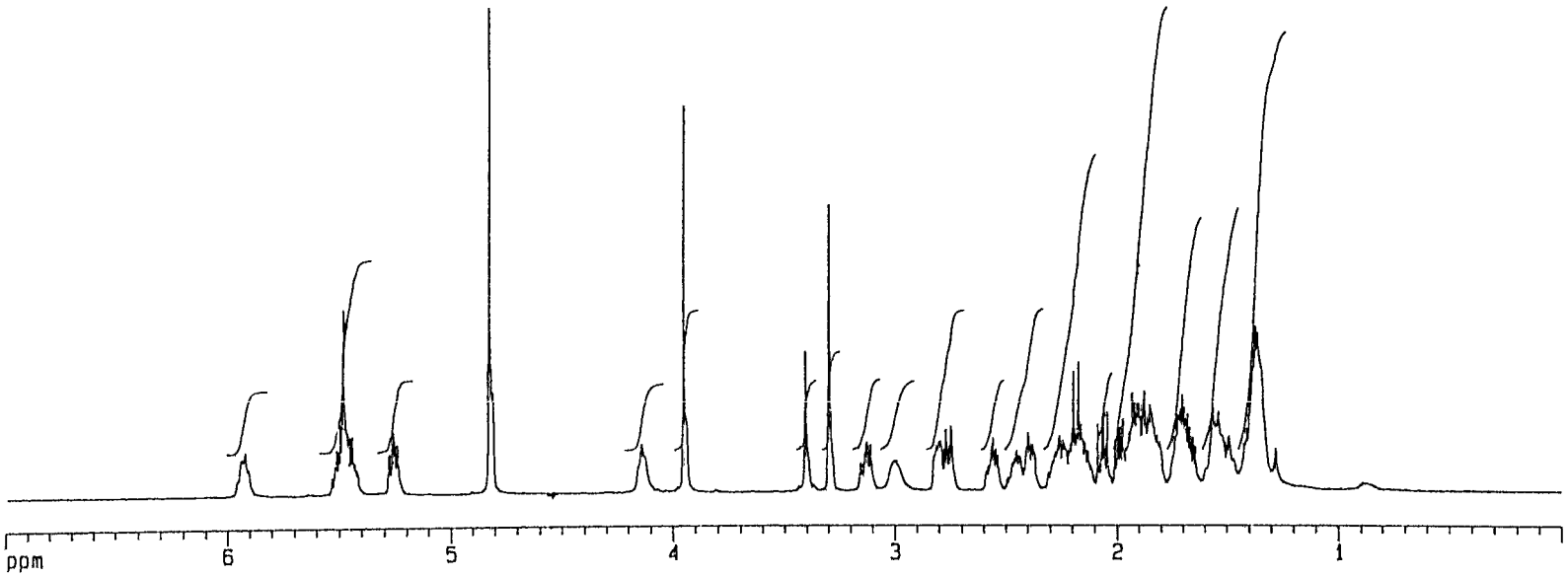
^{13}C NMR (125 MHz, CD_3OD) of IRCINOL A (27)





