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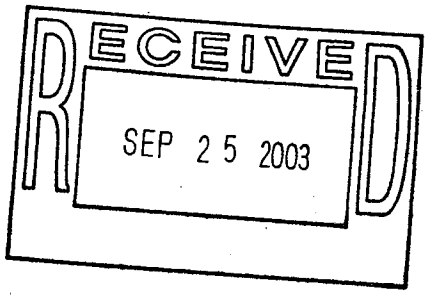

An Intramolecular Formal *Aza*-[3 + 3] Cycloaddition Approach to Indoloquinolizidine Alkaloids. A Concise Stereoselective Total Synthesis of (±)-Tangutorine.

authored by

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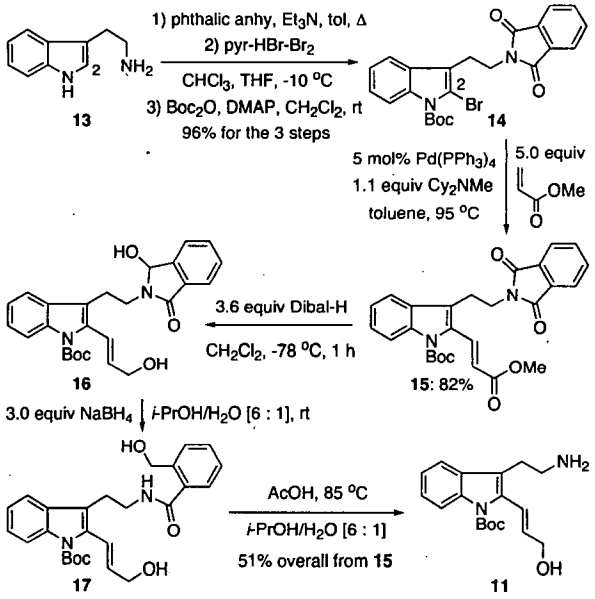


Compound 14

Tryptamine **13** (517 mg, 3.23 mmol) and phthalic anhydride (527 mg, 3.56 mmol) were heated in toluene (20 mL) at reflux for 16 h. Concentration of the reaction under reduced pressure gave the crude product that was used in the next step without further purification. R_f = 0.08 (ethyl acetate:hexane = 1:3); mp 173-174 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.18 (t, 2H, J = 7.7 Hz), 4.03 (t, 2H, J = 7.8 Hz), 7.13 (dd, 1H, J = 1.2, 6.6 Hz), 7.14 (dt, 1H, J = 1.1, 7.4 Hz), 7.21 (dt, 1H, J = 1.3, 7.8 Hz), 7.37 (td, 1H, J = 1.1, 7.8 Hz), 7.72 (dd, 2H, J = 3.0, 5.0 Hz), 7.76 (dd, 1H, J = 0.8, 7.7 Hz), 7.86 (dd, 2H, J = 3.3, 5.0 Hz), 8.04 (brs, 1H, -NH).

The above crude phthaloyltryptamine was dissolved in 10 mL of THF:$CHCl_3$ (1:1). The solution was cooled to –10 °C and treated with pyridinium bromide perbromide (1.16 g, 3.62 mmol). When the reaction was complete as indicated by TLC, the reaction was allowed to warm to rt and 50 mL of CH_2Cl_2 was added. The solution was washed with sat aq $Na_2S_2O_3$ and the aqueous washes were extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, concentrated under reduced pressure, and the crude product was used in the next step without further purification. R_f = 0.27 (ethyl acetate:hexane = 1:3); mp 180-181 °C ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.12 (t, 2H, J = 7.4 Hz), 3.96 (t, 2H, J = 7.4 Hz), 7.10 (dt, 1H, J = 1.3, 7.4 Hz), 7.16 (dt, 1H, J = 1.5, 7.5 Hz), 7.28 (d, 1H, J = 7.8 Hz), 7.64 (d, 1H, J = 8.1 Hz), 7.71 (dd, 2H, J = 3.0, 5.0 Hz), 7.83 (dd, 2H, J = 3.0, 5.0 Hz), 8.01 (brs, 1H, -NH).

The above crude bromide and DMAP (79 mg, 0.65 mmol) were dissolved in 15 mL CH_2Cl_2 and Boc_2O (1.76 g, 8.08 mmol) was added. The reaction was stirred at rt until the reaction was complete as indicated by TLC. The mixture was concentrated under reduced pressure and the crude product was purified by silica gel flash column chromatography (gradient eluent: ethyl acetate:hexane, 1:10-1:5) to afford **14** (1.45g, 96% from **13**) as a colorless solid. R_f = 0.37 (ethyl acetate:hexane = 1:3); mp 118-120 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.69 (s, 9H), 3.13 (t, 2H, J = 7.5 Hz), 3.94 (t, 2H, J = 7.5 Hz), 7.22 (dt, 1H, J = 1.0, 7.8 Hz), 7.27 (dt, 1H, J = 1.5, 7.8 Hz), 7.62 (dd, 1H, J = 1.5, 7.8 Hz), 7.71 (dd, 2H, J = 3.0, 5.5 Hz), 7.84 (dd, 2H, J = 3.0, 5.5 Hz), 8.06 (d, 1H, J = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.5, 28.1, 36.4, 84.8, 109.7, 115.2, 117.9, 119.4, 122.9, 123.1, 124.4, 128.5, 132.0, 133.8, 136.4, 148.9,

168.0; IR (thin film) cm^{-1} 2980m, 2937w, 2362w, 1772m, 1736s, 1713s, 1367s, 1158m, 710m; mass spectrum (LCMS): m/e (% relative intensity) 469 (2) ($M+H^+$), 371 (98), 369 (100), 289 (96).

Compound 15

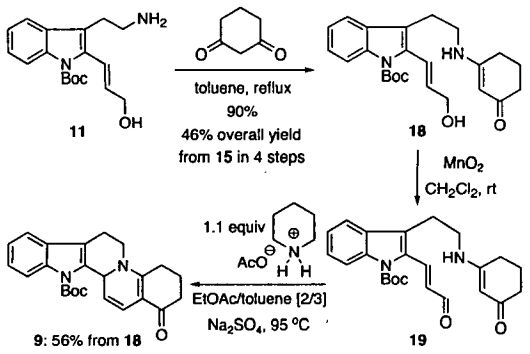
Bromide **14** (1.43 g, 3.06 mmol) and $Pd(PPh_3)_4$ (177 mg, 0.15 mmol) were placed in a 50 mL round-bottomed flask and purged with N_2. Toluene (15 mL) was added and followed by methyl acrylate (1.38 mL, 15.3 mmol) and dicyclohexylmethylamine (0.72 mL, 3.37 mmol). The reaction was heated at 85 °C for 48 h, and then filtered through celite. The solvent was removed under reduced pressure and the crude product was purified by silica gel flash column chromatography (gradient eluent: ethyl acetate:hexane, 1:8-1:4) to afford **15** (1.19g, 82%) as a colorless solid. R_f = 0.25 (ethyl acetate:hexane, 1:3); mp 194-196 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 1.67 (s, 9H), 3.17 (t, 2H, J = 8.3 Hz), 3.86 (s, 3H), 3.94 (t, 2H, J = 8.3 Hz), 6.38 (d, 1H, J = 16.0 Hz), 7.28 (t, 1H, J = 7.8 Hz), 7.36 (t, 1H, J = 7.5 Hz), 7.73 (dd, 2H, J = 3.5, 5.5 Hz), 7.76 (d, 1H, J = 8.0 Hz), 7.86 (dd, 2H, J = 3.0, 5.5 Hz), 8.02 (d, 1H, J = 17.0 Hz), 8.16 (d, 1H, J = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.2, 28.1, 37.6, 51.8, 84.7, 115.6, 119.3, 119.7, 119.9, 123.2, 123.3, 126.0, 129.4, 132.0, 132.2, 134.0, 136.1, 136.5, 150.0, 167.0, 168.1; IR (thin film) cm^{-1} 3649w, 2924m, 2358m, 1770m, 1711s, 1635m, 1457m, 1364s, 1163s, 720m; mass spectrum (LCMS): m/e (% relative intensity) 475 (4) ($M + H^+$), 375 (100).

Compound 16

To a solution of compound **15** (1.00 g, 2.11 mmol) in 20 mL of CH_2Cl_2 at –78 °C was added dropwise DIBAL-H (1 *M* in hexane, 7.60 ml, 7.60 mmol) and stirred at –78 °C for 1 h, at which time methanol (2 mL) was added. The mixture was poured into 30 mL of sat aq potassium sodium tartrate, and 20 mL each of CH_2Cl_2 and H_2O were added. Separation and extraction with CH_2Cl_2, drying of the organic layer (Na_2SO_4), and concentration under reduced pressure led to the crude product **16** as a yellow foam which was used in the next step without further purification. R_f = 0.44 (ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, 1H, J = 8.0 Hz), 7.63 (d, 1H, J = 7.0 Hz), 7.58 (d, 1 H, J = 7.0 Hz), 7.49 (m, 2 H), 7.36 (dd, 1H, J = 6.5, 7.0 Hz), 7.20 (m, 2H), 6.53 (d, 1H, J = 15.5 Hz), 6.06 (dt, 1H, J = 6.5, 15.5 Hz), 5.66 (d, 1H, J = 9.0 Hz), 4.11 (m, 2H), 3.65 (m, 2H), 3.12 (brs, 1H), 3.06 (m, 2H), 1.60 (s, 9H).

Compound 11

The above crude **16** was dissolved in 20 mL *i*-PrOH/H_2O (6:1) and $NaBH_4$ (241 mg, 6.33 mmol) was added in portions. The reaction was stirred at rt for 18 h before AcOH (1.8 mL) was added. Following evolution of gas, the mixture was heated at 80 °C for 10 h. The reaction was then cooled, and the contents were partitioned between 30 mL 10% NH_4OH and 30 mL CH_2Cl_2. Separation and extraction with CH_2Cl_2, drying of the organic layer (Na_2SO_4), and concentration in *vacuo* gave a crude oil [~51% estimated overall crude yield from **15**, consisting of both amino-alcohol **11** and phthalide]. R_f = 0.14 (ethyl acetate). It was difficult to obtain meaningful characterizations for amino-alcohol **11**.



Compound 18

The above crude product **11** was dissolved in 20 mL toluene and 1,3-cyclohexanedione (236 mg, 2.11 mmol) was added. After being heated at reflux for 1 h, TLC indicated complete consumption of the starting material. Removal of the solvent and purification by column chromatography (gradient eluent: ethyl acetate:acetone, 9:1-1:9) gave the vinylogous amide **18** (395 mg, 90% for this step and 46% from **15**) as a red solid. R_f = 0.34 (acetone); mp 68-70 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.70 (s, 9H), 2.01 (t, 2H, J = 6.2 Hz), 2.32-2.41 (m, 4H), 2.54 (t, 1H, J = 6.6 Hz), 3.09-3.14 (m, 2H), 3.34-3.41 (m, 2H), 4.43 (d, 2H, J = 5.1 Hz), 5.24 (brs, 1H), 5.39 (s, 1H), 6.11 (td, 1H, J = 5.1, 16.2 Hz), 6.87 (d, 1H, J = 16.2 Hz), 7.28 (t, 1H, J = 6.9 Hz), 7.35 (t, 1H, J = 7.9 Hz), 7.51 (d, 1H, J = 7.4 Hz), 8.19 (d, 1H, J = 8.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 22.9, 28.2, 29.7, 36.0, 43.1, 62.5, 84.0, 96.9, 115.6, 115.7, 118.0, 121.6, 122.7, 124.5, 129.5, 134.8, 135.3, 135.6, 150.3, 164.9, 198.1; IR (thin film) cm^{-1} 3584br m, 3263m, 3076m, 2939m, 1728s, 1538s, 1456m, 1368m, 2926s, 1141s; mass spectrum (LCMS): m/e (% relative intensity) 411 (47) M+H$^+$, 393 (25), 337 (100), 293 (45); m/e calcd (FAB) for $C_{24}H_{31}N_2O_4$ 411.2284 (M + H$^+$), found 411.2280.

Compound 19

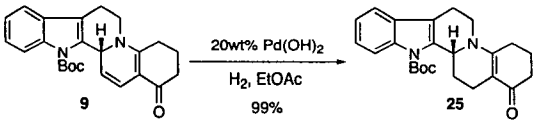
To a solution of vinylogous amide **18** (349 mg, 0.85 mmol) in 10 mL of CH_2Cl_2 was added manganese (IV) oxide (88%, 1.48 g, 1.50 mmol), and the mixture was stirred at rt for 1.5 h (it was monitored by TLC). The reaction mixture was filtered through celite to give the crude enal **19** that was used without further purification. R_f = 0.39 (acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (d, 1H, J = 7.5 Hz), 8.12 (d, 1H, J = 8.5 Hz), 7.99 (d, 1H, J = 16.5 Hz), 7.56 (d, 1H, J = 8.0 Hz), 7.42 (ddd, 1H, J = 1.0, 7.5, 7.5 Hz), 7.31 (dd, 1H, J = 7.5, 7.5 Hz), 6.36 (dd, 1H, J = 7.5, 16.5 Hz), 5.25 (s, 1H), 4.39 (brs, 1H), 3.44 (dt, 2H, J = 1.0, 7.0 Hz), 3.13 (t, 2H, J = 7.0 Hz), 2.35 (t, 2H, J = 6.5 Hz), 2.23 (t, 2H, J = 6.5 Hz), 1.97 (tt, 2H, J = 6.5, 6.5 Hz), 1.70 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 23.9, 28.1, 29.5, 36.4, 42.4, 85.2, 97.0, 115.8, 119.4, 122.4, 123.4, 126.7, 129.4, 129.7, 131.8, 136.7, 143.2, 150.1, 164.1, 193.3, 197.1; IR (neat) cm^{-1} 3264m, 2934m, 1727s, 1684s, 1543s, 1458m, 1143s.

Compound 9

The above enal **19**, Na_2SO_4 (0.86 g), and piperidinium acetate (143 mg, 0.98 mmol) were dissolved in 10 mL of ethyl acetate:toluene (2:3). The reaction mixture was then heated slowly to 95 °C. After stirred at 95 °C for 7 h, the mixture was cooled to rt and filtered through celite. The solvent was removed under reduced pressure and the crude product **9** was used without further purification [~56% estimated crude yield from **18**]. R_f = 0.53 (acetone); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (s, 9H), 2.07 (m, 2H), 2.22-2.51 (m, 2H), 2.67 (dt, 2H, J = 5.2, 5.9 Hz), 2.74-2.92 (m, 2H), 3.26 (m, 1H), 4.24 (dd, 1H, J = 4.2, 12.3 Hz),

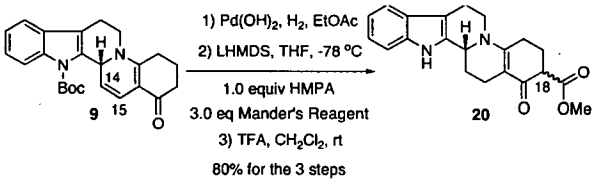
5.27 (dd, 1H, J = 2.1, 9.6 Hz), 5.62 (t, 1H, J = 2.3 Hz), 6.77 (dd, 1H, J = 2.4, 9.6 Hz), 7.27 (dt, 1H, J = 1.2, 7.4 Hz), 7.33 (dt, 1H, J = 1.2, 8.1 Hz), 7.44 (d, 1H, J = 7.2 Hz), 8.19 (d, 1H, J = 8.1 Hz); mass spectrum (LCMS): m/e (% relative intensity) 391 (100) (M + H^+), 291 (42).

NOTE: Pentacycle **9** contains traces amount of impurity, but it can be assigned and fully characterized after being hydrogenated to give **25**.



Compound 25

To a solution of the above crude **9** in 3 mL of EtOAc was added palladium hydroxide (20mol% Pd, <50% water, 130mg, 0.09 mmol, 0.2 equiv). The flask was equipped with a hydrogen balloon. After 6h, the reaction was complete (by TLC). The mixture was filtered through celite and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash column chromatography (gradient eluent: ethyl acetate:hexane, 2:1 - 8:1) to afford **25** (187 mg, 56% purified overall yield from **18**) as a colorless oil. R_f = 0.36 (acetone) or R_f = 0.34 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (dddd, 1H, J = 2.4, 4.8, 13.1, 13.1 Hz), 1.68 (s, 9H), 1.92-2.14 (m, 2H), 2.30-2.44 (m, 3H), 2.55 (dd, 1H, J = 4.8, 5.4 Hz), 2.58 (dd, 1H, J = 2.4, 3.0 Hz), 2.62 (t, 1H, J = 5.4 Hz), 2.66-2.71 (m, 1H), 2.78 (t, 1H, J = 2.7 Hz), 2.80 (t, 1H, J = 2.1 Hz), 3.26 (td, 1H, J = 6.9, 13.8 Hz), 4.20 (td, 1H, J = 3.1, 12.9 Hz), 4.83 (dd, 1H, J = 1.8, 10.5 Hz), 7.27 (dt, 1H, J = 1.1, 7.3 Hz), 7.33 (dt, 1H, J = 1.5, 7.7 Hz), 7.45 (td, 1H, J = 0.8, 7.8 Hz), 8.17 (td, 1H, J = 0.8, 8.4 Hz); ^{13} C NMR (75 MHz, $CDCl_3$) δ 20.6, 21.9, 22.7, 27.6, 28.2, 29.6, 35.6, 43.2, 56.0, 84.4, 107.6, 115.6, 117.0, 118.1, 123.0, 124.7, 128.4, 135.3, 137.1, 150.0, 158.8, 194.6; IR (thin film) cm^{-1} 2977m, 2933m, 1729s, 1613m, 1556s, 1455s, 1436s, 1367s; mass spectrum (LCMS): m/e (% relative intensity) 393 (100) (M+H^+), 293(25); m/e calcd (FAB) for $C_{24}H_{29}N_2O_3$ 393.2178 (M + H^+), found 393.2173.



