

Supporting Information for

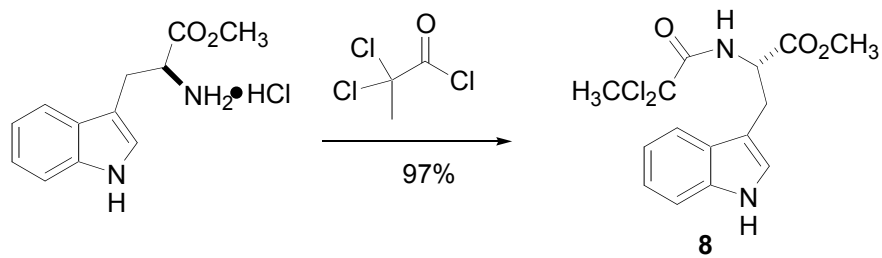
Dragmacidin E Synthesis Studies. Preparation of a Model Cycloheptannelated Indole Fragment.

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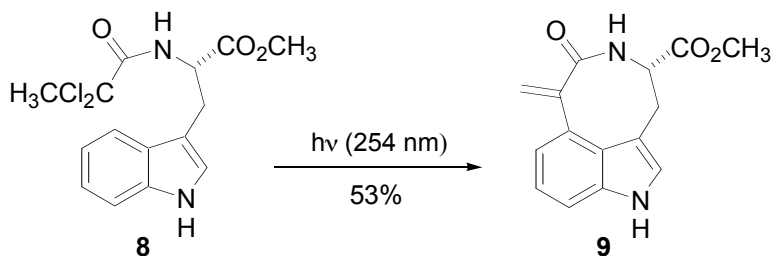
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General Experimental	S2	¹ H NMR 11	S30
8	S2	¹³ C NMR 11	S31
9	S4	¹ H NMR SM3	S32
SM1	S5	¹³ C NMR SM3	S33
SM2	S6	¹ H NMR 12	S34
11	S7, S8	¹³ C NMR 12	S35
SM3	S7, S9	¹ H NMR SM4	S36
12	S9	¹³ C NMR SM4	S37
SM4	S10	¹ H NMR SM5	S38
SM5	S11	¹³ C NMR SM5	S39
13	S12	¹ H NMR 13	S40
15	S13	¹³ C NMR 13	S41
16	S14	¹ H NMR <i>cis</i> - 15	S42
SM6	S15	¹³ C NMR <i>cis</i> - 15	S43
17	S16	¹ H NMR <i>trans</i> - 15	S44
SM7	S17	¹³ C NMR <i>trans</i> - 15	S45
18	S18	¹ H NMR 16	S46
¹ H NMR 8	S20	¹³ C NMR 16	S47
¹³ C NMR 8	S21	¹ H NMR SM6	S48
¹ H NMR 9	S22	¹³ C NMR SM6	S49
¹³ C NMR 9	S23	¹ H NMR 17	S50
¹ H NMR SM1	S24	¹³ C NMR 17	S51
¹³ C NMR SM1	S25	¹ H NMR SM7	S52
¹ H NMR <i>trans</i> - SM2	S26	¹³ C NMR SM7	S53
¹³ C NMR <i>trans</i> - SM2	S27	¹ H NMR 18	S54
¹ H NMR <i>cis</i> - SM2	S28	¹³ C NMR 18	S55
¹³ C NMR <i>cis</i> - SM2	S29	MM calc's of 15 -imine	S56

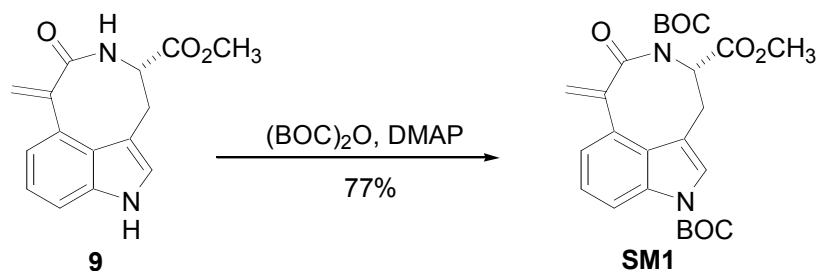
General Experimental. Unless stated otherwise, moisture and oxygen sensitive reactions were carried out in flame-dried glassware under a nitrogen or argon atmosphere using anhydrous, deoxygenated solvents. Tetrahydrofuran was dried by passage through an activated alumina column under a nitrogen atmosphere or distillation from sodium benzophenone ketyl under an argon atmosphere. Dichloromethane and acetonitrile were dried by passage through an activated alumina column under a nitrogen atmosphere or distillation from calcium hydride under an argon atmosphere. HPLC grade acetonitrile was also used as received for large scale photochemical reactions and it did not significantly lower the yield of the product. Methanol was dried by distillation from calcium hydride under a nitrogen or argon atmosphere. Absolute ethanol was used as received. All other commercially obtained reagents were used as received. Microwave reactions were performed in the CEM Focused MicrowaveTM Synthesis System, Model Discover. Flash chromatography was performed on 32-63 μm silica gel. The characterization data were obtained on the solid material that resulted from evaporation of the chromatography solvents used for purification. Melting points were taken with a Melt-Temp apparatus and are uncorrected. Chemical shifts of ^1H NMR spectra are reported relative to Me_4Si (δ 0.00) or DMSO (δ 2.49) if the former was absent. ^{13}C NMR spectra are reported relative to Me_4Si (δ 0.0), or CDCl_3 (δ 77.0) or DMSO (δ 39.5) if the former was absent.



Methyl 2-(2,2-Dichloropropionylamino)-3-(1*H*-indol-3-yl) Propionate (8). To a solution of 2,2-dichloropropionic acid (90%, 6.7 mL, 59 mmol) in CH₂Cl₂ (50 mL) was added 2 drops of DMF followed by oxalyl chloride (10.0 mL, 119 mmol). The reaction mixture was stirred for 2.5 h until bubbling stopped. The resulting yellow acid chloride solution was concentrated under reduced pressure and then redissolved in CH₂Cl₂ (40 mL). The acid chloride solution was cannulated to an ice-cooled solution of L-tryptophan methyl ester hydrochloride (10.01 g, 39 mmol) and dimethylaminopyridine (10.05 g, 82 mmol) in CH₂Cl₂ (60 mL). The resulting red solution was stirred in an ice bath for 3 h and then at room temperature for 12 h. The reaction mixture was poured into ice water (50 mL) and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (2 x 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (2:1 hexanes/EtOAc) to afford the dichloroamide **8** as a light brown solid (13.13 g, 97%). mp 143-144 °C; $[\alpha]_D^{20} +51^\circ$ (*c* 1.00, CHCl₃); IR (film) 3368, 3315, 1728, 1678 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.26 (br s, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.29 (br s, 1H), 7.19 (ddd, *J* = 8.0, 7.0, 1.3 Hz, 1H), 7.11 (ddd, *J* = 7.8, 7.0, 1.1 Hz, 1H), 7.02 (d, *J* = 2.1 Hz, 1H), 4.86 (ddd, *J* = 7.7, 5.3, 5.3 Hz, 1H), 3.69 (s, 3H), 3.42 (dd, *J* = 18.5, 5.2 Hz, 1H), 3.37 (dd, *J* = 18.9, 5.1 Hz, 1H), 2.25 (s, 3 H); ¹³C NMR (300 MHz, CDCl₃) δ 171.4, 165.9, 136.1, 127.3, 123.0, 122.3, 119.7, 118.5, 111.3, 109.2, 82.1, 53.8, 52.6, 33.9, 27.2; LRMS(ESI) *m/z* (relative intensity) 365.0 (100%, M+Na⁺); HRMS (ESI) *m/z* calcd for [C₁₅H₁₆N₂O₃Cl₂Na]⁺: 365.0436, found 365.0426.