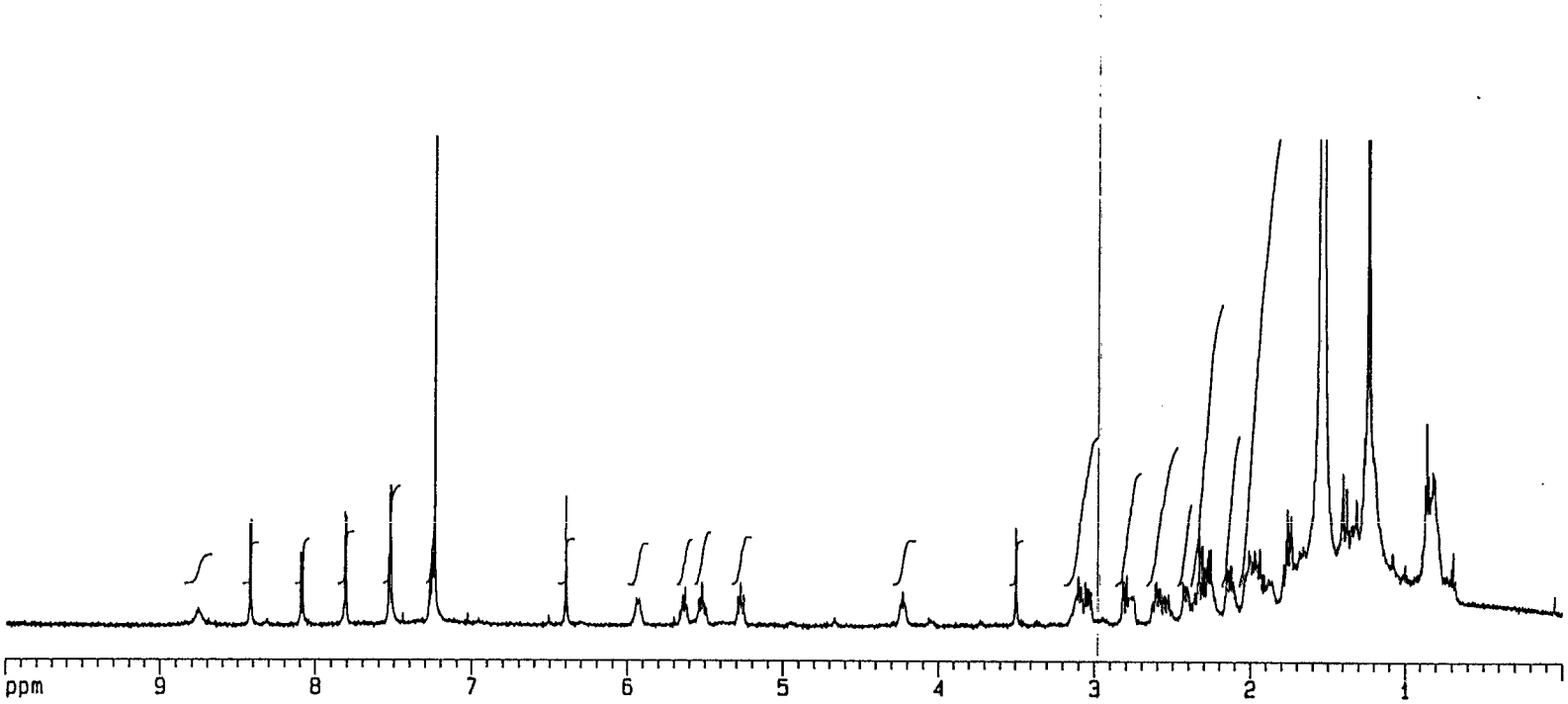
^{1}H NMR (500 MHz, CD_3OD) of IRCINOL A (27)