Compound 20

To a solution of ketone **25** (185 mg, 0.47 mmol) in dry THF (5 mL) at –78 °C was added dropwise LHMDS (1 *M* in THF, 0.71 mL, 0.71 mmol). The solution was stirred at –78 °C for 1 h and then HMPA (0.08 mL, 0.47 mmol) was added dropwise followed by Mander's reagent (0.11 mL, 1.41 mmol). The resulting solution was allowed to warm slowly to rt overnight. The reaction was then diluted with CH_2Cl_2 and washed with H_2O followed with sat aq NaCl. The organic layer was dried (Na_2SO_4), filtered, concentrated under reduced pressure, and the crude product was purified by silica gel flash column chromatography (gradient eluent: ethyl acetate:hexane, 1:1-4:1) to afford the Boc-protected ketoester as a mixture of diasteromers (1.6 : 1.0). R_f = 0.53 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) major isomer: δ 1.20-1.24 (m, 1H), 1.64 (s, 9H), 2.21-2.54 (m, 6H), 2.61-2.93 (m, 4H), 3.15-3.34 (m, 1H),

3.78 (s, 3H), 3.92 (d, 1H, J = 13.2 Hz), 4.85 (t, 1H, J = 10.4 Hz), 7.22 (t, 1H, J = 7.4 Hz), 7.28 (t, 1H, J = 7.4 Hz), 7.40 (d, 1H, J = 7.2 Hz), 8.12 (d, 1H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) major isomer: δ 20.8, 22.7, 25.9, 29.7, 32.6, 42.6, 43.5, 44.2, 52.9, 56.3, 84.5, 109.3, 115.8, 116.7, 118.1, 123.0, 124.7, 128.3, 135.0, 137.0, 150.0, 154.9, 171.7, 193.8; IR (thin film) cm^{-1} 2977brm, 2359brm, 1729s, 1617m, 1556s, 1457s, 1367m; mass spectrum (LCMS): m/e (% relative intensity) 451 (100) ($M+H^+$); m/e calcd (FAB) for $C_{26}H_{31}N_2O_5$ 451.2233 ($M + H^+$), found 451.2233.

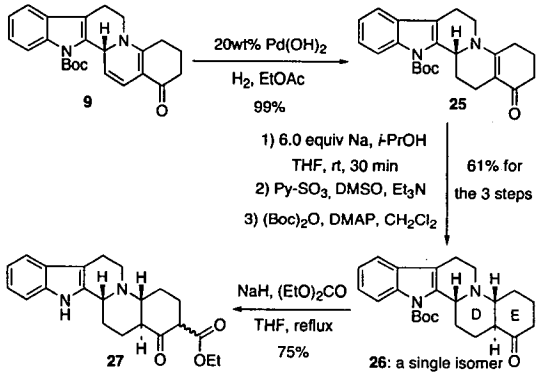
The above Boc-protected ketoester was dissolved in 4 mL of CH_2Cl_2 and 0.5 mL of trifluoroacetic acid was added. The reaction mixture was stirred at rt for 20 h, and then diluted with CH_2Cl_2 and washed with H_2O followed with sat aq NaCl. The organic layer was dried (Na_2SO_4), filtered, concentrated under reduced pressure, and the crude product was purified by silica gel flash column chromatography (gradient eluent: ethyl acetate:hexane, 4:1-10:1) to afford **20** (135mg, 80% from **9** or 82% from **25**) as a mixture of diastereomers (1.6:1.0). R_f = 0.24 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) major isomer: δ 1.25-1.28 (m, 1H), 1.78-1.87 (m, 1H), 2.20-2.32 (m, 1H), 2.34-2.51 (m, 3H), 2.68-2.75 (m, 1H), 2.78-2.91 (m, 3H), 3.26 (ddd, 1H, J = 4.5, 12.0, 14.5 Hz), 3.74 (d, 1H, J = 4.5 Hz), 3.82 (s, 3H), 3.98 (dd, 1H, J = 3.8, 13.5 Hz), 4.62-4.65 (m, 1H), 7.13 (t, 1H, J = 7.5 Hz), 7.20 (t, 1H, J = 7.5 Hz), 7.36 (d, 1H, J = 8.0 Hz), 7.50 (d, 1H, J = 7.5 Hz), 7.89 (brs, 1H, -NH); ^{13} C NMR (125 MHz, $CDCl_3$) major isomer: δ 19.0, 22.4, 26.1, 27.8, 32.5, 42.5, 45.4, 52.8, 54.6, 108.2, 111.1, 116.8, 118.1, 119.7, 122.1, 126.6, 133.4, 136.1, 155.3, 171.7, 193.9; IR (thin film) cm^{-1} 3852m, 3200brm, 2358brm, 1730s, 1539s, 1437m, 733m; mass spectrum (LCMS): m/e (% relative intensity) 351 (100) ($M+H^+$); m/e calcd (FAB) for $C_{21}H_{23}N_2O_3$ 351.1709 ($M+H^+$), found 351.1688.

Compound 21, 22, 23

To a solution of compound **20** (40 mg, 0.11 mmol) in AcOH (1 mL) was added $NaBH_4$ (42 mg, 1.10 mmol) in portions. The reaction mixture was stirred at rt and monitored by TLC and LCMS. After 48h, 10% of the desired hydroxyester **22**, 50% of the over reduced product **21** and 5% of compound **23** (as a mixture of isomers) were obtained (the yields were by LCMS).

Compound 24

To a solution of compound **23** (2mg, 0.006 mmol) in 0.5 mL of dry THF at 0 °C was added lithium aluminum hydride (1 mg, 0.026 mmol). The solution was stirred at 0 °C for 30 min and the reaction mixture was diluted with 2 mL of THF and then a drop of water was added. The solution was dried over Na_2SO_4. Filtration and concentration gave the crude product **24** as a mixture of isomers (characterized by LCMS).



Compound 26

The vinylogous amide **25** (157 mg, 0.4 mmol) was dissolved in a mixture of *i*-PrOH (0.4 mL) and THF (1 mL). The resulting solution was treated with an excess of sodium metal (55.2 mg, 2.4 mmol) and stirred at rt for 30 min. After quenching of the uncharged sodium, the reaction mixture was poured into sat aq NH_4Cl. The resulting mixture was extracted with equal volume of CH_2Cl_2, and the organic layer was washed with sat aq NaCl and dried over Na_2SO_4. Removal of the solvent under reduced pressure produced the crude amino alcohol as an orange oil that was used without further purification.

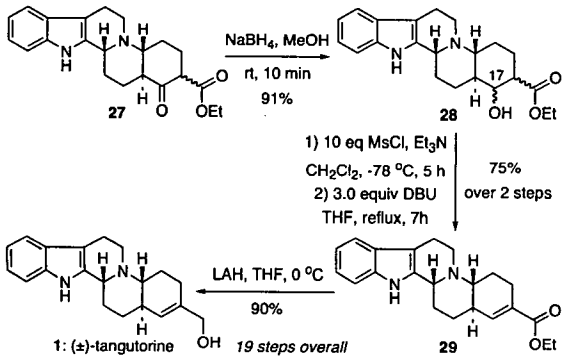
To a solution of the above amino alcohol in CH_2Cl_2 (10 mL) at 0 °C were added anhydrous DMSO (0.31 mL, 4.0 mmol) and anhydrous Et_3N (0.28 mL, 2.0 mmol). SO_3-Pyridine complex (254 mg, 1.6 mmol) was then added in portions. The reaction mixture was stirred at 0 °C for 2 h and its progress was being monitored using TLC. After completion, the reaction mixture was diluted with CH_2Cl_2 and washed with H_2O followed with sat aq NaCl.. The organic layer was dried (Na_2SO_4), filtered, concentrated under reduced pressure. The crude ketone was used in the next step without further purification.

To a solution of the above crude ketone in 10 mL of CH_2Cl_2 were added DMAP (10.0 mg, 0.08 mmol) and Boc_2O (218 mg, 1.0 mmol). The resulting mixture was stirred at rt and monitored by TLC. After completion, the solution was concentrated under reduced pressure to give the crude product that was purified by silica gel flash column chromatography (gradient eluent: ethyl acetate:hexane, 1:4-7:3) to afford **26** (96.0 mg, 61% from **25**) as a colorless oil. R_f = 0.33 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.66 (s, 9H), 1.68 – 1.78 (m, 4H), 2.0 – 2.2 (m, 4H), 2.34 (ddd, 1H, J = 6.0, 13.5, 13.9 Hz), 2.44 (td, 1H, J = 2.0, 13.0 Hz), 2.50 (ddd, 1H, J = 3.5, 10.0, 11.5 Hz), 2.81 (dt, 2H, J = 4.5, 15.5 Hz), 3.02 (ddd, 1H, J = 3.7, 10.8, 11.5 Hz), 3.12 (t, 2H, J = 6.8 Hz), 4.38 (d, 1H, J = 9.0 Hz), 7.22 (dt, 1H, J = 1.5, 7.0 Hz), 7.27 (dt, 1H, J = 1.5, 7.0 Hz), 7.41 (d, 1H, J = 6.5 Hz), 8.08 (d, 1H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.2, 23.5, 24.6, 25.3, 28.4, 30.0, 37.0, 41.6, 48.0, 58.4, 67.2, 83.8, 114.8, 115.9, 117.9, 122.7, 124.0, 129.2, 136.6, 136.8, 150.0, 211.5; IR (thin film) cm^{-1} 2974s, 2938s, 2864m, 2360w, 1727s, 1701s, 1151s; mass spectrum (LCMS): m/e (% relative intensity) 395 (100) (M + H$^+$), 295 (7).

Compound 27

To a solution of compound **26** (78.8 mg, 0.2 mmol) in anhy THF (5 mL) were added NaH (60% dispersion in mineral oil, 16.8 mg, 0.42 mmol) in portions and diethyl carbonate (48 μL, 0.4 mmol). The resulting solution was heated to reflux for 2 h and then cooled to rt. Sat aq $NaHCO_3$ was added and the solution was extracted with equal volume of CH_2Cl_2. The organic layer was washed with sat aq NaCl and dried over Na_2SO_4. Filtration and concentration under reduced pressure afforded the crude product

that was purified by silica gel flash column chromatography (gradient eluent: ethyl acetate:hexane, 1:4-1:1) to afford **27** (54.9 mg, 75%) as a mixture of diasteromers. R_f = 0.63 (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (m, 3H), 1.60 – 1.79 (m, 4H), 2.00 – 2.18 (m, 2H), 2.30 – 2.48 (m, 3H), 2.52 (m, 2H), 2.79 (td, 1H, J = 2.0, 13.0 Hz), 2.94 (m, 1H), 3.37 (brd, 1H, J = 11.0 Hz), 3.46 (dd, 1H, J = 6.0, 13.5 Hz), 3.60 (m, 1H), 4.25 (m, 2H), 7.09 (dt, 1H, J = 1.0, 7.5 Hz), 7.15 (dt, 1H, J = 1.0, 7.5 Hz), 7.31 (d, 1H, J = 8.0 Hz), 7.80 (d, 1H, J = 8.0 Hz), 7.82 (brs, 1H, -NH); ^{13}C NMR (125 MHz, $CDCl_3$) major isomer: δ 14.4, 22.2, 23.3, 26.0, 28.4, 28.8, 46.6, 53.8, 56.5, 59.7, 61.1, 66.9, 108.1, 110.8, 118.2, 119.4, 121.5, 127.2, 134.8, 136.1, 169.8, 205.2; IR (thin film) cm^{-1} 3396brs, 2937brs, 2360w, 1736s, 1710s, 1453s, 1307s, 741m; mass spectrum (LCMS): m/e (% relative intensity) 367 (100) (M + H$^+$).



Compound 28

To a solution of compound **27** (20 mg, 0.055 mmol) in methanol (2 mL) was added $NaBH_4$ (2.5 mg, 0.066 mmol). The reaction mixture was stirred at rt for 10 min, and then 0.5 mL of acetone was added to quench the excess of $NaBH_4$. The solution was concentrated under reduced pressure and the residue was purified by silica gel flash column chromatography (gradient eluent: acetone:hexane, 1:3-1:1) to afford **28** (18 mg, 90%) as a mixture of isomers. R_f = 0.26 (50% acetone/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (t, 3H, J = 7.5 Hz), 1.50 (m, 1H), 1.65 – 1.76 (m, 2H), 1.87 – 1.94 (m, 1H), 1.97 – 2.02 (m, 2H), 2.04 – 2.10 (m, 1H), 2.11 – 2.18 (m, 2H), 2.28 – 2.38 (m, 2H), 2.40 (td, 1H, J = 3.5, 12.5 Hz), 2.47 (m, 1H), 2.52 (dt, 1H, J = 4.0, 10.8 Hz), 2.76 (brd, 1H, J = 13.0 Hz), 2.88 – 2.98 (m, 1H), 3.39 (m, 1H), 3.52 – 3.62 (m, 1H), 4.19 (m, 2H), 7.08 (t, 1H, J = 7.5 Hz), 7.13 (t, 1H, J = 7.5 Hz), 7.30 (d, 1H, J = 7.5 Hz), 7.47 (d, 1H, J = 7.5 Hz), 7.77 (brs, 1H, -NH); ^{13}C NMR (125 MHz, $CDCl_3$) major isomer: δ 14.2, 22.2, 22.3, 27.3, 29.7, 30.0, 45.0, 46.7, 47.1, 60.1, 60.8, 70.4, 73.7, 108.2, 110.7, 118.2, 119.3, 121.3, 127.3, 135.4, 136.1, 175.7; IR (thin film) cm^{-1} 3400brm, 2929brs, 2358m, 1716s,1453m, 1313w, 741m; mass spectrum (LCMS): m/e (% relative intensity) 369 (100) (M + H$^+$), 327 (13).

Compound 29

To a solution of **28** (10.0 mg, 0.027 mmol) in 2 mL of dry CH_2Cl_2 was added Et_3N (66 μL, 0.46 mmol). The mixture was cooled to –78 °C and a solution of MsCl (21 μL, 0.27 mmol) in 1 mL of dry CH_2Cl_2 was added dropwise. The resulting mixture was stirred at –78 °C for 5 h before it was quenched with sat aq $NaHCO_3$. The solution was warmed to rt and extracted with equal volume of CH_2Cl_2. The organic layer was washed with sat aq NaCl and dried over Na_2SO_4. Filtration and concentration afforded the crude mesylate that was used directly without purification.

To a solution of the above mesylate in 2 mL of dry THF was added DBU (12 μL, 0.081 mmol). The reaction solution was heated to reflux for 7 h and then cooled to rt. Sat aq $NaHCO_3$ was added and the solution was extracted with equal volume of CH_2Cl_2. The organic layer was washed with sat aq NaCl and dried over Na_2SO_4. Filtration and concentration afforded a pale yellow solid that was purified by silica gel flash column chromatography (gradient eluent: acetone:hexane, 1:9-1:4) to afford **29** (3.8 mg, 40%) and (eluent: acetone:hexane, 2:3-1:1) to afford the uncharged **28** (4.7 mg, 47%). R_f = 0.45 (50% acetone/hexane); colorless crystals, mp: 202-204 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (t, 3H, J = 7.2 Hz), 1.46 (ddt, 1H, J = 3.8, 12.5, 12.5 Hz), 1.56 (ddt, 1H, J = 6.0, 12.0, 12.0 Hz), 1.83 (ddt, 1H, J = 4.0, 12.0, 12.0 Hz), 2.06 (dd, 1H, J = 3.0, 12.5 Hz), 2.18 (dd, 1H, J = 3.5, 12.3 Hz), 2.22 (dt, 1H, J = 2.0, 11.0 Hz), 2.35 (td, 1H, J = 3.5, 11.5 Hz), 2.41 (dt, 1H, J = 4.0, 10.8 Hz), 2.51-2.65 (m, 2H), 2.80 (brd, 1H, J = 15.0 Hz), 2.94 (dddd, 1H, J = 2.1, 5.2, 10.3, 15.5 Hz), 3.49 (brd, 1H, J = 11.0 Hz), 3.63 (td, 1H, J = 2.8, 8.5 Hz), 4.06 (m, 1H), 4.23 (q, 2H, J = 7.2 Hz), 6.68 (brs, 1H), 7.09 (dt, 1H, J = 1.0, 7.5 Hz), 7.14 (dt, 1H, J = 1.0, 7.5 Hz), 7.31 (d, 1H, J = 8.5 Hz), 7.48 (d, 1H, J = 8.0 Hz), 7.72 (brs, 1H, for –NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 22.1, 25.0, 26.0, 30.0, 31.0, 40.7, 45.7, 60.5, 64.0, 68.2, 108.3, 110.7, 118.2, 119.4, 121.4, 127.3, 129.5, 135.2, 136.1, 141.5, 167.2; IR (thin film) cm^{-1} 3733m, 2925m, 2358w, 1706s, 1650m, 1258s; mass spectrum (LCMS): m/e (% relative intensity) 351 (100) (M + H$^+$), 337 (10), 178 (12).

(±)-Tangutorine: 1

To a solution of **29** (2.40 mg, 0.0069 mmol) in anhy THF (0.5 mL) at 0 °C was added lithium aluminum hydride (1 mg, 0.026 mmol). The solution was stirred at 0 °C for 30 min and the reaction mixture was diluted with 3 mL of THF and then a drop of water. The solution was dried over Na_2SO_4. Filtration and concentration gave the crude product that was purified by silica gel flash column chromatography (gradient eluent: methanol in chloroform, 5%) to afford **1** (1.9 mg, 90%) as colorless crystals. R_f = 0.1(10% methanol/chloroform); mp: 273-275 °C (Lit: 276-278 °C); ^{1}H NMR (500 MHz, 4.8% CD_3OD in $CDCl_3$) δ 1.35 (ddt, 1H, J = 3.9, 12.3, 12.8 Hz), 1.56 (ddt, 1H, J = 5.9, 11.5, 11.8 Hz), 1.77 (ddt, 1H, J = 3.9, 12.0, 12.9 Hz), 1.94 (dd, 1H, J = 2.8, 12.8 Hz), 2.16-2.29 (m, 5H), 2.35 (dd, 1H, J = 6.0, 12.0 Hz), 2.41 (dt, 1H, J = 4.3, 10.8 Hz), 2.79 (brd, 1H, J = 15.0 Hz), 2.92 (dddd, 1H, J = 2.0, 5.5, 10.3, 15.3 Hz), 3.51 (brd, 1H, J = 11.0 Hz), 3.59 (ddd, 1H, J = 3.5, 5.5, 11.0 Hz), 3.97 (d, 1H, J = 13.0 Hz), 4.00 (d, 1H, J = 13.0 Hz), 5.38 (brs, 1H), 7.05 (dt, 1H, J = 1.0, 7.0 Hz), 7.10 (dt, 1H, J = 1.0, 7.0 Hz), 7.29 (d, 1H, J = 7.5 Hz), 7.45 (d, 1H, J = 7.5 Hz), 7.70 (brs, 1H, NH see only when in $CDCl_3$); ^{13}C NMR (125 MHz, 4.8% CD_3OD in $CDCl_3$) δ 21.8, 25.9, 26.2, 29.2, 31.0, 39.0, 45.9, 60.9, 65.2, 65.9, 107.3, 110.9, 118.0, 119.0, 121.1, 125.6, 127.0, 135.2, 136.6, 136.7; IR (thin film) cm^{-1} 3852m, 2957m, 2917s, 2849m, 2358w, 1454m, 1261s, 1088s, 1021s, 800s; mass spectrum (LCMS): m/e (% relative intensity) 309 (100) (M+H+), 291(10); m/e calcd (EI)for $C_{20}H_{25}N_2O$ 309.1961 (M + H$^+$), found 309.1957.