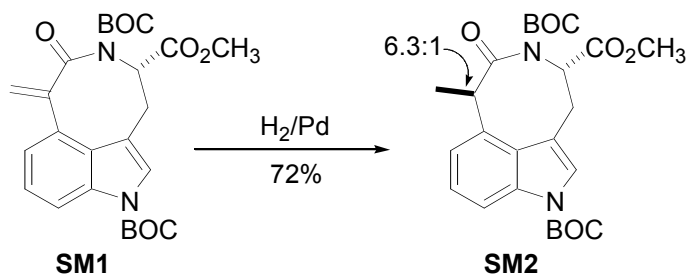
Methyl 7-Methylene-6-oxo-1,3,4,5,6,7-hexahydro-azocino[4,5,6-*cd*]indole-4 Carboxylate (9). A solution of dichloroamide **8** (150 mg, 0.44 mmol) in CH₃CN (87.5 mL) in a quartz vessel was purged with dry argon for 30 min. This solution was irradiated at 254 nm in a Rayonet photochemical reactor for 3 h. The resulting light brown solution was concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:3 hexanes/EtOAc) to afford the bridged indole **9** as a yellow solid (63 mg, 53%). mp 194-195 °C; $[\alpha]_D^{20}$ -347° (*c* 0.60, CHCl₃); IR (film) 3305, 1741, 1653 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.42 (br s, 1H), 7.35 (ddd, *J* = 8.2, 4.5, 3.5 Hz, 1H), 7.20-7.15 (m, 2H), 7.07 (dd, *J* = 1.3, 1.2 Hz, 1H), 6.33 (d, *J* = 9 Hz, 1H), 5.60 (d, *J* = 0.9 Hz, 1H), 5.50 (d, *J* = 0.7 Hz, 1H), 5.07 (ddd, *J* = 11.8, 9.0, 2.8 Hz, 1H), 3.84 (s, 3H), 3.56 (ddd, *J* = 16.3, 3.0, 0.9 Hz, 1H), 3.29 (ddd, *J* = 16.3, 11.8, 0.9 Hz, 1H); ¹³C NMR (300 MHz, CDCl₃) δ 172.7, 171.7, 147.8, 136.6, 129.8, 124.2, 122.9, 122.0, 121.7, 116.6, 112.2, 110.4, 55.7, 52.9, 33.1; LRMS(ESI) *m/z* (relative intensity) 293.1 (97%, M+Na⁺); HRMS (ESI) *m/z* calcd for [C₁₅H₁₄N₂O₃Na]⁺: 293.0896, found 293.0902. Anal. Calcd for C₁₅H₁₄N₂O₃: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.75; H, 5.32; N, 10.20.



1,5-Di-*tert*-butyl 4-Methyl 7-Methylene-6-oxo-3,4,6,7-tetrahydro-azocino[4,5,6-*cd*]indole 1,4,5-Tricarboxylate (SM1). A solution of di-*tert*-butyldicarbonate (1.13 g, 5.18 mmol) in CH₃CN (6 mL) was cannulated into a suspension of indole **9** (335 mg, 1.24 mmol) and 4-dimethylaminopyridine (34 mg, 0.28 mmol) in CH₃CN (6 mL). After the addition was complete, the indole **9** slowly became soluble and it all went into solution in less than 10 min. The reaction mixture was stirred at room temperature for 2 h. The resulting dark brown solution was poured into ice water (20 mL) and extracted with ether (3 x 20 mL). The organic extracts were combined, washed with brine solution (20 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (3:2 hexanes/ether) to afford the desired protected product as a white solid (446 mg, 77%). mp 118-120 °C; $[\alpha]_D^{20} +61^\circ$ (*c* 1.00, CHCl₃); IR (film) 1734, 1693 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.30 (d, *J* = 6.5 Hz, 1H), 7.53 (s, 1H), 7.38-7.29 (m, 2H) 6.47 (d, *J* = 1.0 Hz, 1H), 6.05 (d, *J* = 1.0 Hz, 1H), 4.77 (dd, *J* = 12.7, 4.3 Hz, 1H), 3.85 (s, 3H), 3.30 (dd, *J* = 15.3, 4.3 Hz, 1H), 3.11 (ddd, *J* = 15.2, 12.8, 1.2 Hz, 1H), 1.67 (s, 9H), 1.08 (s, 9H); ¹³C NMR (300 MHz, CDCl₃) δ 174.3, 170.7, 151.4, 149.0, 144.6, 136.6, 129.5, 129.4, 127.2, 125.7, 124.3, 124.0, 116.1, 115.7, 83.9, 82.9, 57.4, 52.6, 28.1, 27.4, 26.7; LRMS(ESI) *m/z* (relative intensity) 493.2 (100%, M+Na⁺); HRMS (ESI) *m/z* calcd for [C₂₅H₃₀N₂O₇Na]⁺:

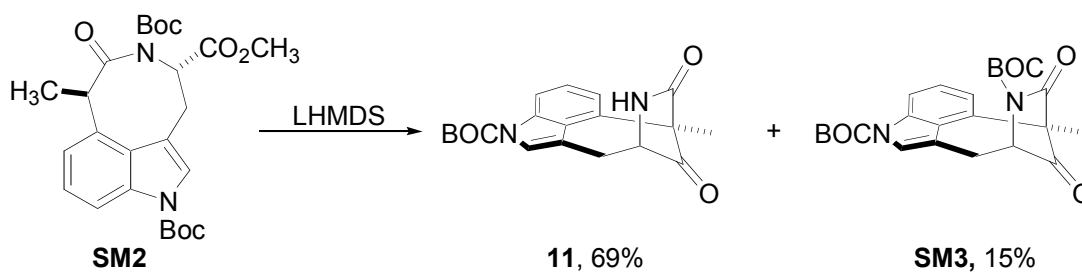
493.1951, found 493.1944. Anal. Calcd for $C_{25}H_{30}N_2O_7$: C, 63.82; H, 6.43; N, 5.95.