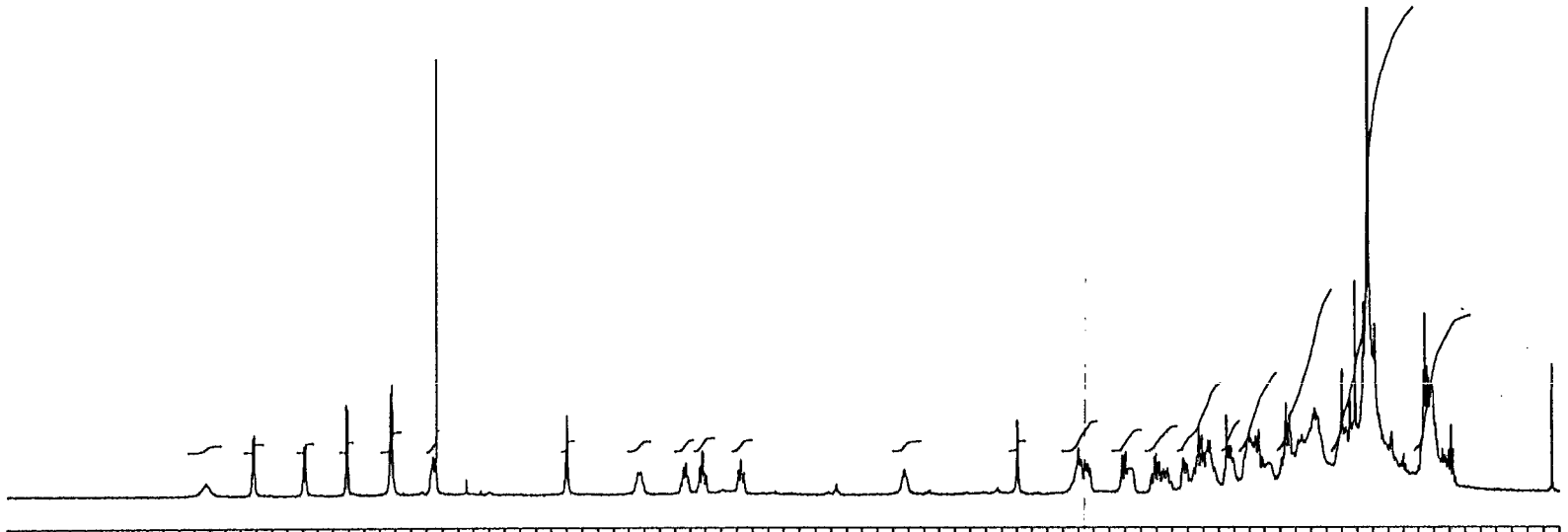
MANZAMINE A

(SYNTHETIC)