Spectroscopic Comparisons for the Synthetic (±)-Tangutorine.

TABLE 1: ^{1}*H NMR* **[Solvent: 4.8% CD_3OD in $CDCl_3$]**

Reported	Literature	Δ δ
1.39 (m, 1H)	1.35 (ddt, 1H, J = 3.9, 12.3, 12.8 Hz)	- 0.04
1.55 (m, 1H)	1.56 (ddt, 1H, J = 5.9, 11.5, 11.8 Hz)	+ 0.01
1.77 (m, 1H)	1.77 (ddt, 1H, J = 3.0, 12.0, 12.9 Hz)	0.00
1.97 (m, 1H)	1.94 (dd, 1H, J = 2.8, 12.8 Hz)	- 0.03
2.21 (m, 1H)	2.16-2.29 (m, 5H)	- 0.05 to
2.23 (m, 1H)		- 0.03
2.29 (m, 1H)		
2.32 (m, 1H)		
2.37 (m, 1H)	2.35 (dd, 1H, J = 6.0, 12.0 Hz)	- 0.02
2.45 (m, 1H)	2.41 (dt, 1H, J = 4.3, 10.8 Hz)	- 0.04
2.84 (m, 1H)	2.79 (brd, 1H, J = 15.0 Hz)	- 0.05
2.91 (m, 1H)	***See Note Below.***	
2.94 (m, 1H)	2.92 (dddd, 1H, J = 2.0, 5.5, 10.3, 15.3 Hz)	- 0.02
3.54 (d, 1H, J = 11.3 Hz)	3.51 (brd, 1H, J = 11.0 Hz)	- 0.03
3.61 (m, 1H)	3.59 (ddd, 1H, J = 3.5, 5.5, 11.0 Hz)	- 0.02
3.97 (br s, 2H)	3.97 (d, 1H, J = 13.0 Hz)	
	4.00 (d, 1H, J = 13.0 Hz)	
5.41 (br s, 1H)	5.38 (brs, 1H)	- 0.03
7.03 (t, 1H, J = 7.3 Hz)	7.05 (dt, 1H, J = 1.0, 7.0 Hz)	+ 0.02
7.10 (t, 1H, J = 7.3 Hz)	7.10 (dt, 1H, J = 1.0, 7.0 Hz)	0.00
7.33 (t, 1H, J = 8.3 Hz)	7.29 (d, 1H, J = 7.5 Hz)	- 0.04
7.14 (d, 1H, J = 7.8 Hz)	7.45 (d, 1H, J = 7.5 Hz); ***See Note Below.***	+ 0.31

TABLE II: ^{13}C NMR.

Reported	Literature	Δ δ
22.2	21.8	-0.4
26.4	25.9	-0.5
26.6	26.2	-0.4
29.5	29.2	-0.3
31.5	31.0	-0.5
39.6	39.0	-0.6
46.1	45.9	-0.2
61.6	60.9	-0.7
65.8	65.2	-0.6
66.1	65.9	-0.2
107.4	107.3	-0.1
111.5	110.9	-0.6
118.2	118.0	-0.2
119.2	119.0	-0.2
121.4	121.1	-0.3
125.9	125.6	-0.3
127.4	127.0	-0.4
135.8	135.2	-0.6
137.1	136.6	-0.5
137.2	136.7	-0.5

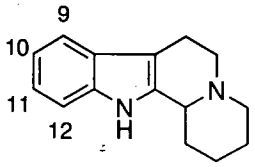
Note: *Carbon NMR resonances of our synthetic sample matched completely with the reported values for all 20 carbons.* However, there appear to be some errors in two of the proton NMR resonances reported in the literature, and they are highlighted in bold in **Table 1**.

First, the reported resonances at 2.91 ppm and 2.94 ppm are both *m* with *1H* assigned for each. However, they cannot be distinguished multiplets given the close proximity of their chemical shifts. In our spectrum, we have a multiplet ranging from 2.89 ppm to 2.95 ppm [centered at 2.92 ppm] with an integration being slightly higher than *1H* but nowhere near *2H*.

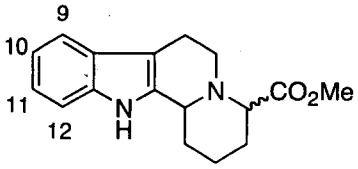
We believe that the resonance at 2.91 ppm may have been mis-assigned in the isolation paper, and there should just be 1H for this multiplet. Intuitively, 2.91 ppm also appears to be too downfield for H19 judging from the resonance of its diastereotopic geminal-H19. This proton should be between 2.15-2.29 ppm since it is unambiguously integrated to *5H* in our spectrum [see both ^{1}H NMR in 4.8% and 5.1% CD_3OD in $CDCl_3$]. There is a water peak near the 2.00-2.19 ppm region due to CD_3OD, and thus, without sufficient resolution, it could have been difficult to judge the integration in a concise manner.

Secondly, authors reported 7.14 ppm for H9 and 7.33 ppm for H12 in the indole ring. While 7.33 ppm could be reasonable for either H9 or H12, 7.14 ppm is unusual given the presence of 7.10 ppm [for H11]. A quick search of literature values for known indoloquinolizidines, it is quite evident that our

values are in excellent agreement with these literature assignments for H9 and H12, which are very consistent for a range of different indoloquinolizidines [see three examples below]. In this case, we believe there is a typo in the isolation paper. Attempts to contact authors regarding this two issues as well as attaining an original natural sample were not successful.

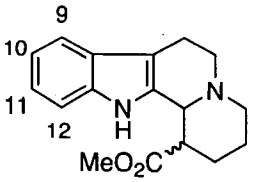


δ ppm [$CDCl_3$]
H_9: 7.47 [d, J = 6.9 Hz, 1H]
H_{12}: 7.32 [d, J = 6.9 Hz, 1H]
H_{11}: 7.13 [dt, J = 1.8, 6.9 Hz, 1H]
H_{10}: 7.08 [dt, J = 1.3, 6.9 Hz, 1H]



δ ppm [$CDCl_3$]
H_9: 7.47 [dd, J = 1.9, 7.5 Hz, 1H]
H_{12}: 7.28 [dd, J = 1.9, 6.8 Hz, 1H]
H_{11}: 7.12 [dt, J = 1.6, 6.8 Hz, 1H]
H_{10}: 7.07 [dt, J = 1.5, 7.7 Hz, 1H]

δ ppm [$CDCl_3$]
NH: 7.77 [brs, 1H]

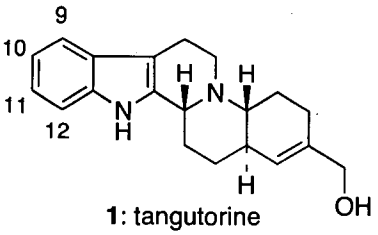


δ ppm [$CDCl_3$]
H_9: 7.47 [d, J = 7.5 Hz, 1H]
H_{12}: 7.27 [d, J = missing Hz, 1H]
H_{11}: 7.13 [dt, J = 1.4, 7.5 Hz, 1H]
H_{10}: 7.06 [dt, J = 1.3, 7.2 Hz, 1H]

δ ppm [$CDCl_3$]
NH: 8.16 [brs, 1H]

Reference: Johansen, J. E.; christie, B. E.; Rapoport, H. *J. Org. cehm.* **1981**, *46*, 4914.

Our Synthetic Sample



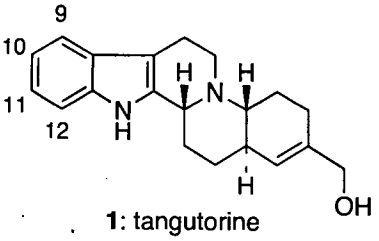
1: tangutorine

δ ppm [$CDCl_3$]
H_9: 7.48 [d, J = 7.5 Hz, 1H]
H_{12}: 7.31 [d, J = 8.0 Hz, 1H]
H_{11}: 7.13 [dt, J = 1.3, 7.5 Hz, 1H]
H_{10}: 7.08 [dt, J = 1.5, 7.2 Hz, 1H]

δ ppm [$CDCl_3$]
NH: 7.70 [brs, 1H]

δ ppm [$CDCl_3$-CD_3OD]
H_9: 7.45 [d, J = 7.5 Hz, 1H]
H_{12}: 7.29 [d, J = 8.0 Hz, 1H]
H_{11}: 7.11 [dt, J = 1.5, 7.5 Hz, 1H]
H_{10}: 7.05 [dt, J = 1.5, 7.5 Hz, 1H]

The Natural Sample



1: tangutorine

δ ppm [$CDCl_3$-CD_3OD]
H_9: 7.33 [d, J = 8.3 Hz, 1H]
H_{12}: 7.14 [d, J = 7.8 Hz, 1H]
H_{11}: 7.10 [t, J = 7.3 Hz, 1H]
H_{10}: 7.03 [t, J = 7.3 Hz, 1H]

SUPPLEMENTARY ^{1}H NMR and SELECTED ^{13}C SPECTRA

for the

communication

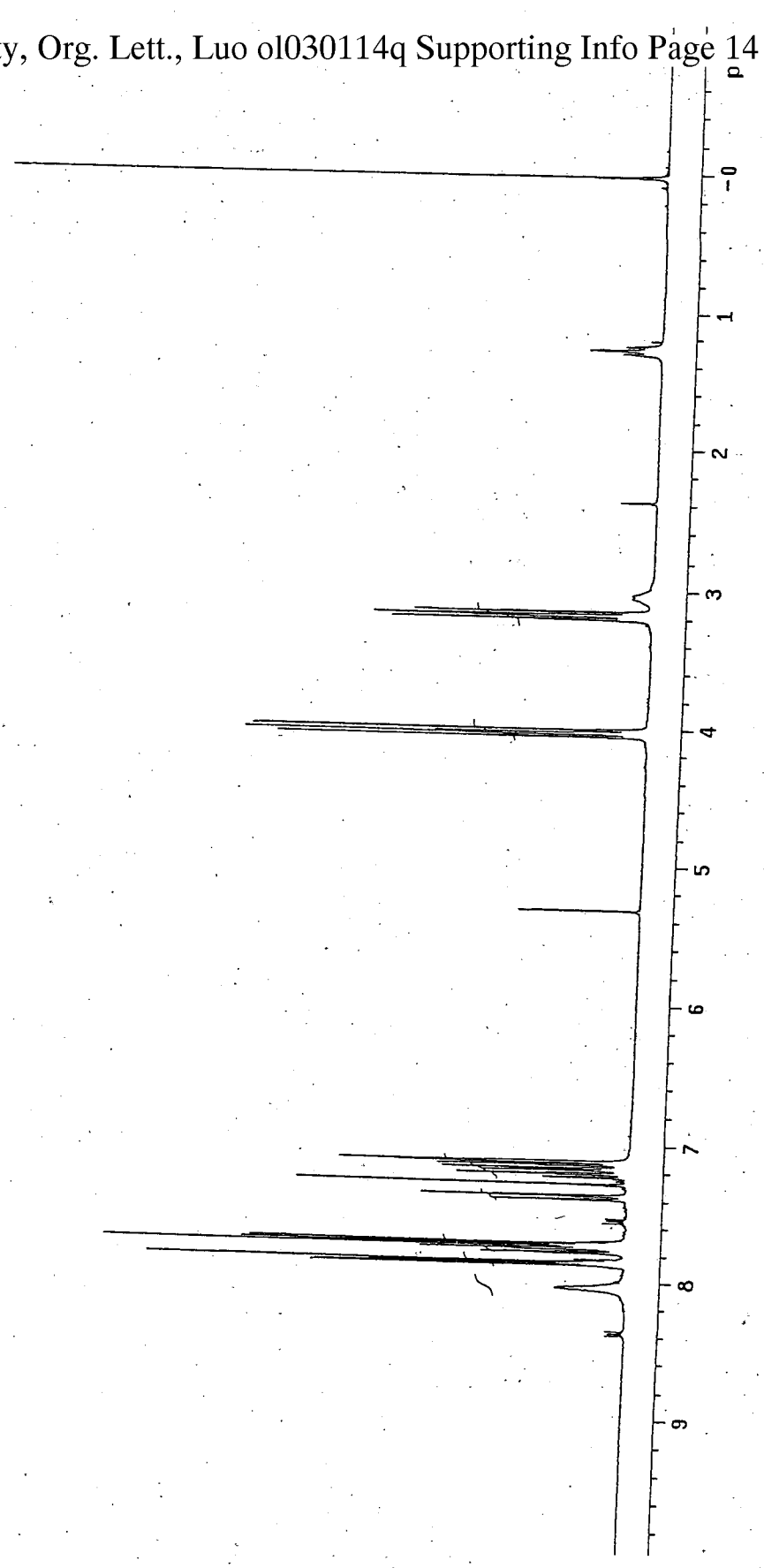
entitled

An Intramolecular Formal *Aza*-[3 + 3] Cycloaddition Approach to Indoloquinolizidine Alkaloids. A Concise Stereoselective Total Synthesis of (±)-Tangutorine.