Found: C, 63.83; H, 6.47; N, 5.83.



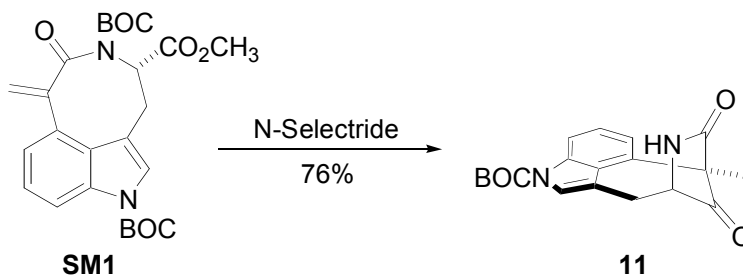
1,5-Di-tert-butyl 4-Methyl 7-Methyl-6-oxo-3,4,6,7-tetrahydro-azocino[4,5,6-cd]indole 1,4,5-Tricarboxylate (SM2). To a solution of indole **SM1** (483 mg, 1.03 mmol) in MeOH (15 mL) was added 10% w/w Pd/C (22 mg, 0.02 mmol). The reaction mixture was stirred under a H_2 atmosphere (1atm) for 2 days. The resulting black suspension was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:1 hexanes/ether) to afford both the *trans*-methyl imide **SM2** as a white solid (309 mg, 62%) and the *cis*-methyl imide **SM2** as a white solid (49 mg, 10%). Major product: mp 167-168 °C; $[\alpha]_D^{20}$ -296° (*c* 1.00, $CHCl_3$); IR (film) 1734 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.1 Hz, 1H), 7.44 (s, 1H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 5.59 (t, *J* = 9.5 Hz, 1H), 4.48 (q, *J* = 6.6 Hz, 1H), 3.84 (s, 3H), 3.57 (d, *J* = 9.5 Hz, 2H), 1.67 (d, *J* = 6.8 Hz, 3H), 1.65 (s, 9H), 1.00 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.9, 172.0, 153.3, 149.3, 135.6, 130.9, 129.0, 125.0, 124.5, 119.6, 114.9, 114.4, 83.8, 82.3, 56.0, 52.9, 43.9, 29.6, 28.1, 27.2, 12.2; LRMS(ESI) *m/z* (relative intensity) 495.1 (30%, $M+Na^+$); HRMS (ESI) *m/z* calcd for $[C_{25}H_{32}N_2O_7Na]^+$: 495.2107, found 495.2111. Minor product: mp 96-98 °C; $[\alpha]_D^{20}$ +216° (*c* 0.33, $CHCl_3$); IR (film) 1737, 1700 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.2 Hz, 1H), 7.50 (s, 1H),

7.27 (t, $J = 7.9$ Hz, 1H), 7.07 (d, $J = 7.2$ Hz, 1H), 4.74 (br d, $J \sim 8.7$ Hz, 1H), 4.54 (br q, $J \sim 5.6$ Hz, 1H), 3.82 (s, 3H), 3.32 (dd, $J = 15.4, 4.5$ Hz, 1H), 3.06 (dd, $J = 14.7, 12.5$ Hz, 1H), 1.66 (s, 9H), 1.50 (d, $J = 7.3$ Hz, 3H), 1.16 (s, 9H); ^{13}C NMR (300 MHz, CDCl_3) δ 183.5, 170.9, 151.5, 149.1, 137.5, 135.4, 126.8, 125.7, 125.6, 124.3, 115.4, 114.3, 83.8, 83.2, 56.8, 52.6, 49.5, 28.2, 27.9, 27.6, 21.4; LRMS(ESI) m/z (relative intensity) 495.1 (72%, $\text{M}+\text{Na}^+$); HRMS (ESI) m/z calcd for $[\text{C}_{25}\text{H}_{32}\text{N}_2\text{O}_7\text{Na}]^+$: 495.2107, found 495.2101.



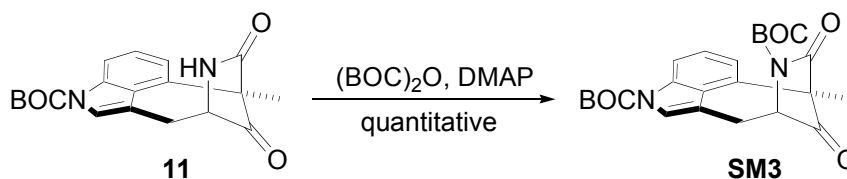
Oxo-amide 11 and **oxo-imide SM3**. To an ice-cooled solution of *trans*-**SM2** (339 mg, 0.72 mmol) in THF (10 mL) was added slowly a 1 M lithium hexamethyldisilazide (LHMDS) solution in THF (800 μL , 0.80 mmol). The reaction mixture was stirred at room temperature for 15 h. The resulting yellow solution was poured into a 1 M aq. H_3PO_4 solution (10 mL) and extracted with ether (3 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (3:2 hexanes/ether and 1:4 hexanes/EtOAc, respectively) to afford the bridging amide **11** as a white solid (169 mg, 69%) and its *N*-protected analogue **SM3** as a light yellow solid (46 mg, 15%). **Oxo-amide 11**. mp 206-208 $^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{20} +24^{\circ}$ (c 0.52, CHCl_3); IR (film) 3241, 1774, 1733, 1704 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.17 (d, $J = 8.2$ Hz, 1H), 7.48 (s, 1H), 7.46 (br s, 1H), 7.34 (t, $J = 8.0$ Hz, 1H), 7.24 (dd, $J = 7.7, 0.9$ Hz, 1H), 4.46 (ddd, $J = 4.1, 3.0, 1.3$ Hz, 1H), 3.27 (ddd, $J = 17.0, 4.0, 1.0$ Hz, 1H), 3.13 (ddd, $J = 17.0,$

2.9, 2.0 Hz, 1H), 1.73 (s, 3H), 1.62 (s, 9H); ^{13}C NMR (300 MHz, CDCl_3) δ 209.8, 175.1, 149.0, 135.8, 128.8, 126.5, 124.9, 124.7, 118.9, 115.3, 113.8, 84.1, 60.9, 56.2, 29.3, 28.1, 12.8; LRMS(ESI) m/z (relative intensity) 363.1 (68%, $\text{M}+\text{Na}^+$); HRMS (ESI) m/z calcd for $[\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_4\text{Na}]^+$: 363.1321, found 363.1317. **Oxo-imide SM3.** mp 122-124 $^\circ\text{C}$; $[\alpha]_D^{20} +10^\circ$ (c 1.00, CHCl_3); IR (film) 1799, 1764, 1742 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.20 (d, $J = 8.2$ Hz, 1H), 7.55 (s, 1H), 7.35 (t, $J = 8.0$ Hz, 1H), 7.25 (dd, $J = 7.6$, 0.9 Hz, 1H), 4.89 (dd, $J = 4.2$, 2.9 Hz, 1H), 3.70 (ddd, $J = 17.1$, 4.3, 0.9 Hz, 1H), 3.16 (ddd, $J = 17.1$, 2.8, 2.0 Hz, 1H), 1.78 (s, 3H), 1.65 (s, 9H), 1.52 (s, 9H); ^{13}C NMR (300 MHz, CDCl_3) δ 207.6, 170.6, 149.3, 149.0, 135.8, 127.6, 126.3, 124.9, 124.7, 118.8, 115.5, 113.2, 84.4, 84.2, 64.8, 59.1, 28.1, 27.9, 26.9, 13.4; LRMS(ESI) m/z (relative intensity) 463.2 (65%, $\text{M}+\text{Na}^+$); HRMS (ESI) m/z calcd for $[\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_6\text{Na}]^+$: 463.1845, found 463.1841.