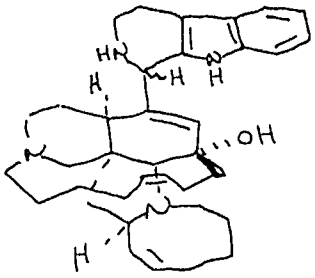


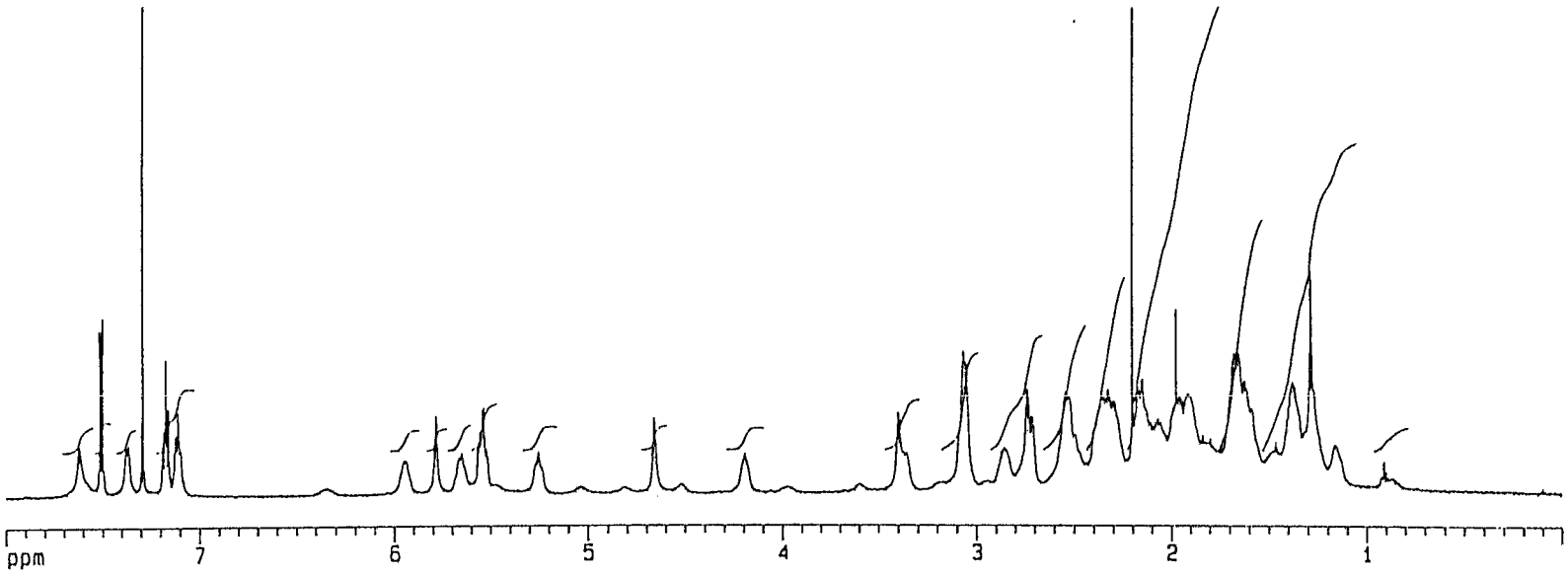
MANZAMINE A

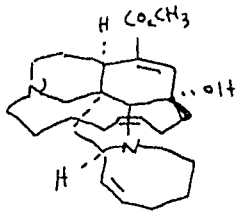
(NATURAL)



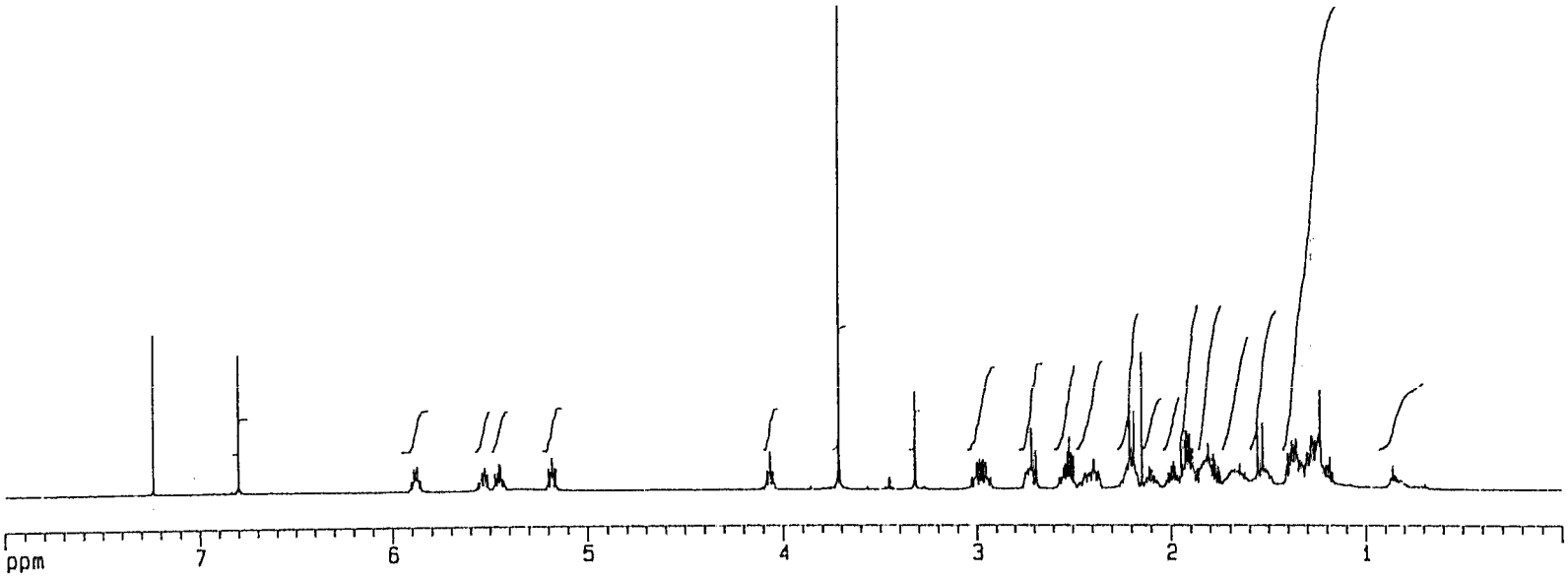
^1H NMR (500 MHz, $CDCl_3$) of Manzamine D (28)