authored by

Shengjun Luo, Craig A. Zificsak, and Richard P. Hsung*

Department of Chemistry, University of Minnesota, Minneapolis, MN 55455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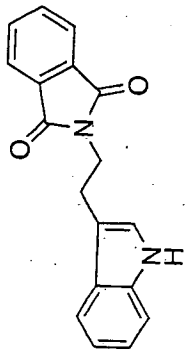
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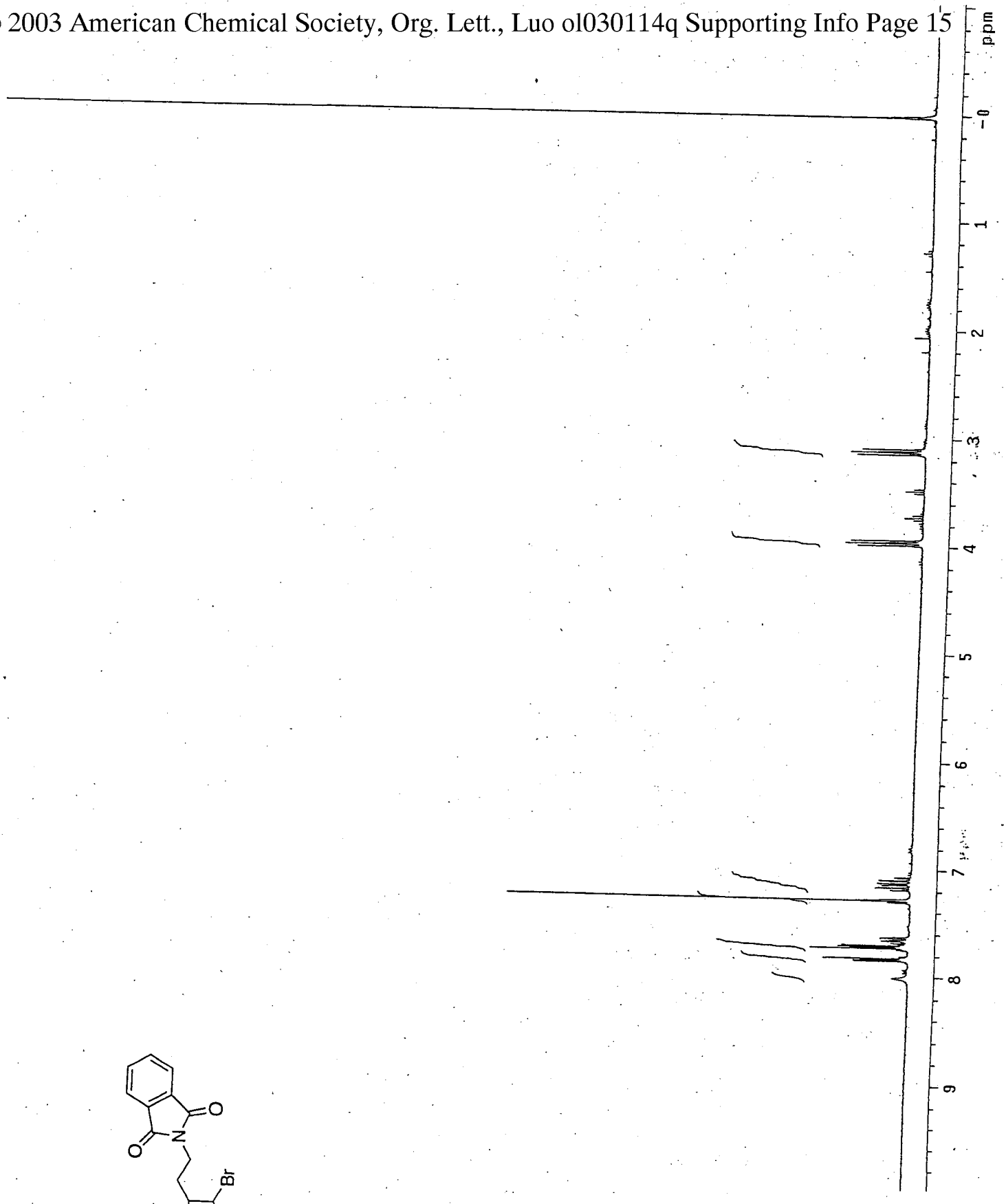
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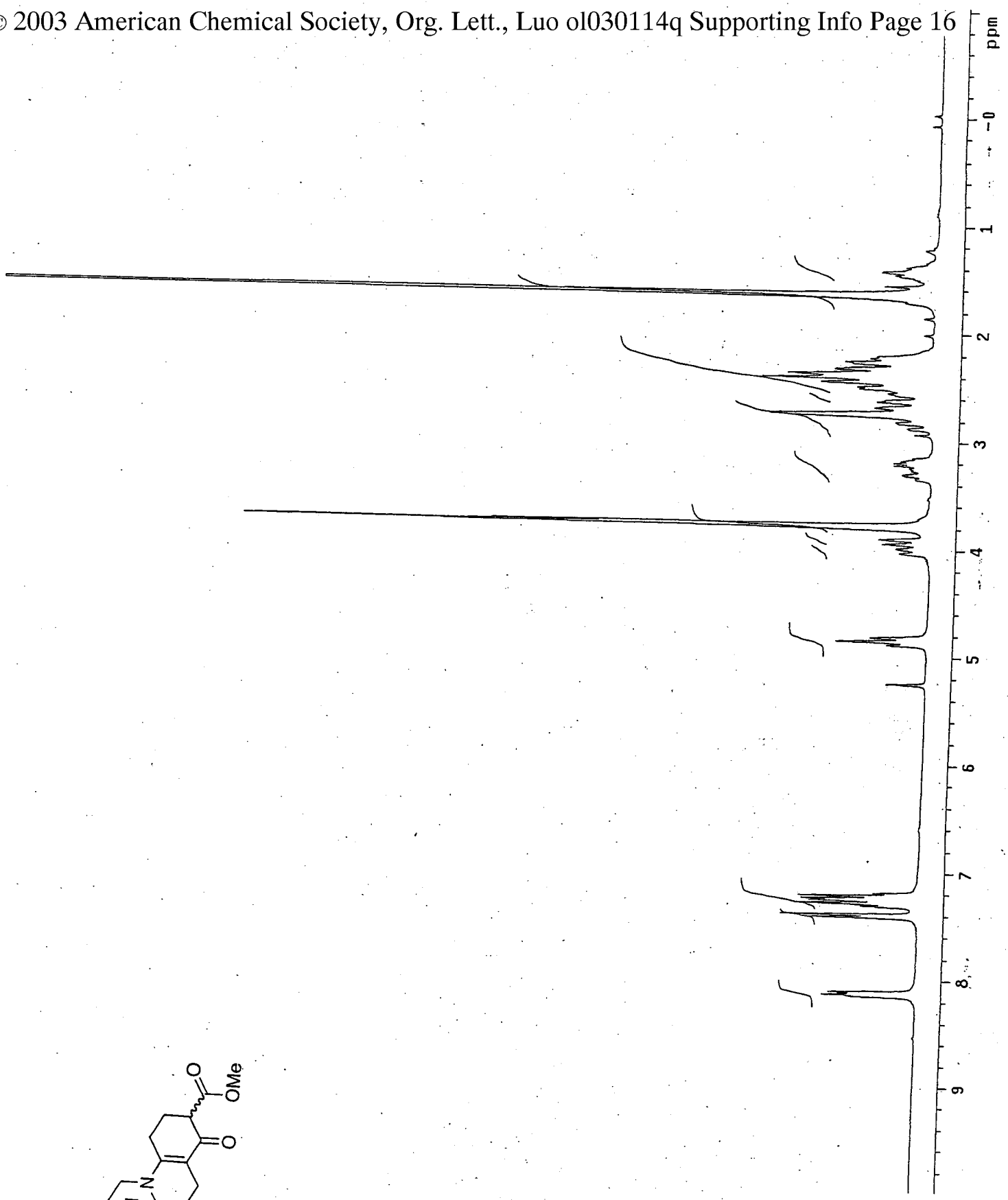
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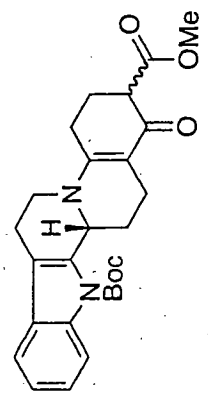
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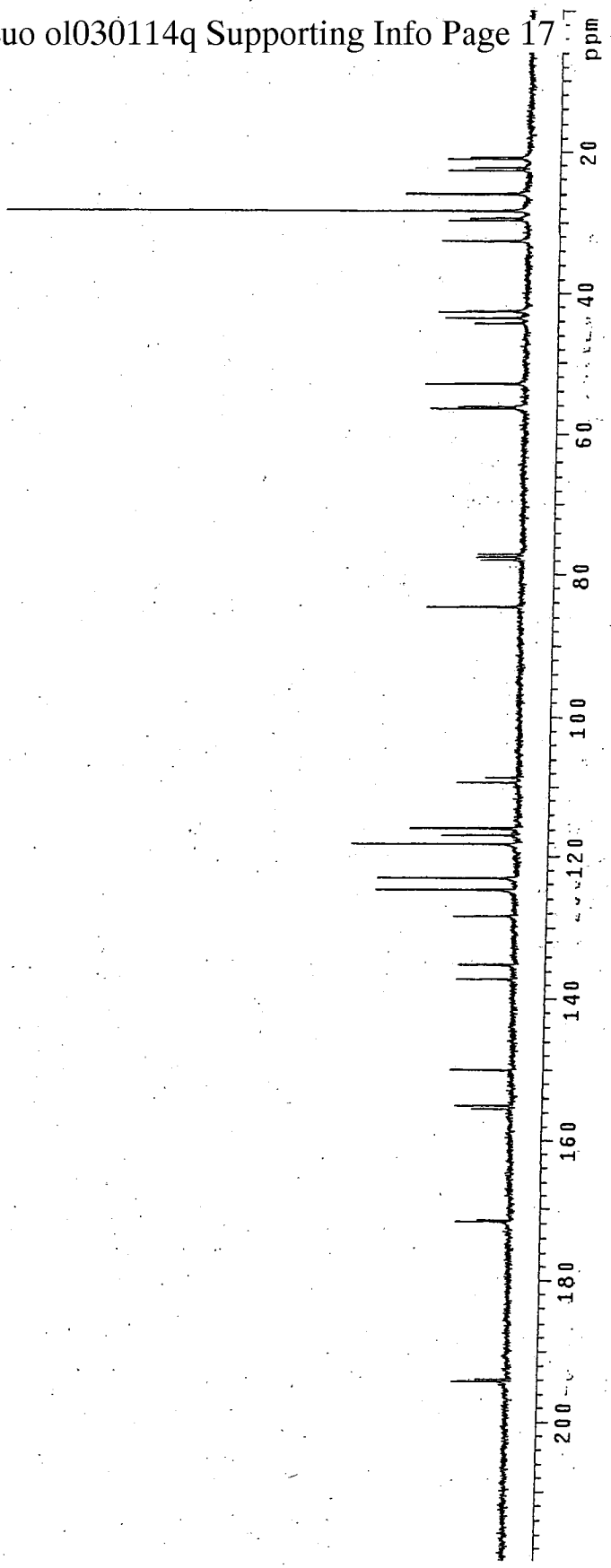
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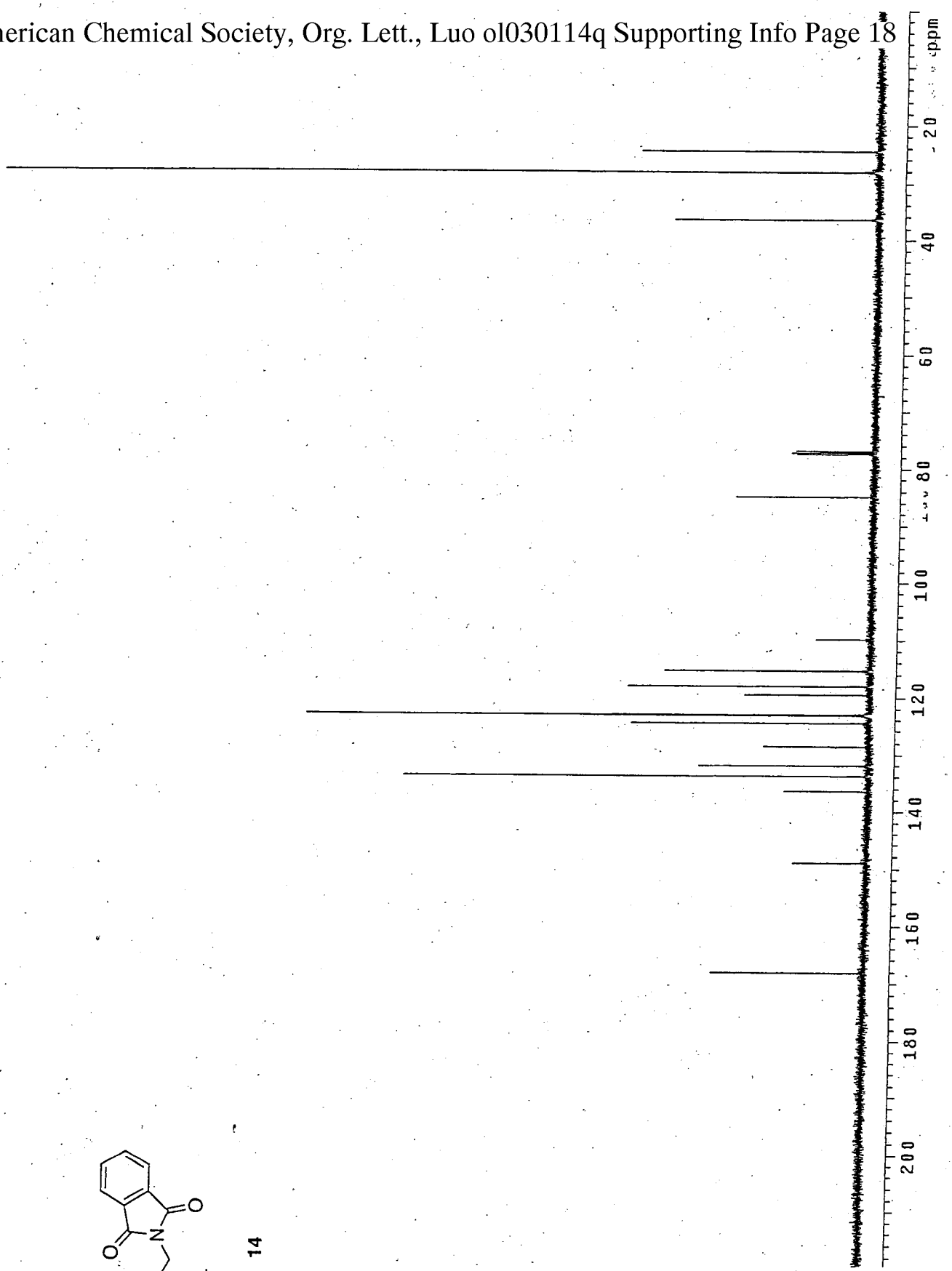

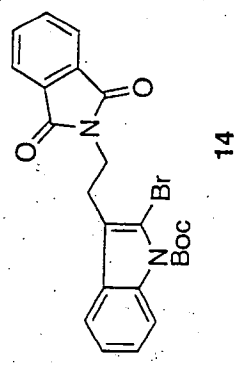

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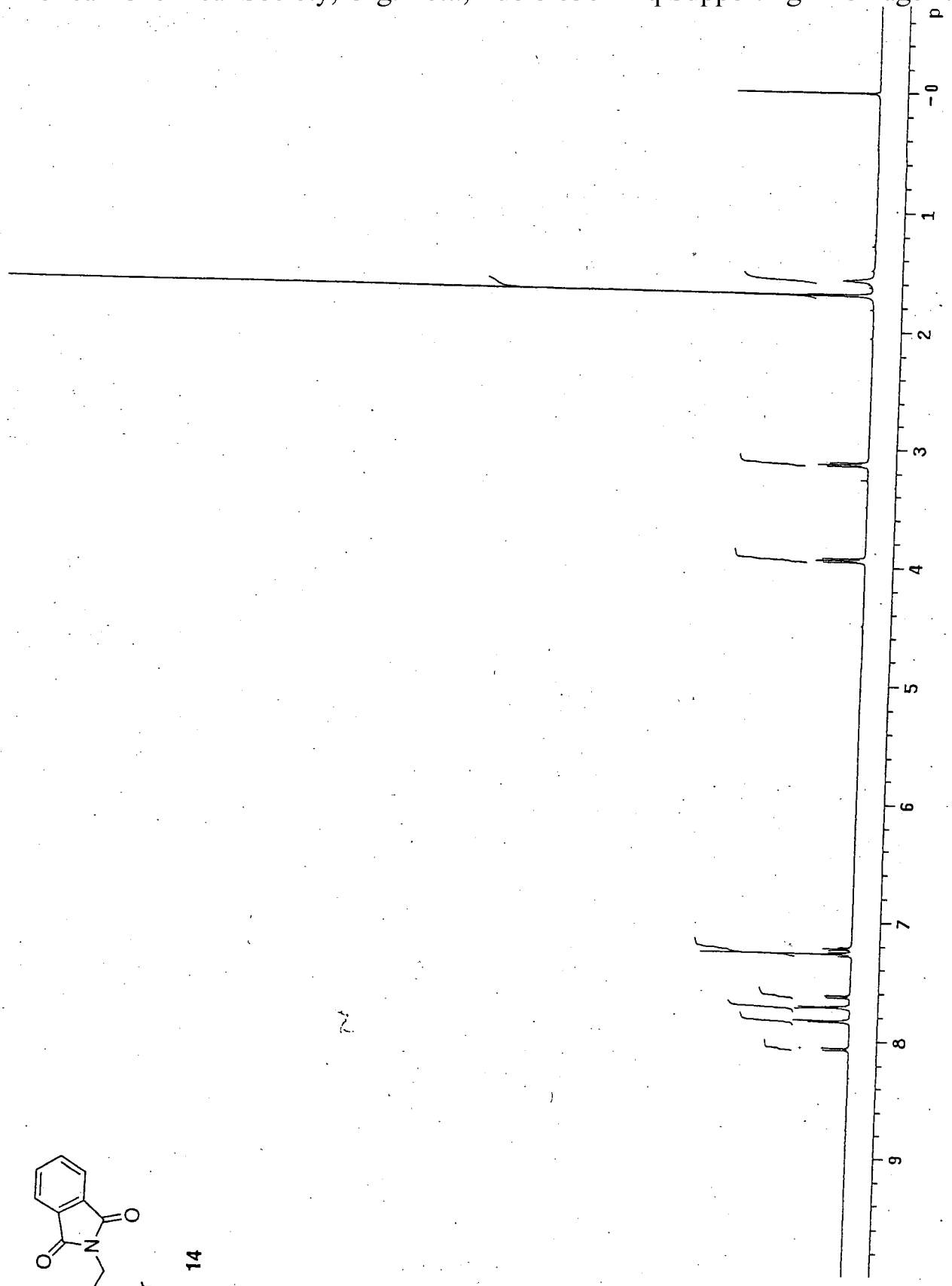

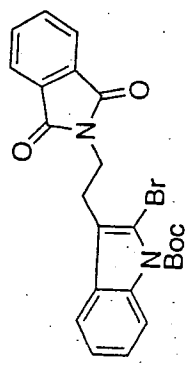

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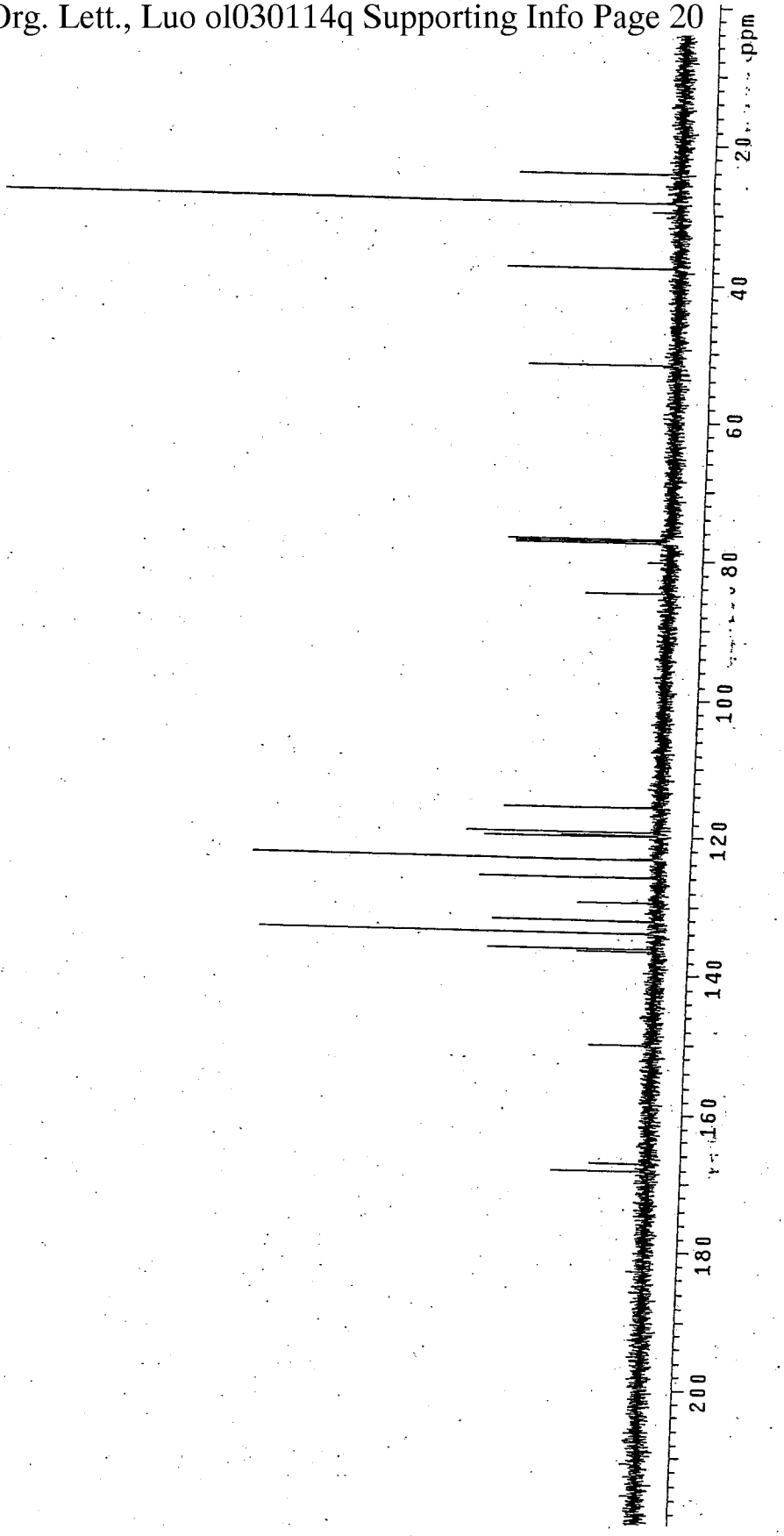