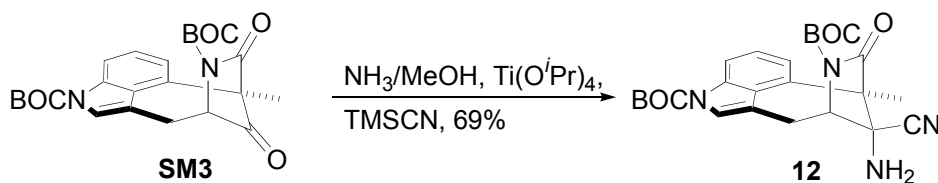


Oxo-amide 11. A solution of indole **SM1** (604 mg, 1.28 mmol) in THF (15 mL) was cooled to -78 °C and a 1 M solution *N*-selectride in THF (1.42 mL, 1.42 mmol) was added slowly. The reaction mixture was stirred at -78 °C for 1 h and then at room temperature for 4 h. The resulting red solution was poured into ice water (15 mL) and extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was

purified by flash chromatography on silica gel (1:3 hexanes/EtOAc and 100% EtOAc, respectively) to afford the bridging amide **11** as a light yellow solid (333 mg, 76%).

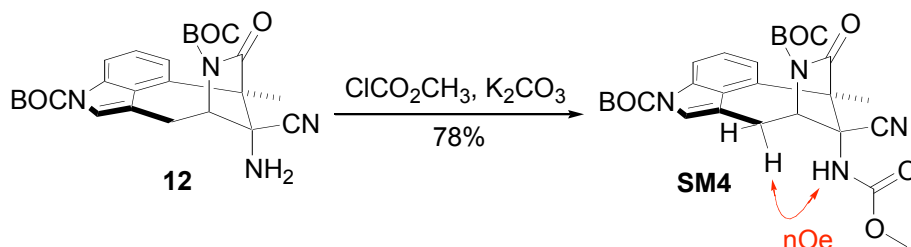


Oxo-imide SM3. A solution of di-*tert*-butyldicarbonate (1.92 g, 8.80 mmol) in CH₃CN (20 mL) was cannulated into a suspension of amide **11** (1.49 g, 4.38 mmol) and 4-dimethylaminopyridine (54 mg, 0.44 mmol) in CH₃CN (20 mL). After the addition was complete, the indole **11** slowly became soluble and it all went into solution in less than 10 min. The reaction mixture was stirred at room temperature for 1 h. The resulting slightly yellow solution was poured into ice water (30 mL) and extracted with ether (3 x 30 mL). The organic extracts were combined, washed with brine solution (30 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (3:2 hexanes/ether) to afford the desired protected product as a white solid (2.09 g, quantitative).



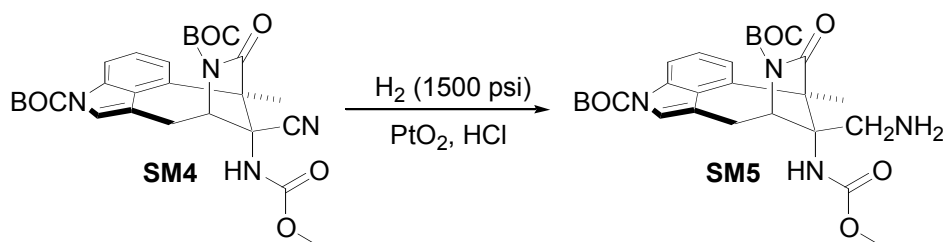
Cyanoamine 12. To a suspension of amide **SM3** (1.00 g, 2.28 mmol) in MeOH (23 mL) was added saturated NH₃/MeOH (3.4 mL) followed by titanium isopropoxide (810 μL, 2.74 mmol). The reaction mixture was stirred at room temperature for 1 h, and then trimethylsilylcyanide (1.20 mL, 9.00 mmol) was added. The reaction mixture was stirred for an additional 4 h. The resulting yellow solution was poured into ice water (25 mL) and extracted with CH₂Cl₂ (3 x 75 mL). The combined organic extracts were dried

over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:2 hexanes/ether) to afford the cyanoamine **12** as a white solid (736 mg, 69%). mp 154-156 °C; [α]_D²⁰ +56° (*c* 0.80, CHCl₃); IR (film) 3381, 3320, 2254, 1785, 1736 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.22 (dd, *J* = 6.4, 2.6 Hz, 1H), 7.53 (s, 1H), 7.38-7.31 (m, 2H), 4.96 (dd, *J* = 3.7, 3.0 Hz, 1H), 3.69 (ddd, *J* = 17.8, 3.9, 0.9 Hz, 1H), 3.24 (ddd, *J* = 17.8, 2.6, 2.1 Hz, 1H), 2.05 (s, 3H), 1.74 (s, 2H), 1.65 (s, 9H), 1.52 (s, 9H); ¹³C NMR (300 MHz, CDCl₃) δ 170.8, 149.4, 149.0, 135.6, 127.6, 127.1, 125.0, 124.8, 122.3, 121.6, 116.2, 113.9, 84.4, 84.2, 62.9, 60.5, 56.7, 28.2, 27.9, 25.1, 18.9; LRMS(ESI) *m/z* (relative intensity) 489.1 (88%, M+Na⁺); HRMS (ESI) *m/z* calcd for [C₂₅H₃₀N₄O₅Na]⁺: 489.2114, found 489.2110.