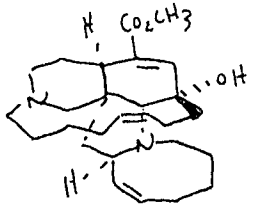


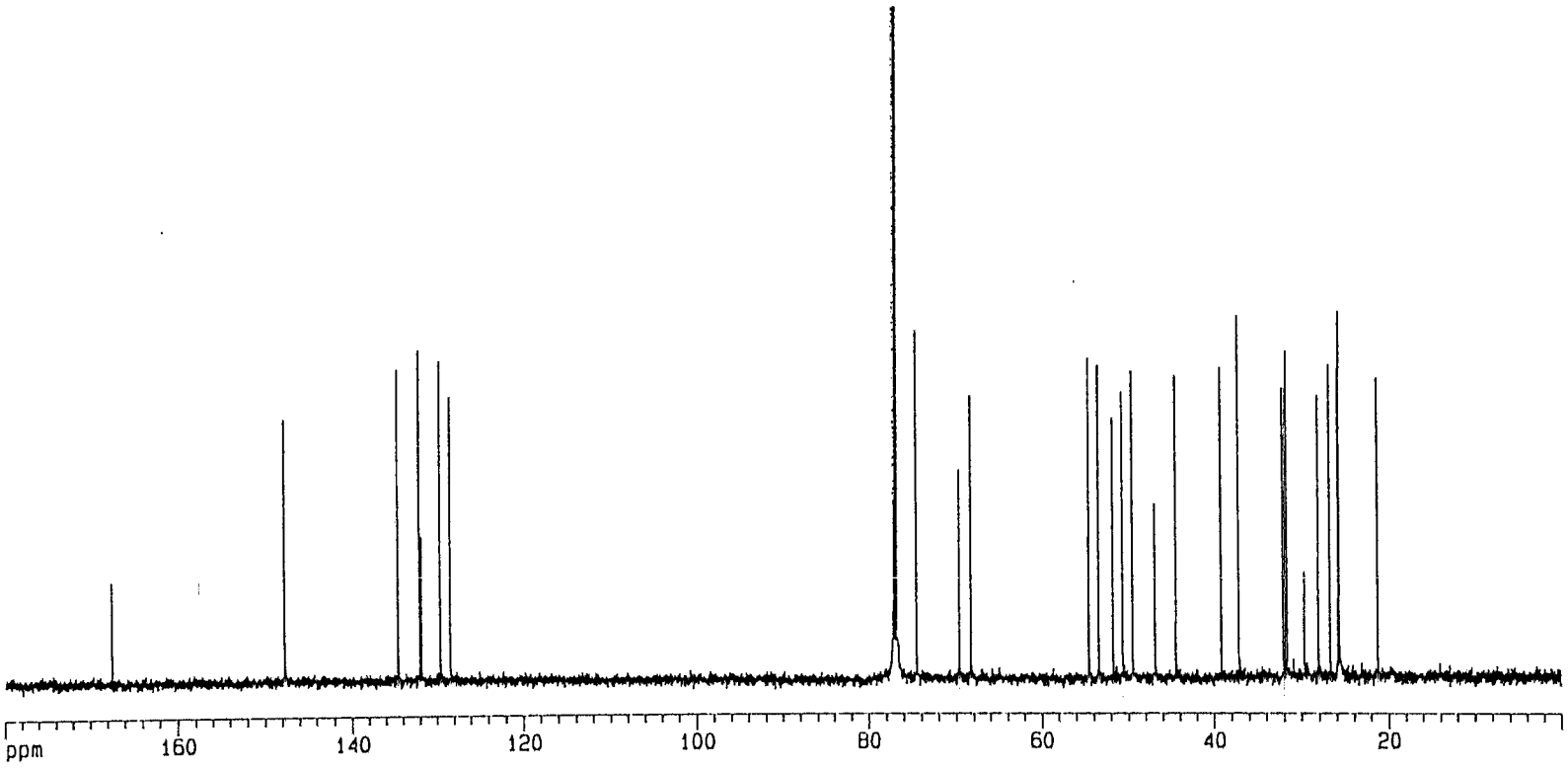


^1H NMR (500 MHz, $CDCl_3$) of compound 25



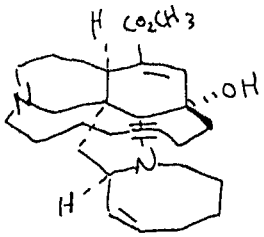
^{13}C NMR (125 MHz, $CDCl_3$) of compound 25