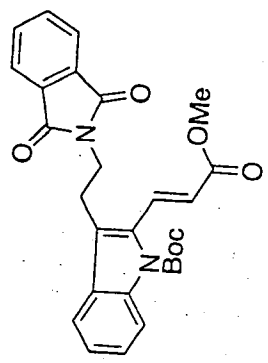

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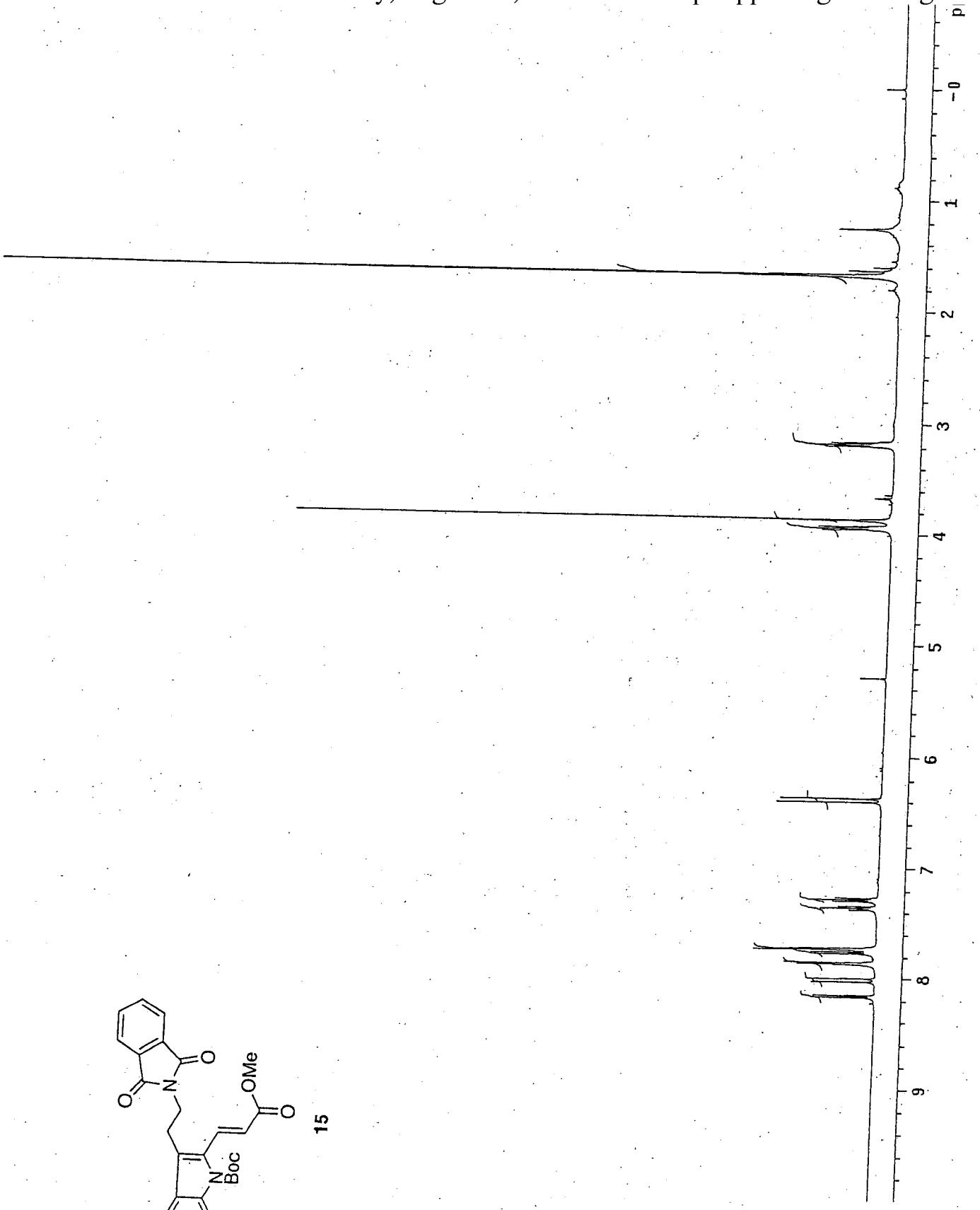

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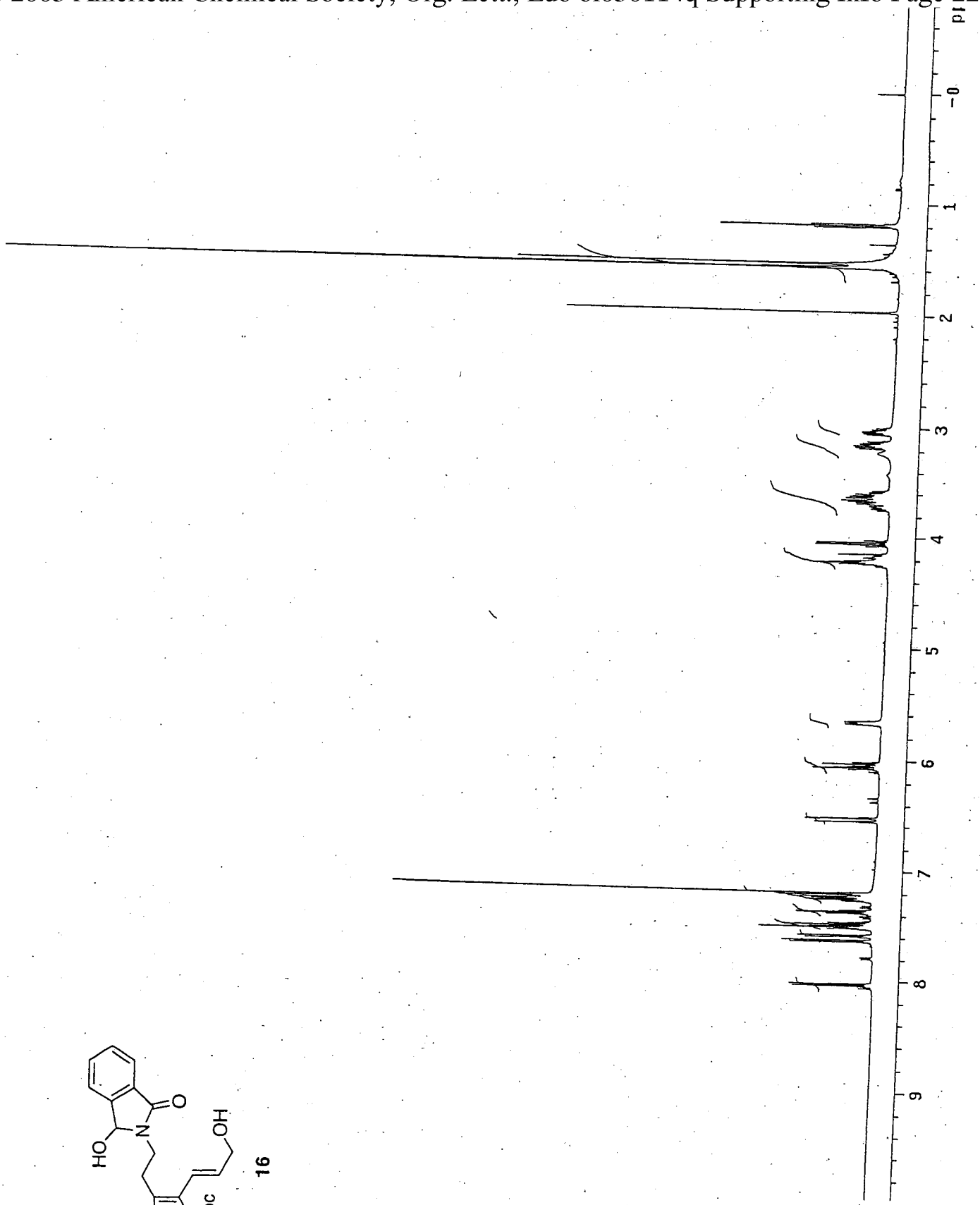

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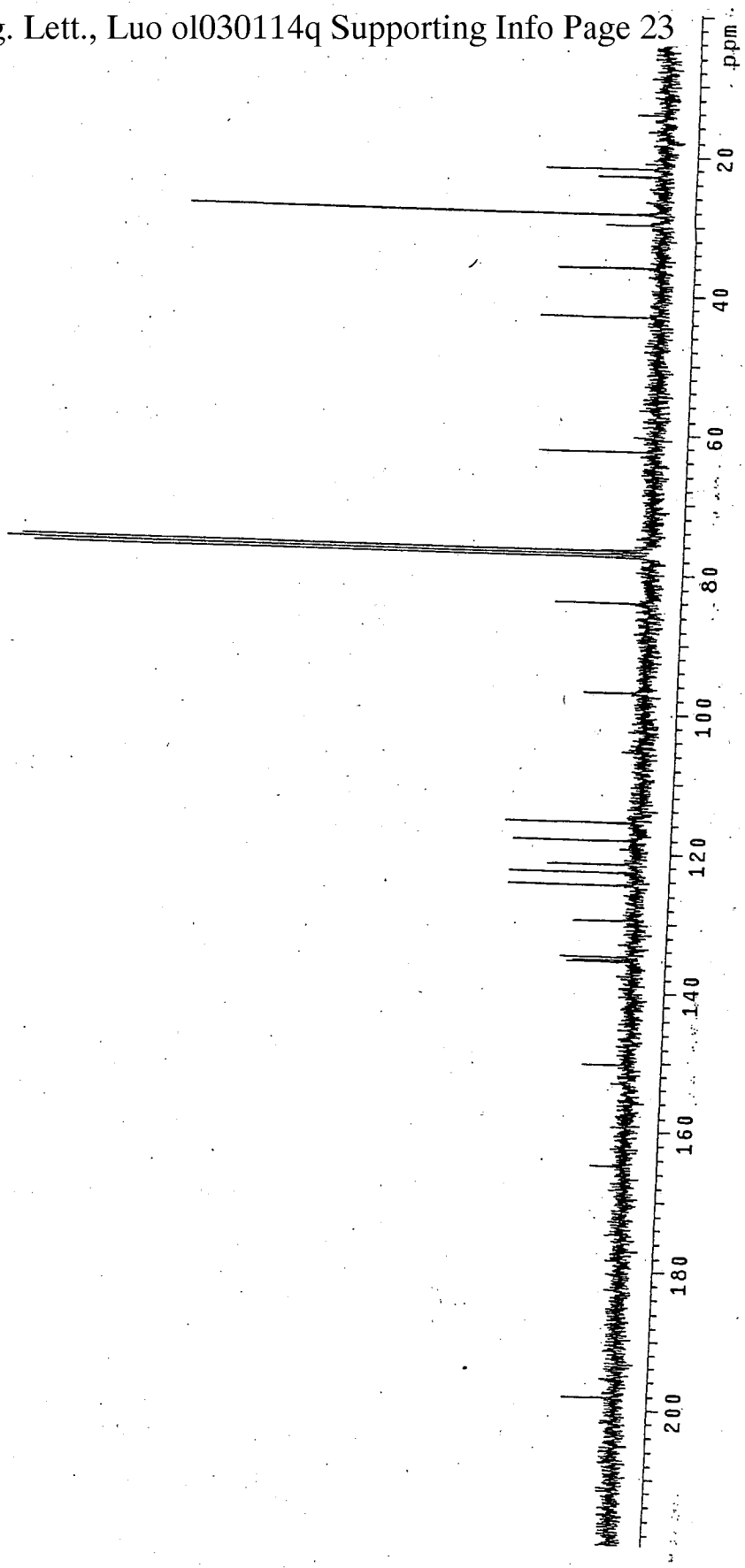

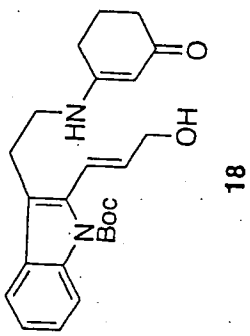

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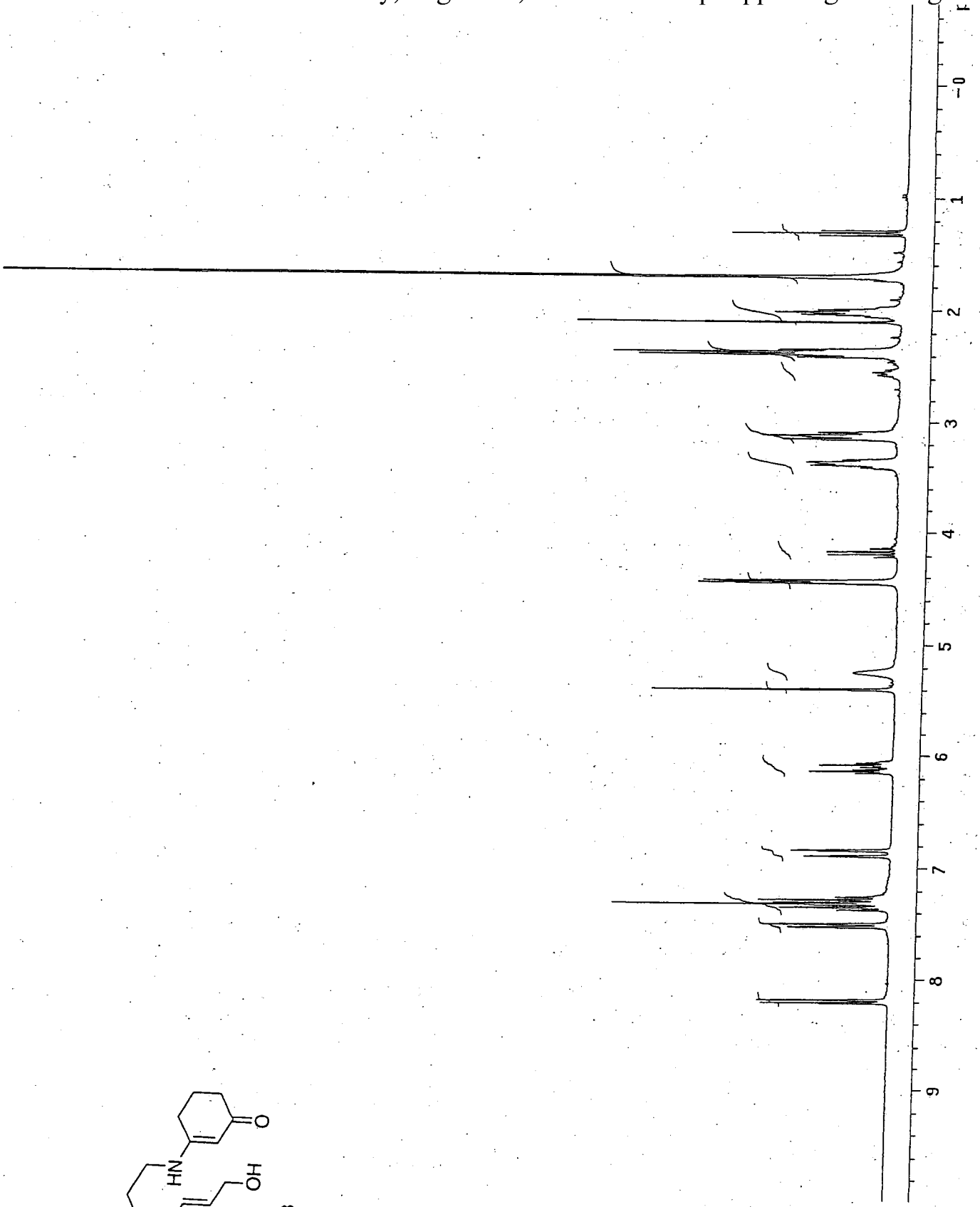

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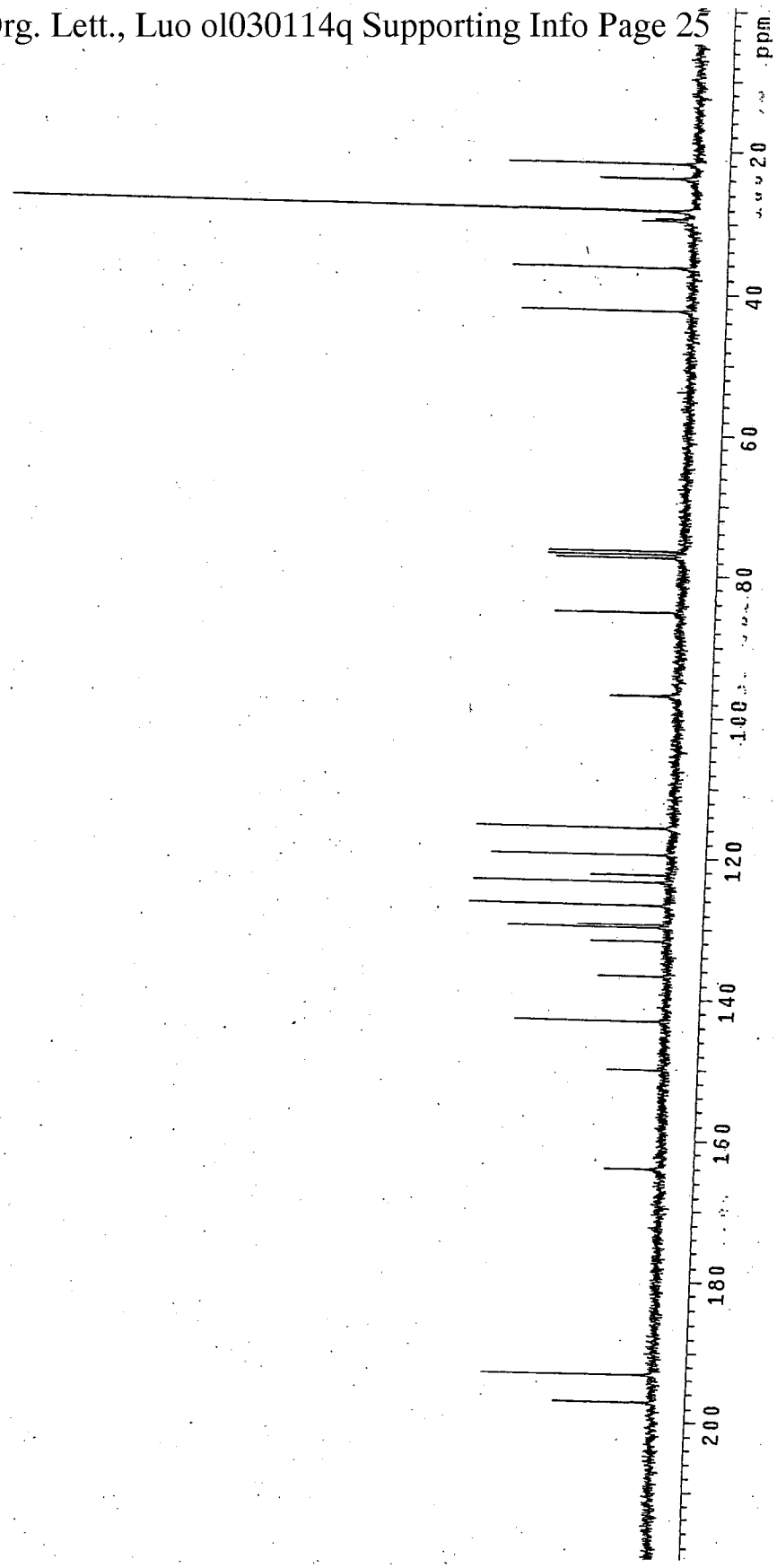