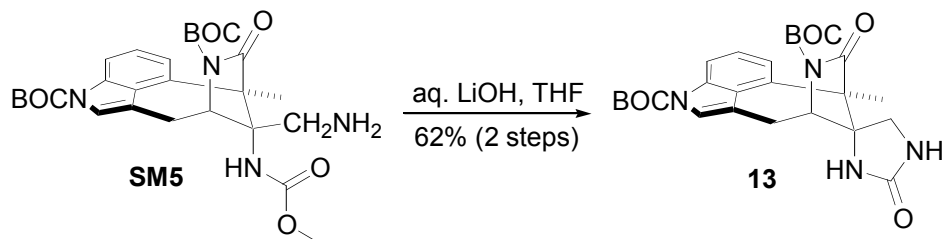
N-Moc Cyanoamine SM4. To a mixture of cyanoamine **12** (602 mg, 1.29 mmol) and K₂CO₃ (357 mg, 2.58 mmol) was added THF (13 mL) followed by methylchloroformate (220 μ L, 2.61 mmol). The reaction mixture was heated to reflux for 20 h. The resulting yellow solution was allowed to cool to room temperature, poured into ice water (15 mL), and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:2 hexanes/ether) to afford the desired protected amine as a white solid (527 mg, 78%). mp 164-166 °C; [α]_D²⁰ +43° (*c* 0.76, CHCl₃); IR (film) 3301, 2256, 1790, 1732 cm⁻¹; ¹H NMR (400 MHz,

CDCl₃) δ 8.24 (app.t, J = 4.3 Hz, 1H), 7.51 (s, 1H), 7.38-7.28 (m, 2H), 5.38 (br s, 1H), 5.19 (br s, 1H), 3.65 (d, J = 18.8 Hz, 1H), 3.60 (s, 3H), 2.98 (d, J = 17.9 Hz, 1H), 2.08 (s, 3H), 1.65 (s, 9H), 1.49 (s, 9H); ¹³C NMR (300 MHz, CDCl₃) δ 169.2, 155.1, 148.8, 148.7, 135.5, 127.4, 125.5, 124.8, 124.6, 122.5, 118.0, 116.6, 113.8, 84.3, 84.1, 61.9, 60.4, 55.4, 52.8, 27.8, 27.6, 24.9, 19.1; LRMS(ESI) m/z (relative intensity) 547.2 (60%, M+Na⁺); HRMS (ESI) m/z calcd for [C₂₇H₃₂N₄O₇Na]⁺: 547.2169, found 547.2165.

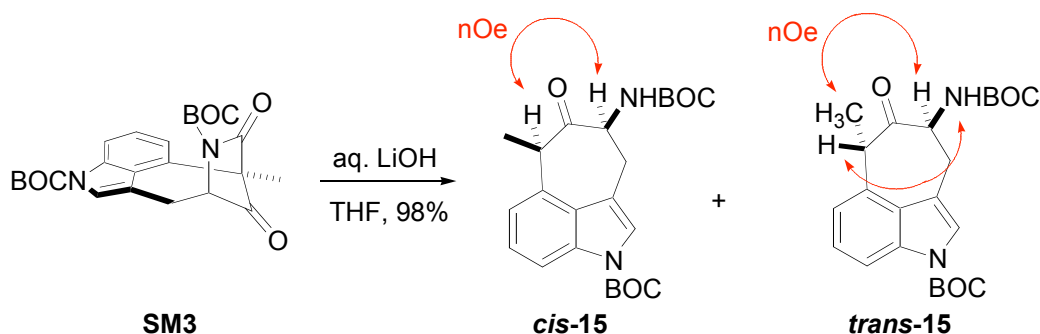


***N*-Moc Diamine **SM5**.** To a solution of cyanoamine **SM4** (669 mg, 1.28 mmol) in a 1:1 mixture of MeOH and EtOH (40 mL) was added PtO₂ (145 mg, 0.64 mmol) followed by a 10% solution of HCl in MeOH (1.05 mL, 1.27 mmol). The reaction mixture was placed in a sealable metal container equipped with a gas inlet and pressure gauge and pressurized with H₂ at 1500 psi for 17 h. The resulting clear and colorless solution with settled black particles was filtered through a Celite pad and the filtrate was poured into ice water (20 mL) and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give the crude residue as a white solid (674 mg). The crude residue was carried on to the next step without purification. IR (film) 3401, 1782, 1731 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.20 (d, J = 7.9 Hz, 1H), 7.47 (s, 1H), 7.34-7.27 (m, 2H), 4.83 (br s, 1H), 4.77 (s, 1H), 3.76 (d, J = 13.7 Hz, 1H), 3.61 (dd, J = 18.1, 3.3 Hz, 1H), 3.48 (s, 3H), 3.24 (d, J = 13.7 Hz, 1H), 3.03 (d, J = 17.9 Hz, 1H), 1.81 (s, 3H), 1.65 (s, 9H), 1.49 (s, 9H), 1.32 (br s, 2H); ¹³C NMR (300 MHz, CDCl₃) δ 172.6, 155.9, 149.7, 149.0, 135.6,

129.4, 128.2, 124.3, 124.1, 121.9, 115.7, 115.6, 83.7, 83.2, 62.7, 61.2, 56.9, 51.9, 46.2, 27.9, 27.8, 25.8, 16.2; LRMS(ESI) m/z (relative intensity) 529.2 (72%, $M+H^+$); HRMS (ESI) m/z calcd for $[C_{27}H_{37}N_4O_7]^+$: 529.2662, found 529.2656.

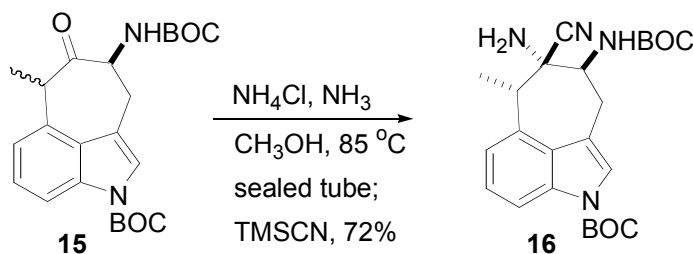


Cyclic Urea 13. To a solution of amine **SM5** (674 mg, 1.28 mmol) in THF (25 mL) was added a deoxygenated 1 M aq. LiOH solution (5.1 mL, 5.1 mmol). The reaction mixture was heated to reflux for 17 h. The resulting slightly yellow solution was allowed to cool to room temperature and then poured into ice water and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a yellow solid (600 mg). Cold ether (10 mL) was added to the resulting yellow solid to dissolve impurities and the desired cyclic urea was collected by filtration (394 mg, 62% over 2 steps). mp 248 °C (dec.); $[\alpha]_D^{20} +88^\circ$ (c 1.00, DMSO); IR (film) 3344, 1782, 1730, 1687 cm^{-1} ; 1H NMR (300 MHz, DMSO- d_6) δ 8.45 (s, 1H), 8.08 (d, $J = 8.2$ Hz, 1H), 7.82 (s, 1H), 7.73 (s, 1H), 7.58 (d, $J = 7.9$, 1H), 7.30 (t, $J = 8.1$ Hz, 1H), 4.27 (dd, $J = 12.4, 3.1$ Hz, 1H), 3.83 (dd, $J = 16.1, 2.9$ Hz, 1H), 3.60 (d, $J = 10.4$ Hz, 1H), 3.34 (s, 3H), 3.21 (d, $J = 8.9$ Hz, 1H), 2.86 (t, $J = 13.5$ Hz, 1H), 1.60 (s, 9H), 1.46 (s, 9H), 1.43 (s, 3H); ^{13}C NMR (300 MHz, DMSO- d_6) δ 175.6, 153.7, 150.9, 148.7, 135.4, 132.5, 127.4, 124.4, 124.2, 123.8, 114.3, 113.6, 83.8, 81.7, 65.9, 55.1, 53.7, 48.6, 27.8, 27.7, 26.4, 19.4; LRMS(ESI) m/z (relative intensity) 519.2 (52%, $M+Na^+$); HRMS (ESI) m/z calcd for $[C_{26}H_{32}N_4O_6Na]^+$: 519.2220, found 519.2227.