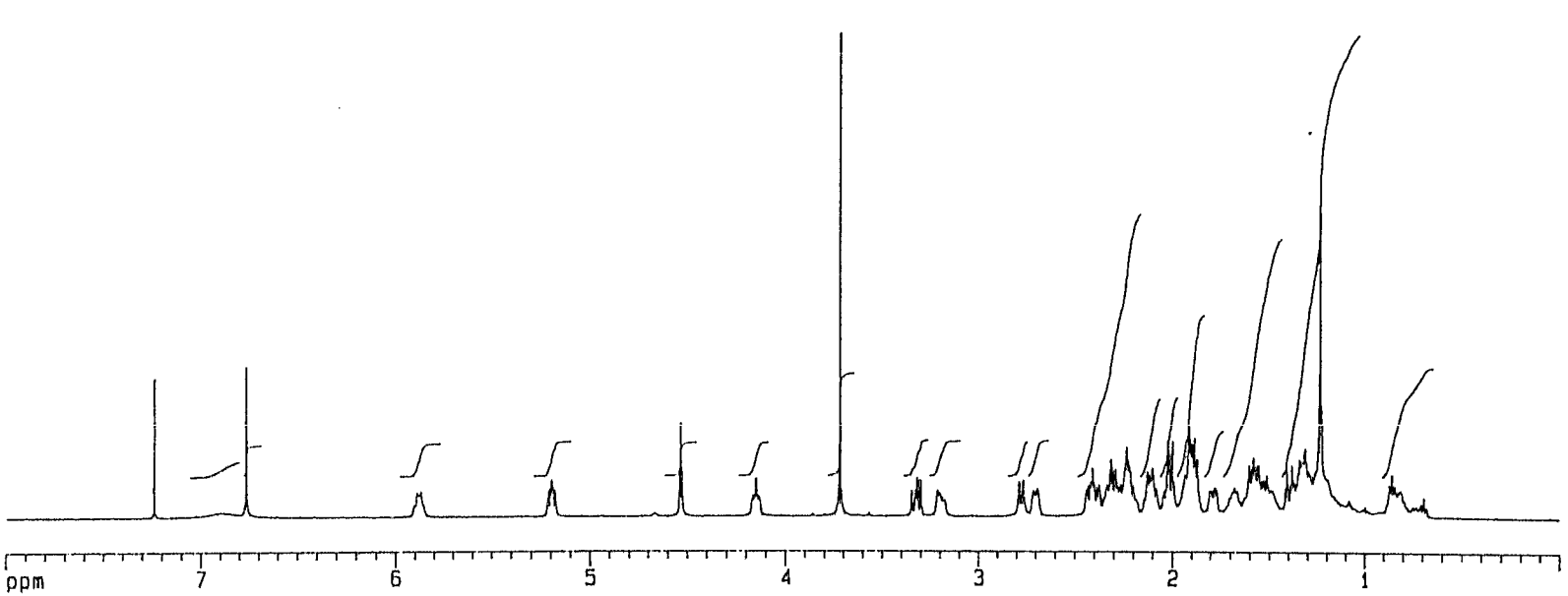




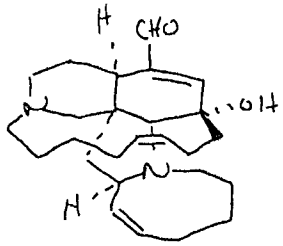
^{13}C NMR (125 MHz, $CDCl_3$)