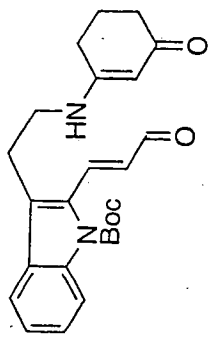

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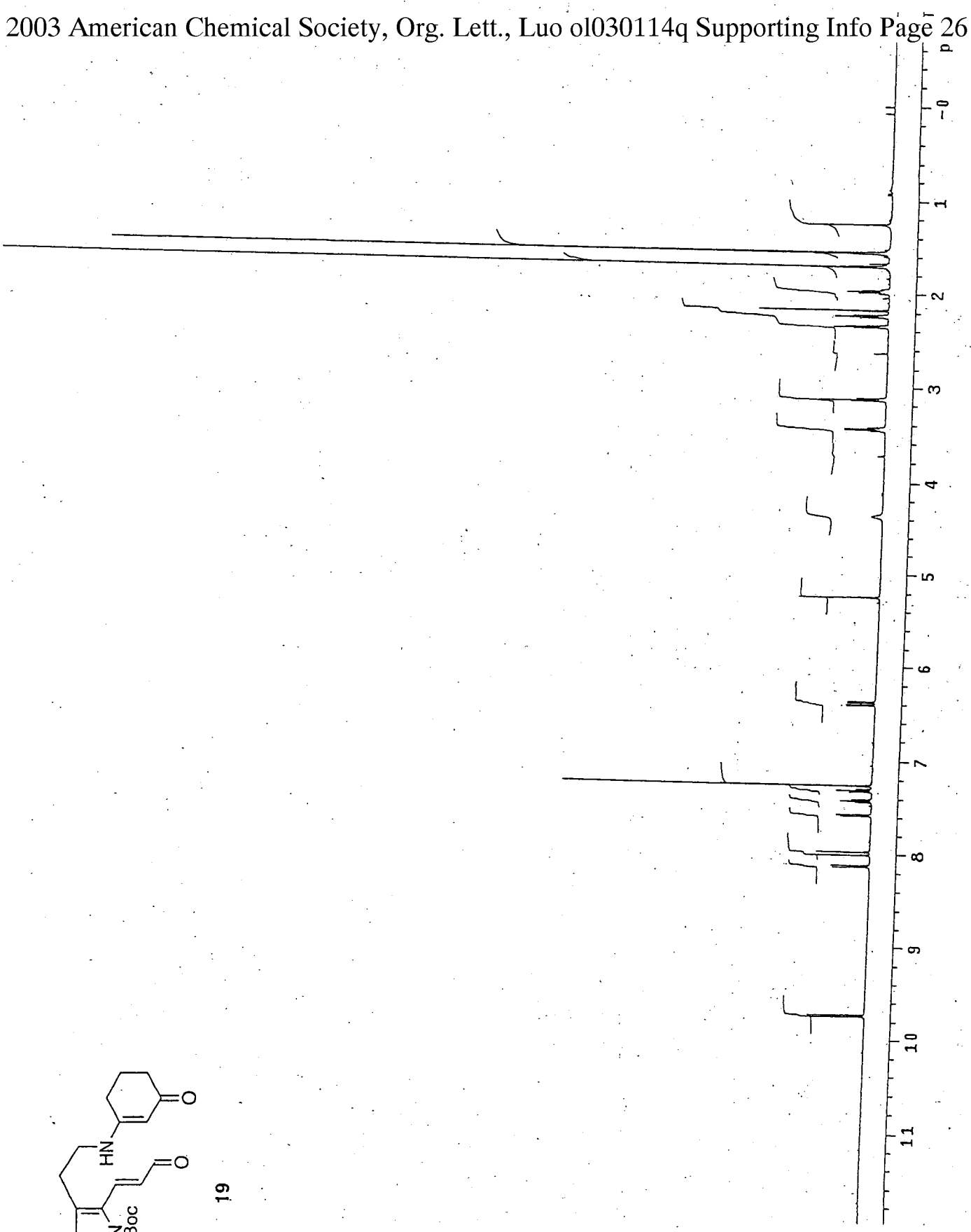

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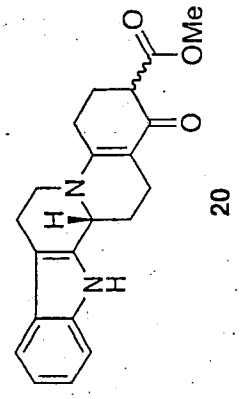

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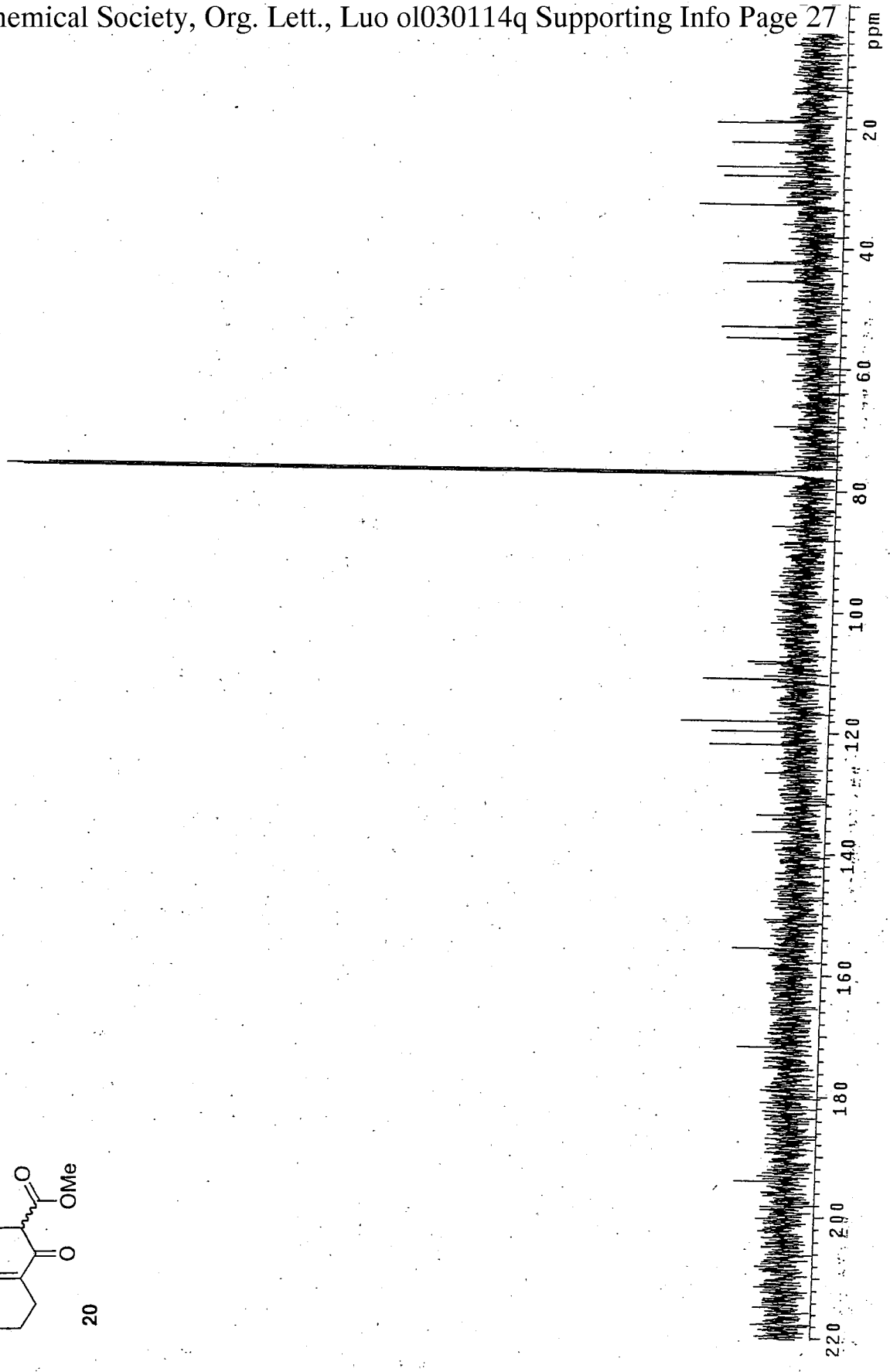

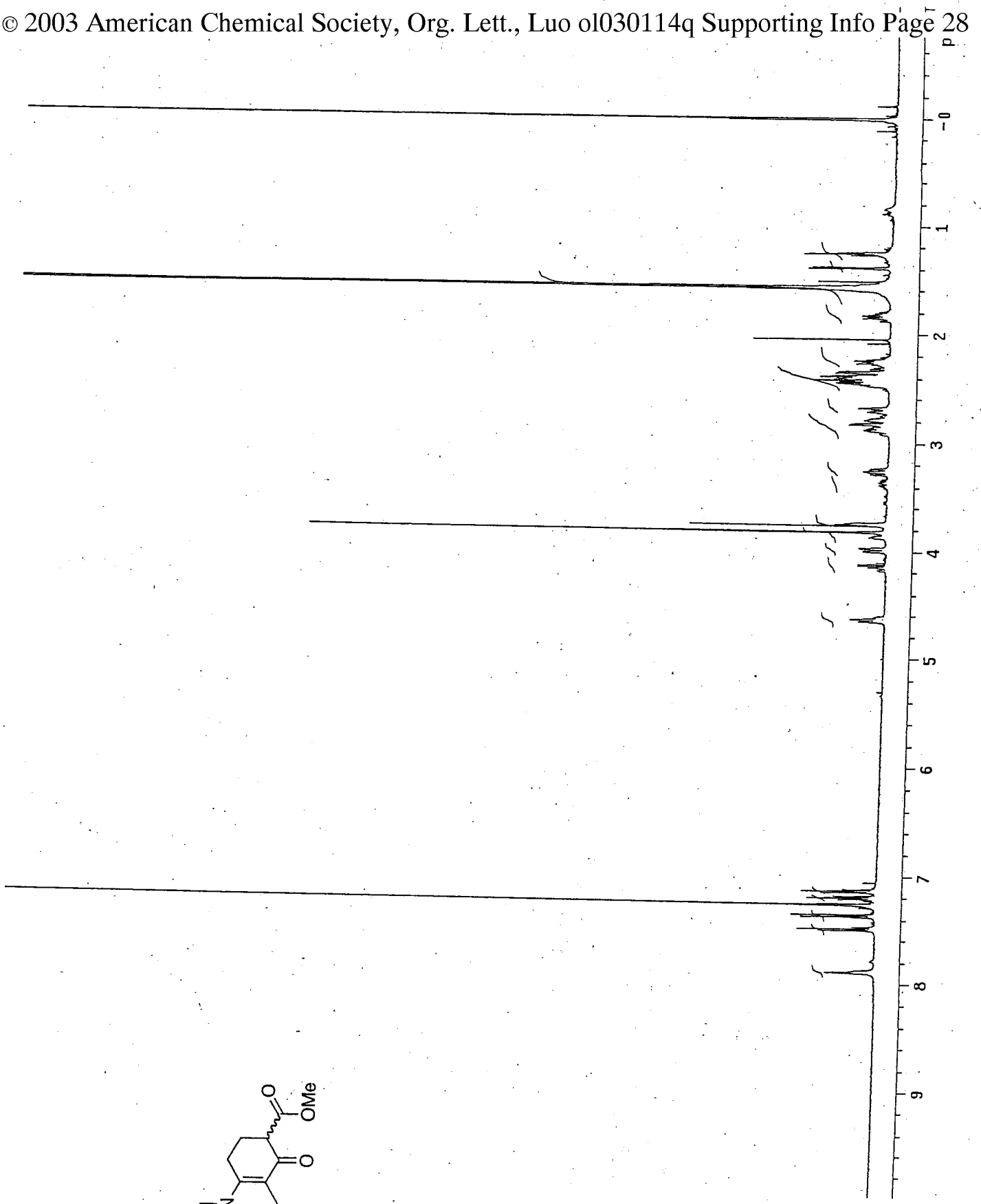

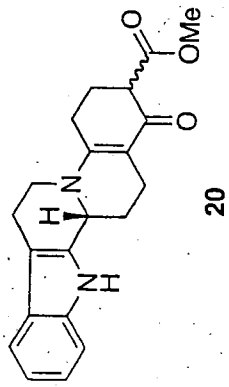

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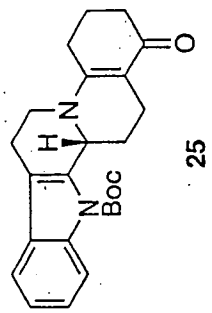

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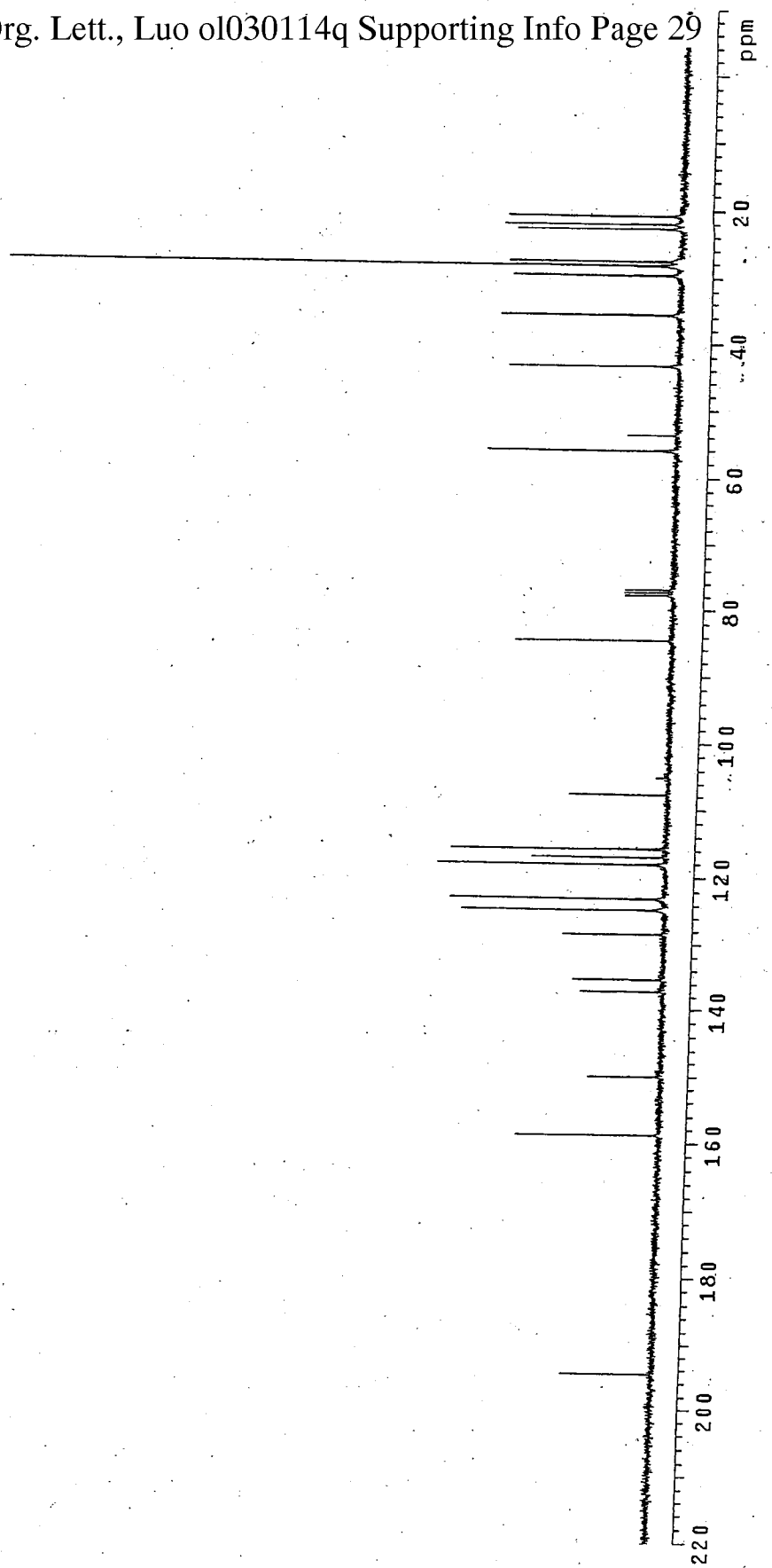