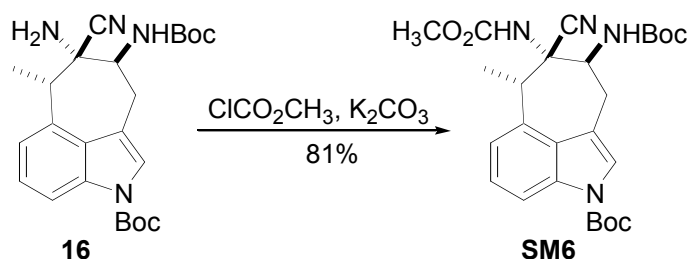
***tert*-Butyl 8-*tert*-Butoxycarbonylamino-6-methyl-7-oxo-6,7,8,9-tetrahydro-2-aza benzo[*cd*]azulene-2 Carboxylate (**15**).** To an ice-cooled solution of amide **SM3** (1.029 g, 2.34 mmol) in THF (47 mL) was added a deoxygenated 1 M aq. LiOH solution (4.7 mL, 4.7 mmol). The reaction mixture was stirred in an ice bath for 1 h and then at room temperature for 14 h. The resulting slightly yellow solution was poured into ice water (30 mL) and extracted with ether (3 x 40 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (3:2 hexanes/ether) to afford a ~ 2:1 diastereomeric mixture of ketones **15** as a white solid (951 mg, 98%). Major product (*cis*-**15**): mp 163-164 °C; [α]_D²⁰ +29° (*c* 1.00, CHCl₃); IR (film) 3416, 1729 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.99 (d, *J* = 8.1 Hz, 1H), 7.43 (s, 1H), 7.26 (t, *J* = 7.9 Hz, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 5.42 (br s, 1 H), 4.74 (br dd, *J* ~ 9.2, 4.6 Hz, 1H), 4.62 (q, *J* = 6.8 Hz, 1H), 3.60 (dd, *J* = 15.7, 4.6 Hz, 1H), 3.17 (dd, *J* = 15.8, 4.2 Hz, 1H), 1.65 (s, 9H), 1.65 (d, *J* = 6.9 Hz, 3H), 1.45 (s, 9H); ¹³C NMR (300 MHz, CDCl₃) δ 206.1, 155.5, 149.2, 135.1, 130.7, 128.3, 125.0, 123.0, 118.7, 116.1, 114.1, 83.5, 79.5, 61.4, 45.7, 28.2, 28.0, 27.6, 14.4; LRMS(ESI) *m/z* (relative intensity) 437.2 (100%, M+Na⁺); HRMS (ESI) *m/z* calcd for [C₂₃H₃₀N₂O₅Na]⁺: 437.2052, found 457.2042. Anal. Calcd for C₂₃H₃₀N₂O₅: C, 66.65; H, 7.30; N, 6.76. Found: C, 66.59; H, 7.32; N, 6.76. Minor product (*trans*-**15**):

mp 170-171 °C; $[\alpha]_D^{20} +90^\circ$ (c 1.00, CHCl_3); IR (film) 3385, 1720 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.06 (d, J = 8.1 Hz, 1H), 7.48 (s, 1H), 7.30 (t, J = 7.9 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 5.52 (br s, 1 H), 4.50 (q, J = 7.0 Hz, 1H), 4.43 (br dd, J ~ 11.9, 5.7 Hz, 1H), 3.29 (dd, J = 14.7, 2.7 Hz, 1H), 3.19 (ddd, J = 15.2, 10.2, 1.4 Hz, 1H), 1.66 (s, 9H), 1.64 (d, J = 7.0 Hz, 3H), 1.45 (s, 9H); ^{13}C NMR (300 MHz, CDCl_3) δ 208.8, 155.4, 149.4, 135.6, 130.7, 128.0, 124.9, 123.1, 120.4, 116.1, 113.9, 83.7, 80.0, 58.9, 49.0, 29.3, 28.3, 28.1, 16.4; LRMS(ESI) m/z (relative intensity) 437.2 (100%, $\text{M}+\text{Na}^+$); HRMS (ESI) m/z calcd for $[\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_5\text{Na}]^+$: 437.2052, found 437.2060.



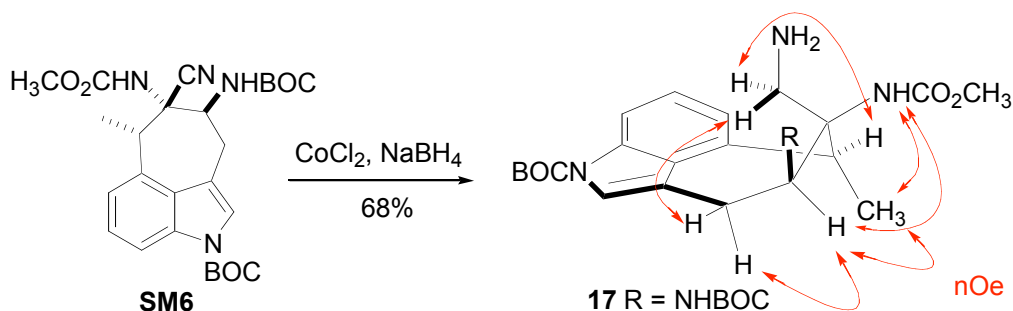
(±)-*tert*-Butyl 7-Amino-8-*tert*-butoxycarbonylamino-7-cyano-6-methyl-6,7,8,9- tetrahydro-2-aza-benzo[*cd*]azulene-2 Carboxylate (16). A solution of the diastereomeric mixture of ketones **15** (645 mg, 1.56 mmol) and NH_4Cl (166 mg, 3.10 mmol) in saturated NH_3/MeOH (15 mL) in a sealed tube was heated to 85 °C for 4 h. The reaction mixture was allowed to cool to room temperature and trimethylsilylcyanide (830 μL , 6.22 mmol) was added. The reaction mixture was stirred in a sealed tube at room temperature for 14 h. The resulting yellow suspension was diluted with CH_2Cl_2 (25 mL) and then poured into ice water (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (2:1 hexanes/EtOAc and