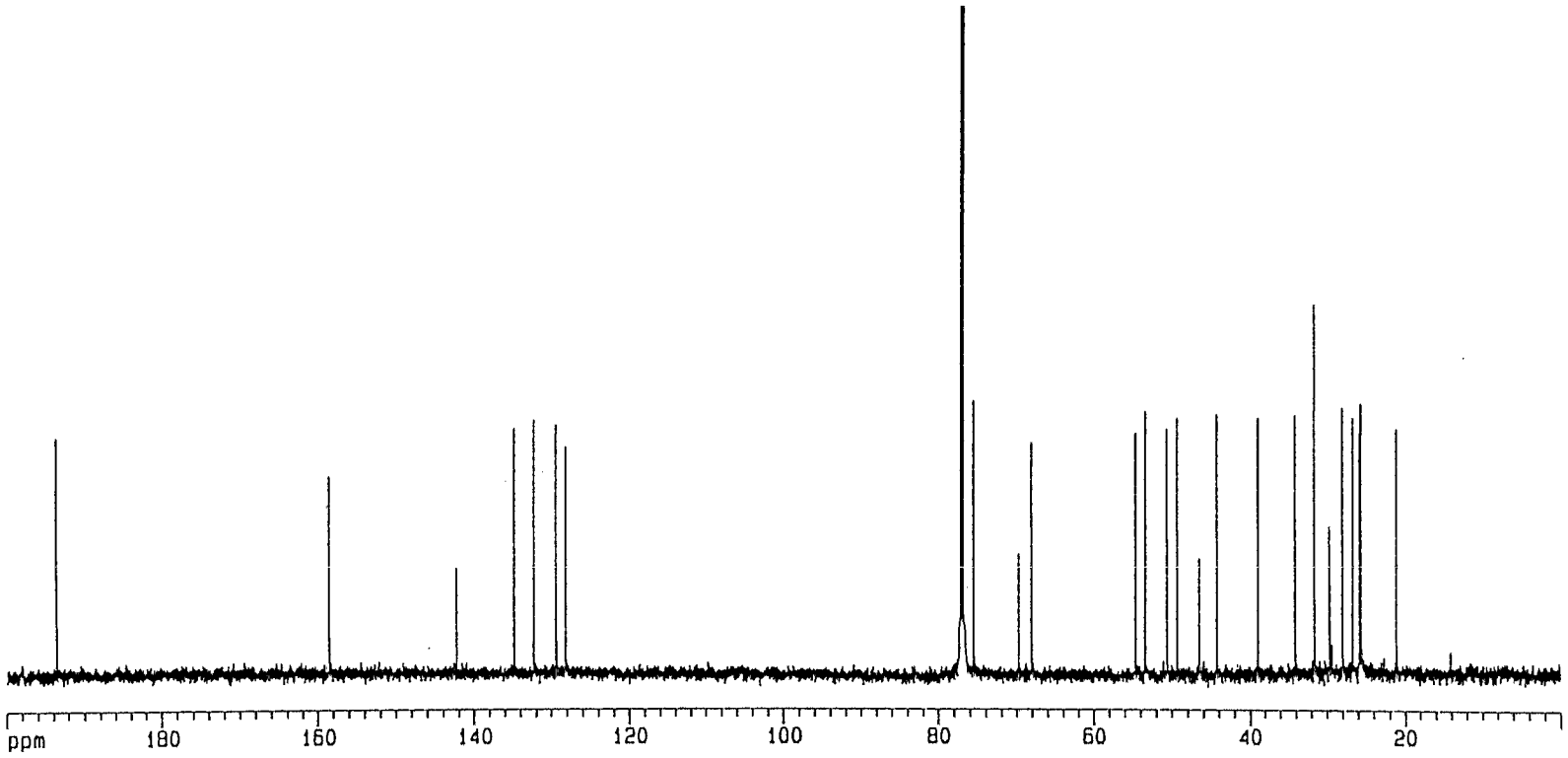
^1H NMR (500 MHz, $CDCl_3$)





^{13}C NMR (125 MHz, $CDCl_3$) of IRCINAL A (4)





^{1}H NMR (500MHz, $CDCl_3$) of IRCINAL A (4)