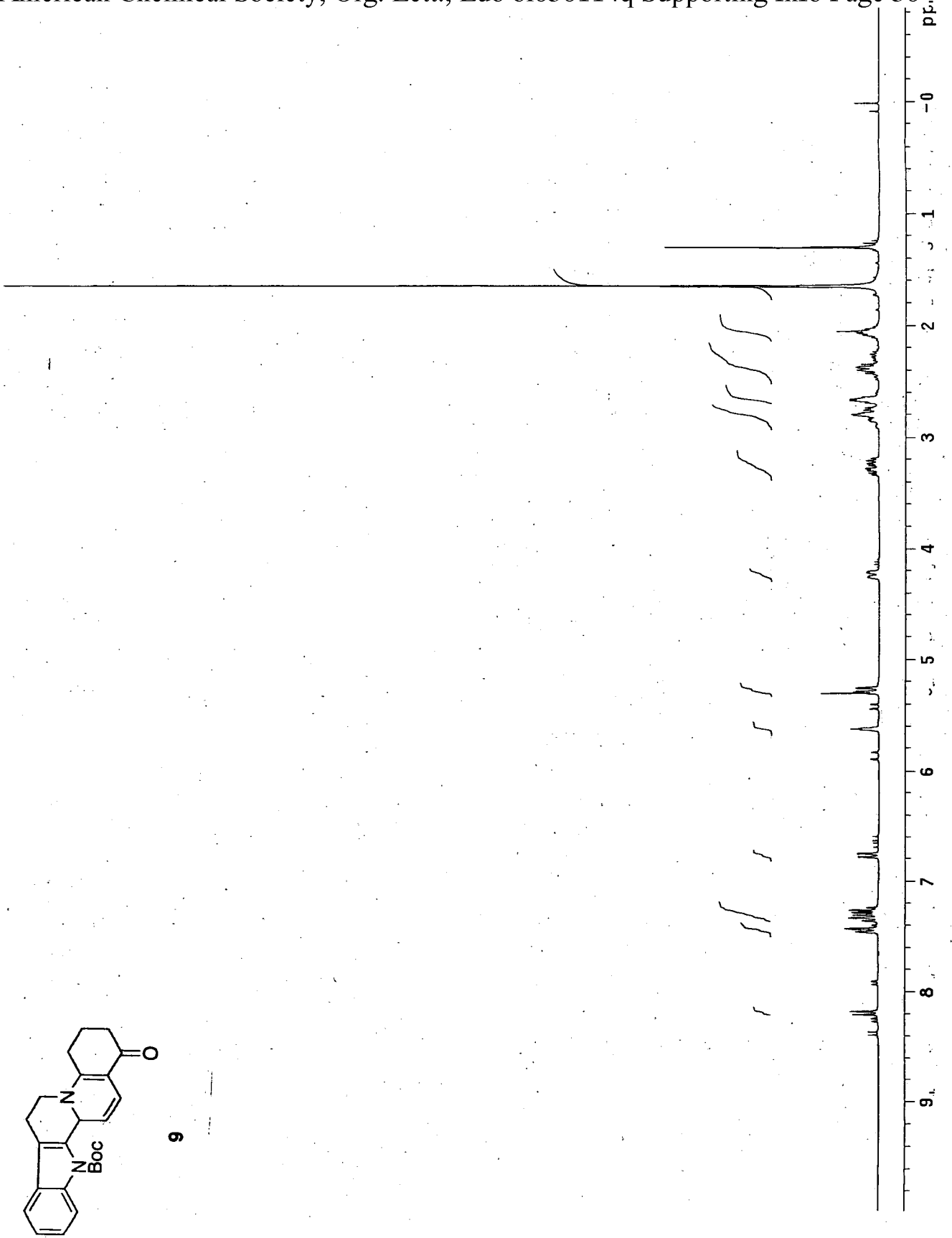
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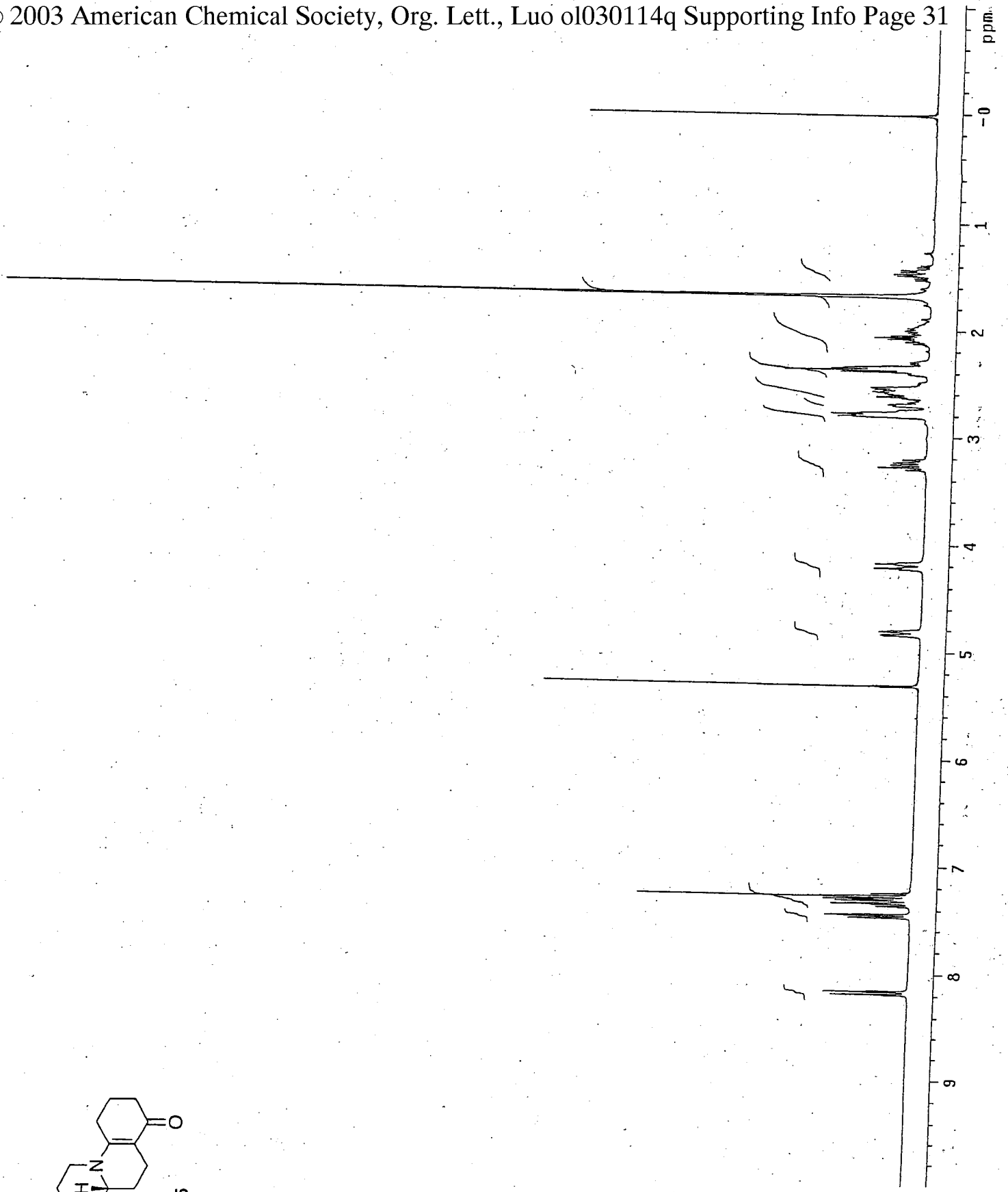

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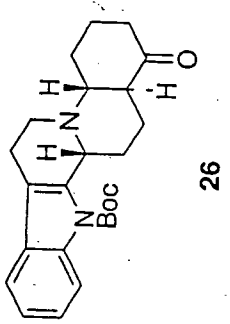

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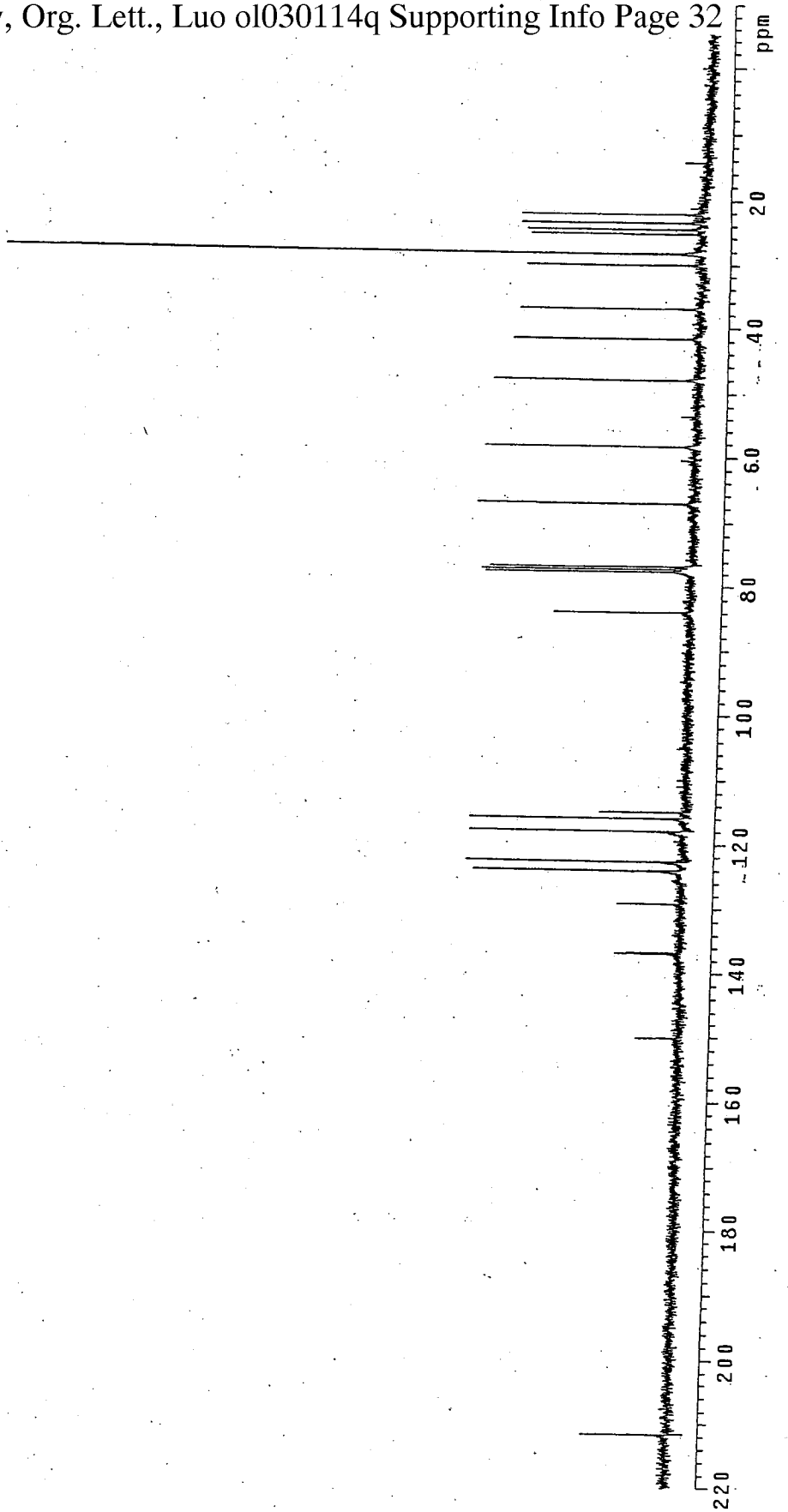

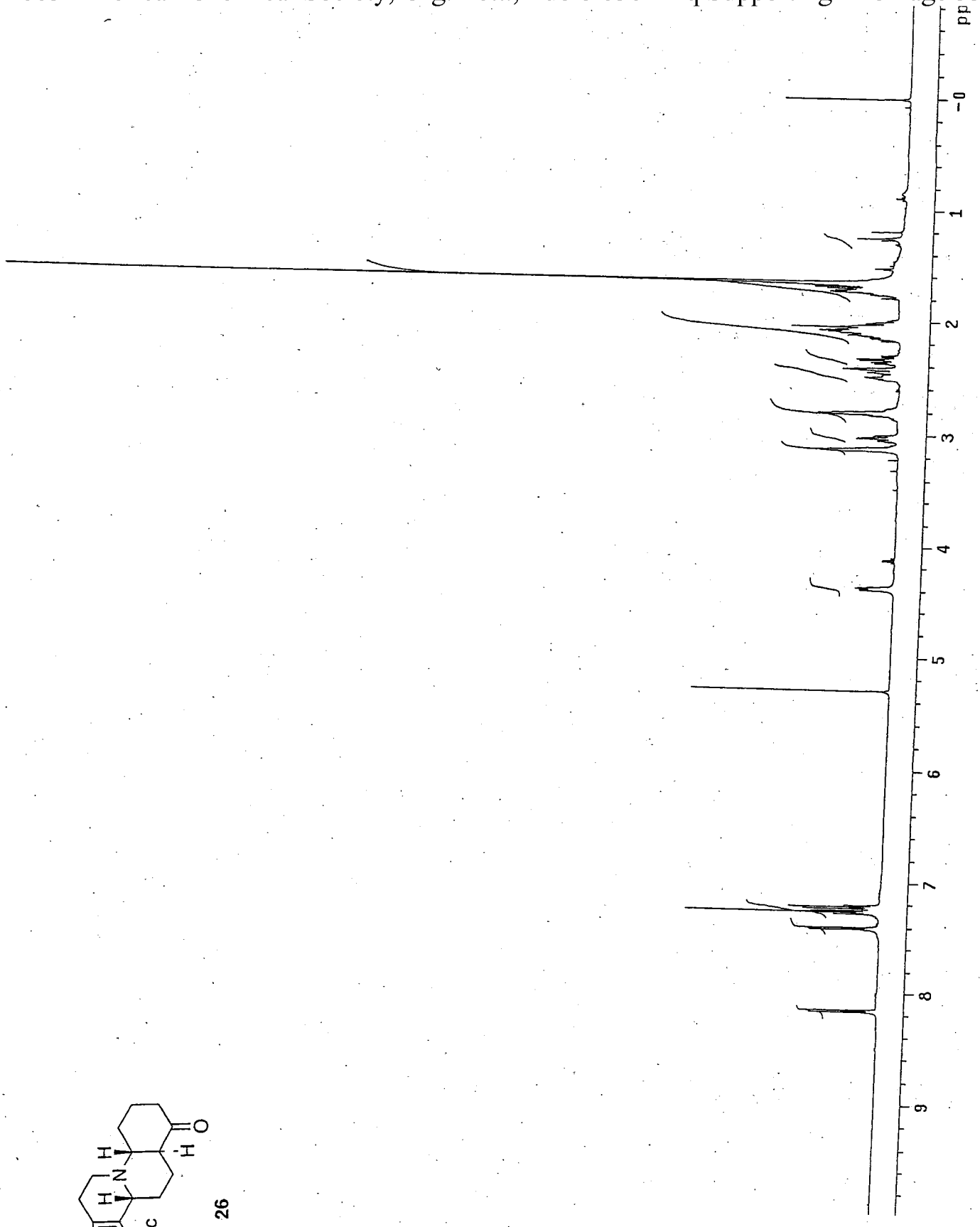

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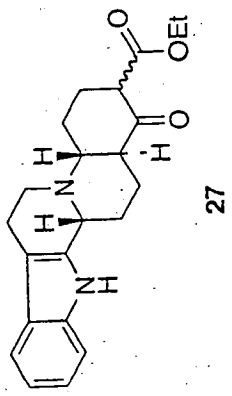

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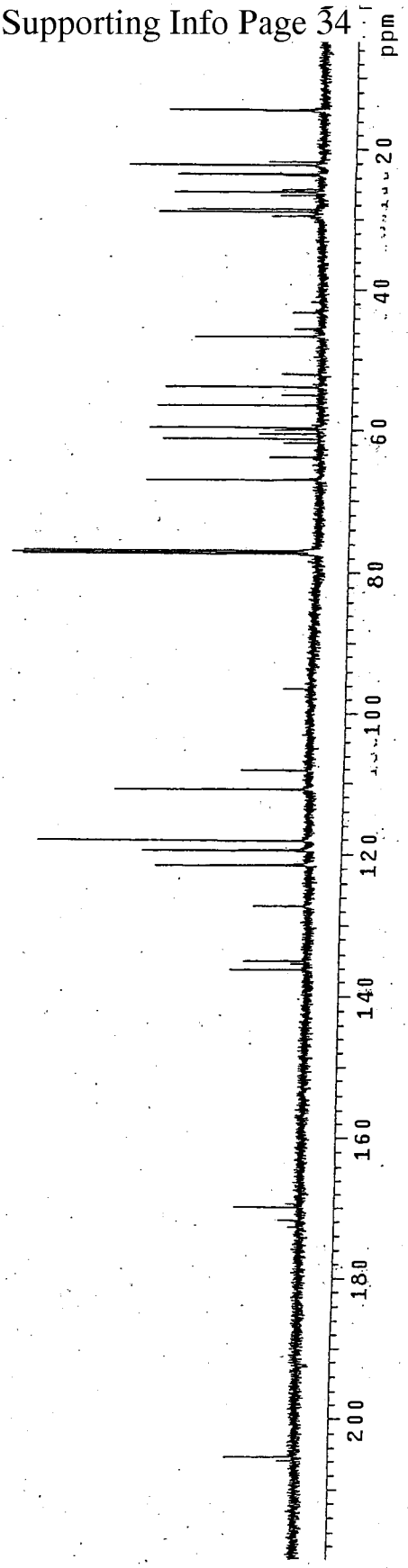

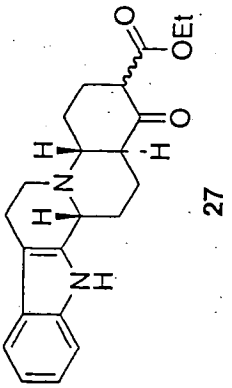

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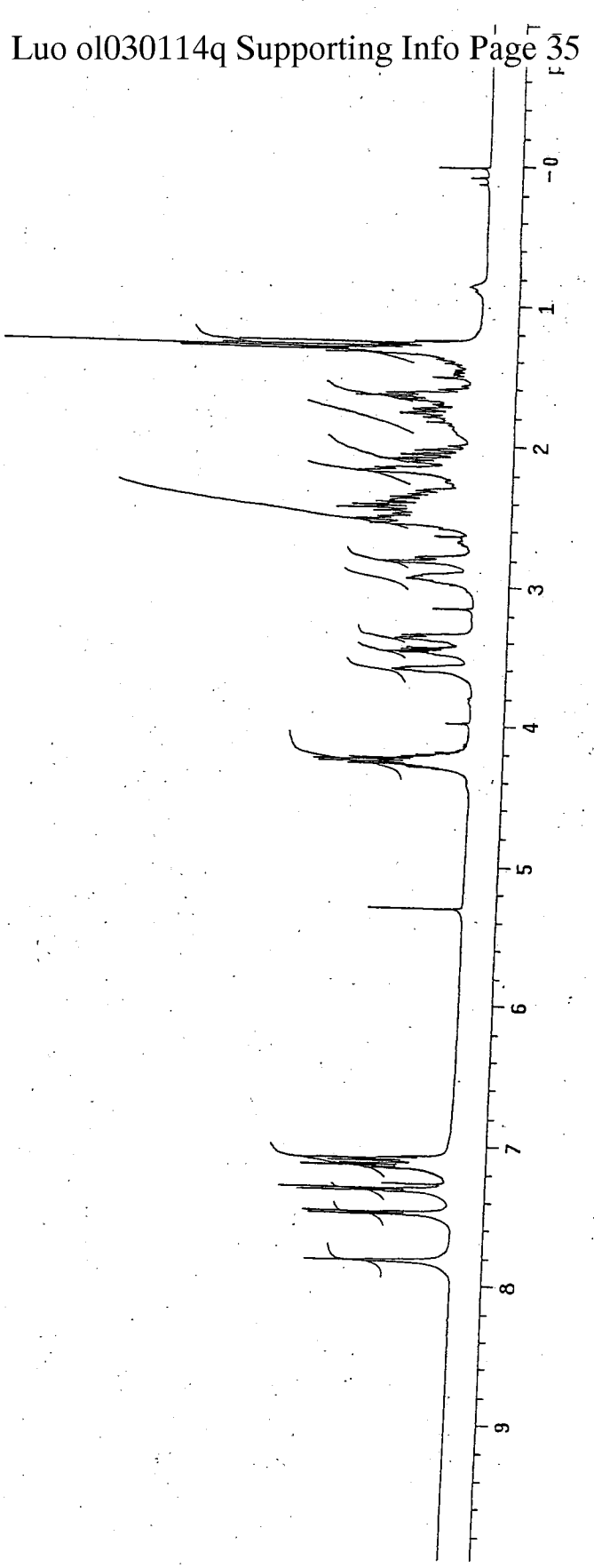