100% EtOAc, respectively) to afford the cyanoamine **16** as a light yellow solid (494 mg, 72%). mp 152-154 °C; $[\alpha]_D^{20}$ -0.8° (*c* 1.00, CHCl₃); IR (film) 3326, 2252, 1727 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.00 (d, *J* = 8.0 Hz, 1H), 7.40 (s, 1H), 7.27 (t, *J* = 7.9 Hz, 1H), 7.06 (d, *J* = 7.4 Hz, 1H), 5.16 (br d, *J* = 9.9, 1H), 4.0 (td, *J* = 9.8, 2.8 Hz, 1H), 3.70 (q, *J* = 7.1 Hz, 1H), 3.24 (dd, *J* = 15.5, 9.5 Hz, 1H), 3.05 (dd, *J* = 15.7, 2.4 Hz, 1H), 2.05 (br s, 2H), 1.66 (s, 9H), 1.62 (d, *J* = 7.2 Hz, 3H), 1.45 (s, 9H); ¹³C NMR (300 MHz, CDCl₃) δ 155.7, 149.5, 135.4, 132.0, 129.1, 124.9, 122.7, 122.3, 121.8, 116.7, 114.5, 83.7, 80.7, 65.2, 57.6, 43.6, 30.4, 28.3, 28.2, 15.6; LRMS(ESI) *m/z* (relative intensity) 441.2 (35%, M+H⁺); HRMS (ESI) *m/z* calcd for [C₂₄H₃₃N₄O₄]⁺: 441.2502, found 441.2497.



(±)-tert-Butyl 8-tert-Butoxycarbonylamino-7-cyano-7-methoxycarbonylamino-6-methyl-6,7,8,9-tetrahydro-2-aza-benzo[cd]azulene-2 Carboxylate (SM6). To a mixture of cyanoamine **16** (84 mg, 0.19 mmol) and K₂CO₃ (53 mg, 0.38 mmol) was added THF (4 mL) followed by methylchloroformate (100 μL, 1.19 mmol). The reaction mixture was heated to reflux and held there for 20 h. The resulting yellow solution was allowed to cool to room temperature, poured into ice water (10 mL), and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (1:2 ether/hexanes) to afford the desired product **SM6** as a

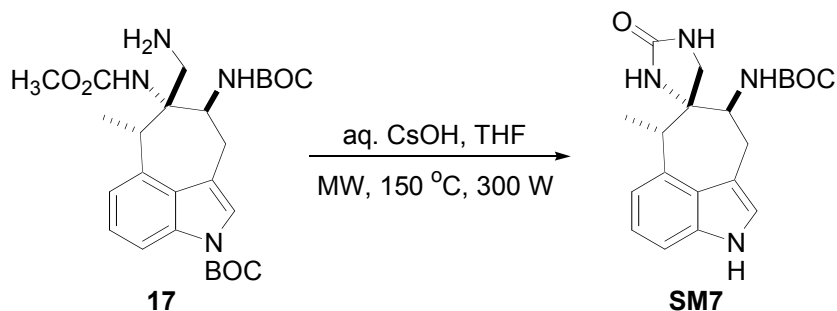
white solid (77 mg, 81%). mp 138-140 °C; $[\alpha]_D^{20} +0.2^\circ$ (c 1.00, CHCl_3); IR (film) 3328, 2254, 1731, 1689 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.02 (d, J = 8.0 Hz, 1H), 7.42 (s, 1H), 7.27 (t, J = 7.9 Hz, 1H), 7.10 (d, J = 7.3 Hz, 1H), 6.50 (br s, 1H), 5.40 (br d, J = 9.1, 1H), 4.43 (td, J = 8.5, 5.5 Hz, 1H), 4.42 (q, J = 7.3 Hz, 1H), 3.73 (s, 3H), 3.42 (dd, J = 16.9, 5.1 Hz, 1H), 3.16 (dd, J = 17.1, 7.8 Hz, 1H), 1.65 (s, 9H), 1.47 (s, 9H), 1.44 (d, J = 7.4, 3H); ^{13}C NMR (300 MHz, CDCl_3) δ 156.8, 155.1, 149.3, 135.6, 133.1, 127.9, 124.9, 123.2, 123.1, 117.4, 114.4, 114.1, 83.7, 81.4, 65.0, 53.0, 52.4, 43.7, 30.4, 28.08, 28.06, 17.5; LRMS(ESI) m/z (relative intensity) 521.2 (100%, $\text{M}+\text{Na}^+$); HRMS (ESI) m/z calcd for $[\text{C}_{26}\text{H}_{34}\text{N}_4\text{O}_6\text{Na}]^+$: 521.2376, found 521.2361. Anal. Calcd for $\text{C}_{26}\text{H}_{34}\text{N}_4\text{O}_6$: C, 62.63; H, 6.87; N, 11.24. Found: C, 62.37; H, 6.97; N, 10.99.



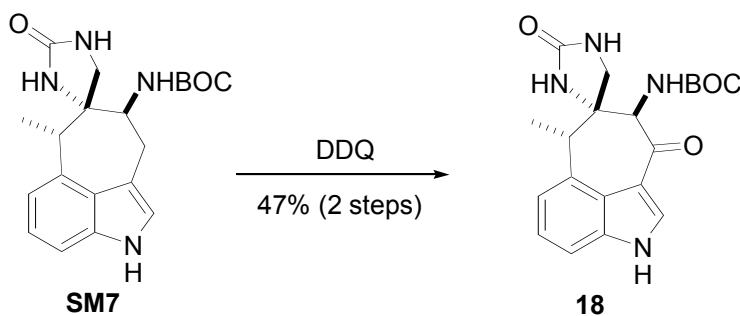
(±)-*tert*-Butyl 7-Aminomethyl-8-*tert*-butoxycarbonylamino-7-methoxycarbonylamino-6-methyl-6,7,8,9-tetrahydro-2-aza-benzo[*cd*]azulene-2 Carboxylate (17).