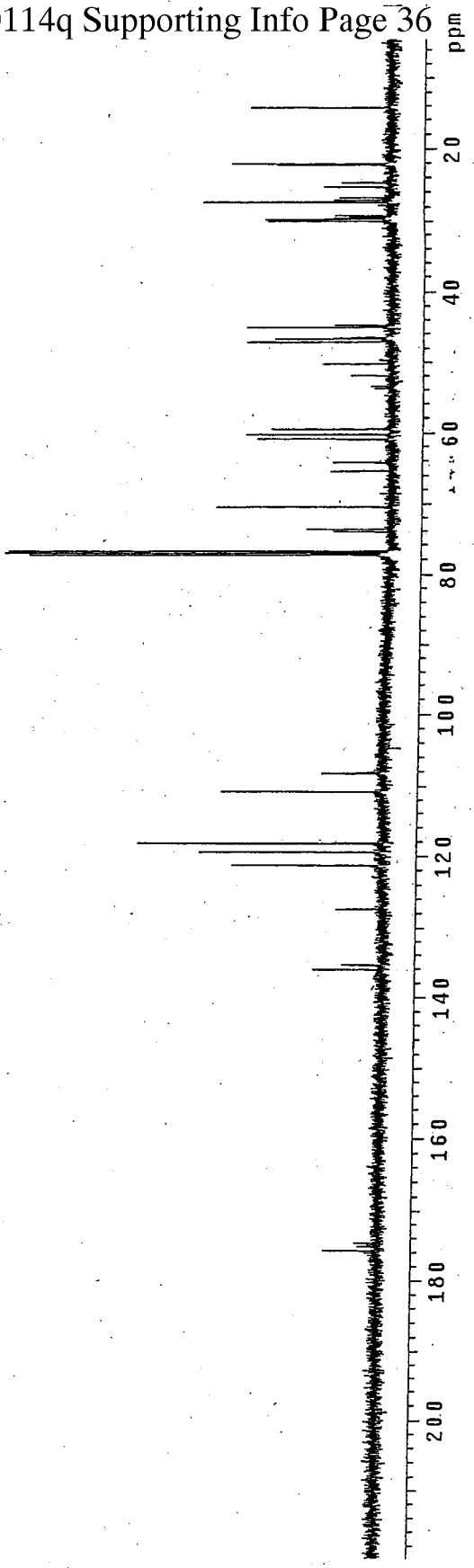

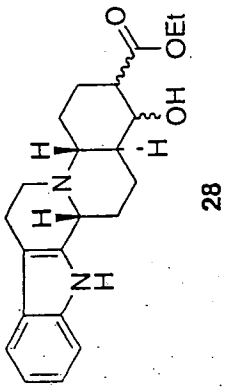

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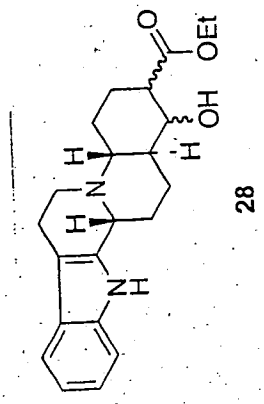

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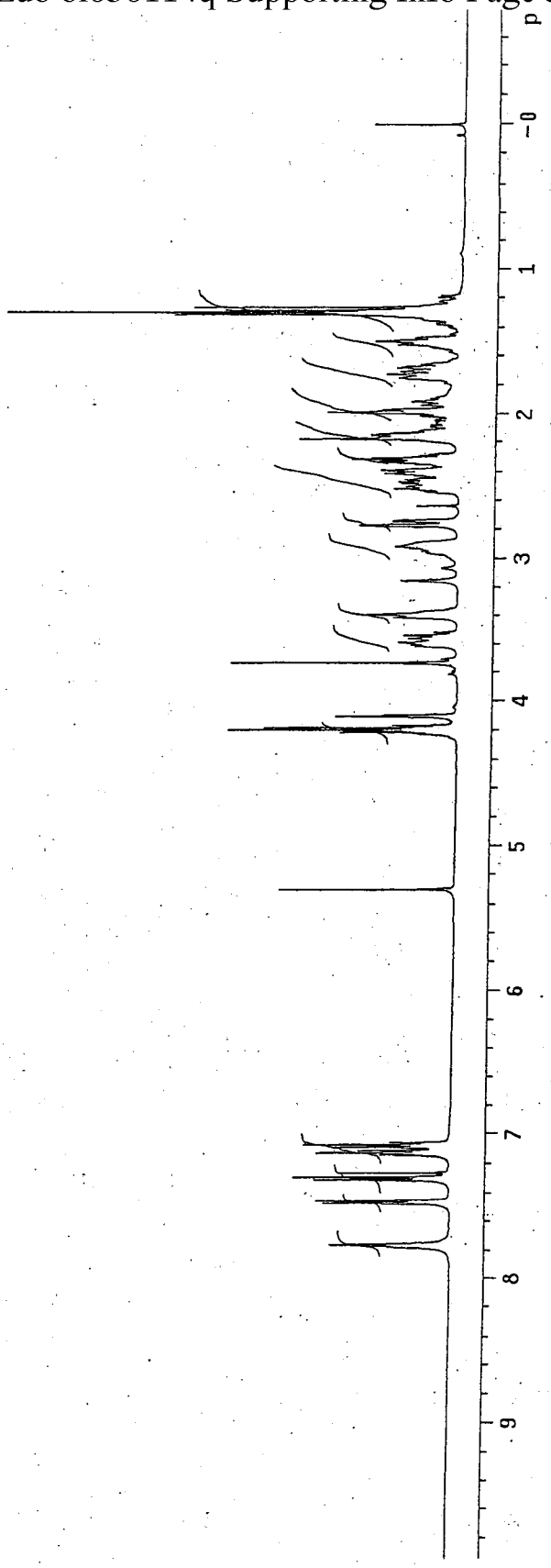

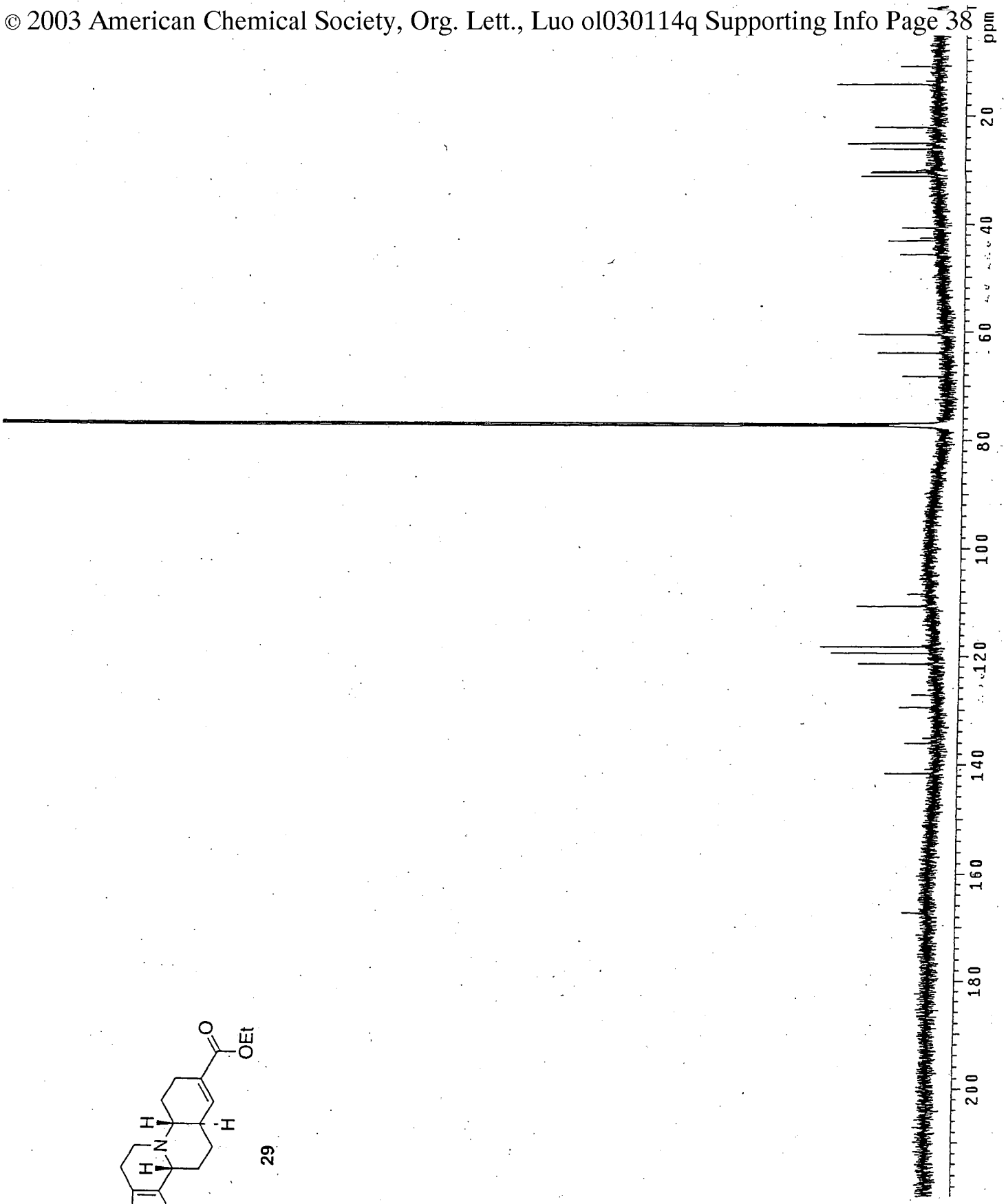

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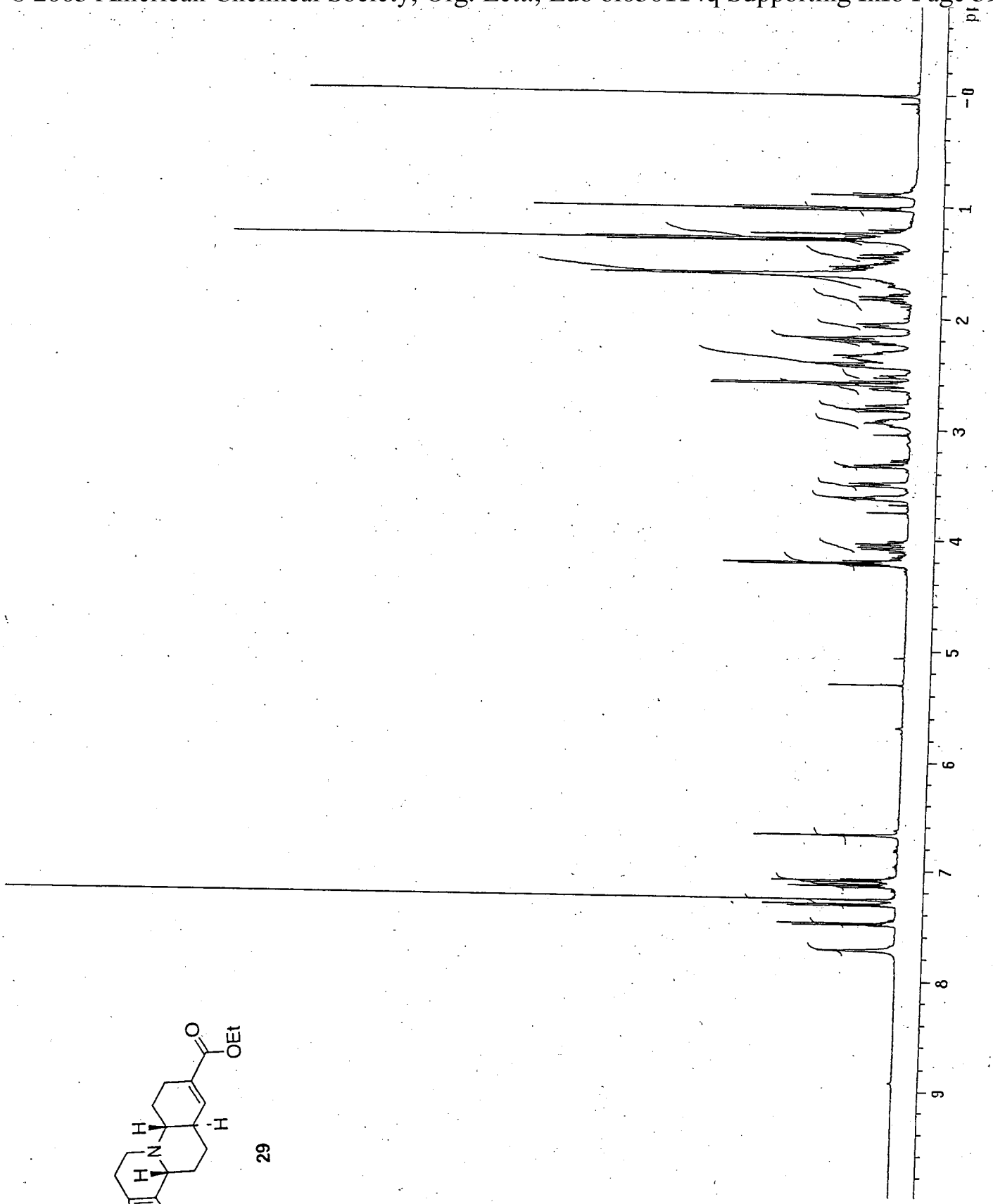

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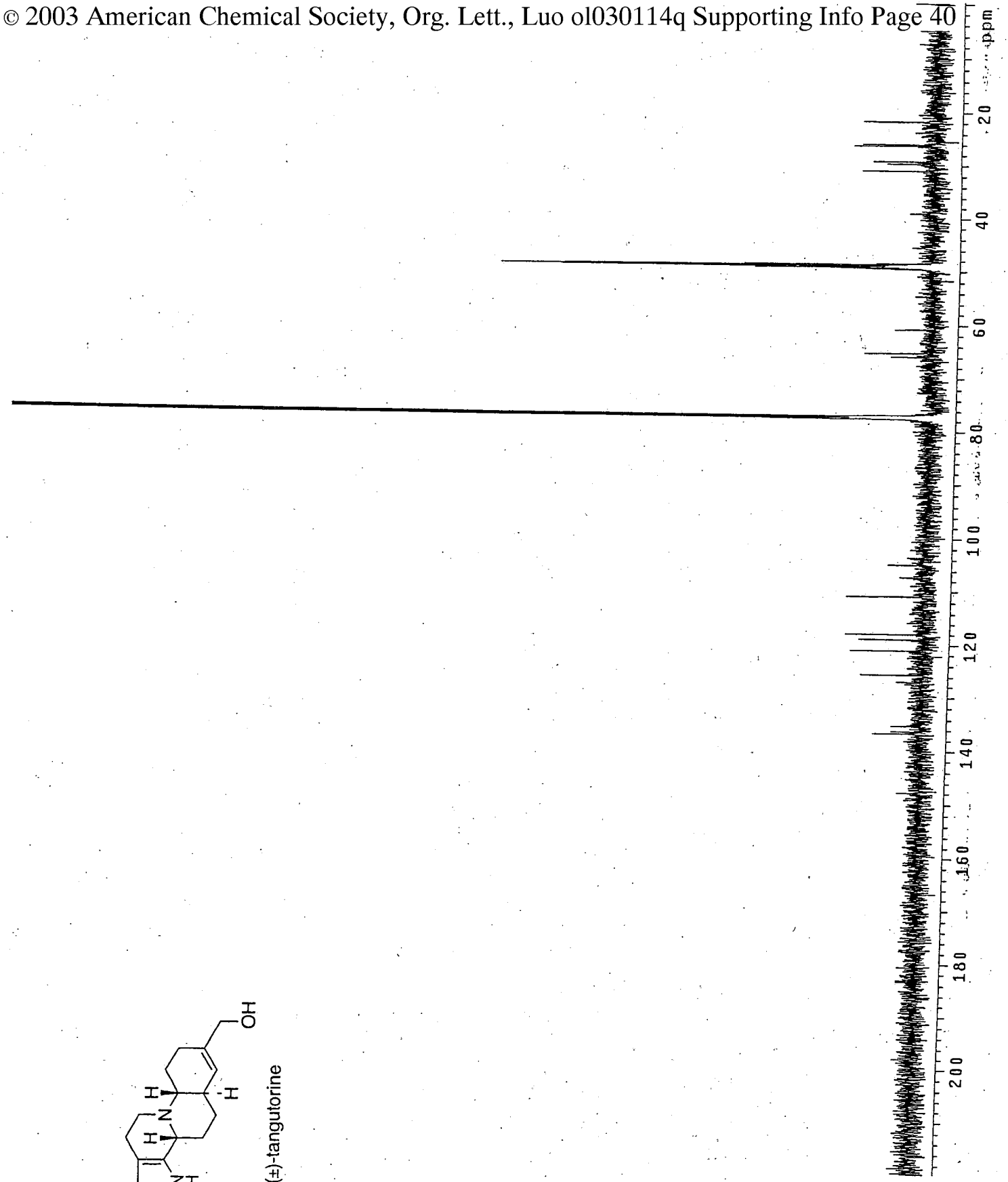

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