To a solution of cyanoamine **SM6** (358 mg, 0.72 mmol) in MeOH (30 mL) was added cobalt (II) chloride (2.33 g, 17.9 mmol). The resulting dark blue solution was cooled in an ice bath and sodium borohydride (679 mg, 17.9 mmol) was added in portions. The resulting black suspension was stirred at room temperature for 3 h. It was then recooled in an ice bath and additional sodium borohydride (679 mg, 17.9 mmol) was added in portions. The reaction mixture was stirred at room temperature for 38 h. The resulting black suspension was diluted with MeOH (30 mL) and acidified with 1 M H_3PO_4 solution

(30 mL). The acidic solution was stirred vigorously for 1 h until it turned pink and clear. The pink solution was diluted with CH₂Cl₂ (30 mL) and made alkaline by the addition of saturated NaHCO₃ (30 mL). The resulting purple precipitate was filtered off and washed with CH₂Cl₂ (30 mL). The organic layer of the filtrate was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 30 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (3:2 hexanes/ether and 100% EtOAc, respectively) to afford the desired amine **17** as a white solid (246 mg, 68%). mp 124-126 °C; $[\alpha]_D^{20}$ -0.2° (*c* 1.00, CHCl₃); IR (film) 3325, 1729 cm⁻¹; ¹H NMR (300 MHz, C₆D₆) δ 8.33 (d, *J* = 7.2 Hz, 1H), 7.23 (s, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 9.5 Hz, 1H), 6.90 (d, *J* = 6.8 Hz, 1H), 5.78 (s, 1H), 4.73 (td, *J* = 10.7, 4.6 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 1H), 3.76 (d, *J* = 13.3 Hz, 1H), 3.47 (s, 3H), 3.29 (dd, *J* = 16.9, 4.6 Hz, 1H), 2.78 (ddd, *J* = 16.6, 12.1, 1.7 Hz, 1H), 2.64 (dd, *J* = 13.2 Hz, 1H), 1.52 (s, 9H), 1.39 (s, 9H), 1.24 (d, *J* = 7.2 Hz, 3H), 0.59 (br s, 2H); ¹³C NMR (300 MHz, CDCl₃) δ 156.4, 155.1, 149.5, 136.4, 135.8, 127.1, 124.5, 123.7, 123.0, 115.6, 113.1, 83.5, 79.8, 62.8, 51.7, 51.3, 43.8, 43.2, 30.2, 28.5, 28.2, 20.5; LRMS(ESI) *m/z* (relative intensity) 503.2 (100%, M+H⁺); HRMS (ESI) *m/z* calcd for [C₂₆H₃₉N₄O₆]⁺: 503.2870, found 503.2874.



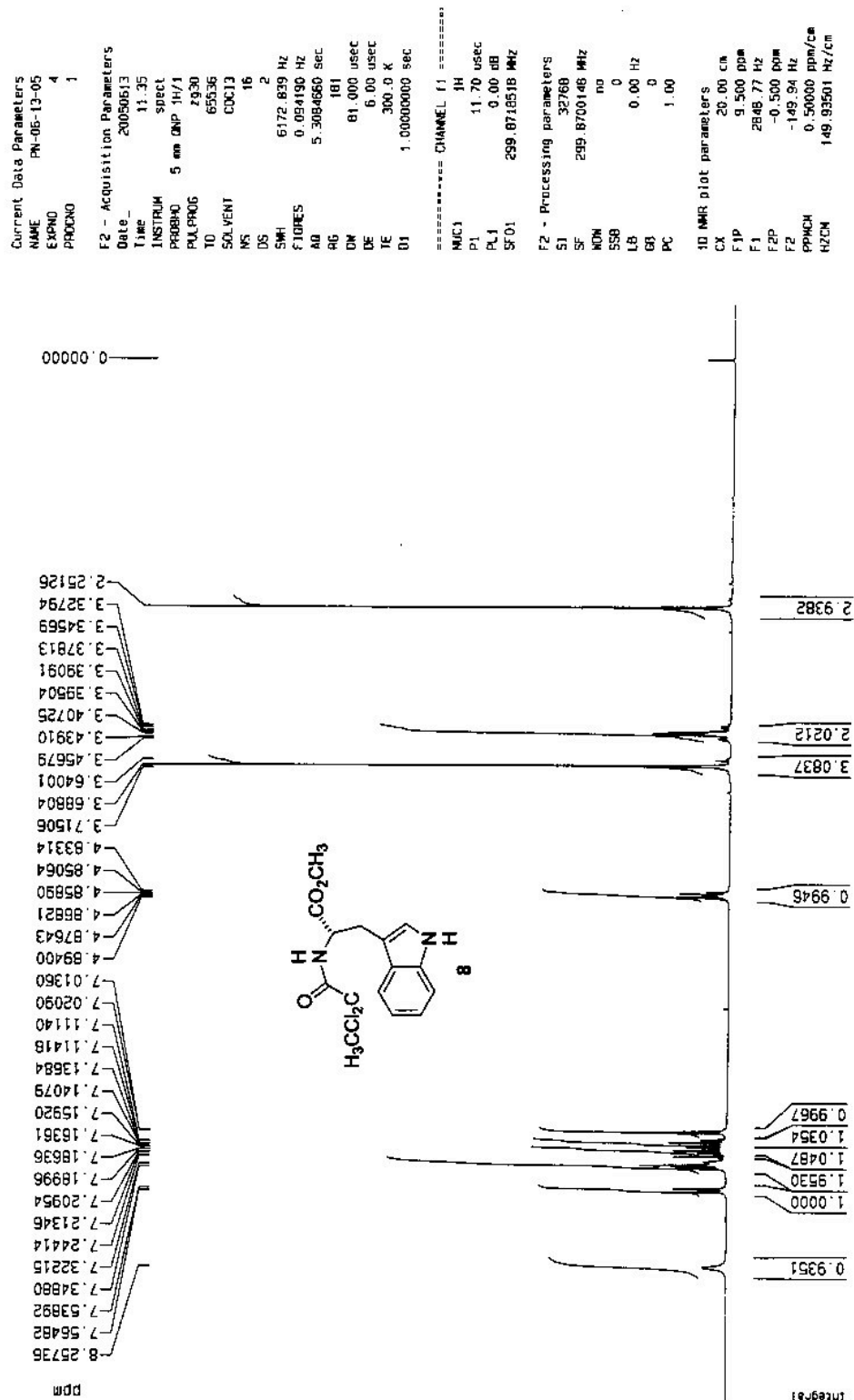
by THF (2 mL). The reaction mixture was heated to 150 °C at 300 W in a microwave reactor for 1 h. The resulting slightly yellow suspension was poured into ice water (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford a light yellow solid (20 mg, 91% crude). The crude residue was carried on to the next step without purification. IR (film) 3416, 1687 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.19 (br s, 1H), 7.23 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.02 (s, 1H), 6.93 (d, *J* = 7.1 Hz, 1H), 5.42 (br s, 1H), 4.98 (br d, *J* = 8.6 Hz, 1H), 4.58 (m, 1H), 4.43 (br s, 1H), 3.69 (q, *J* = 7.1 Hz, 1H), 3.49-3.21 (m, 2H), 3.19 (d, *J* = 9.7, 1H), 2.84 (dd, *J* = 15.4, 11.7 Hz, 1H), 1.48 (s, 9H), 1.40 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (300 MHz, DMSO-d₆) δ 161.6, 155.9, 136.4, 135.2, 123.3, 122.5, 121.1, 119.1, 109.3, 109.2, 77.9, 65.6, 49.3, 49.1, 44.6, 28.4, 28.2, 19.4; LRMS(ESI) *m/z* (relative intensity) 371.2 (100%, M+H⁺); HRMS (ESI) *m/z* calcd for [C₂₀H₂₆N₄O₃Na]⁺: 393.1903, found 393.1898.



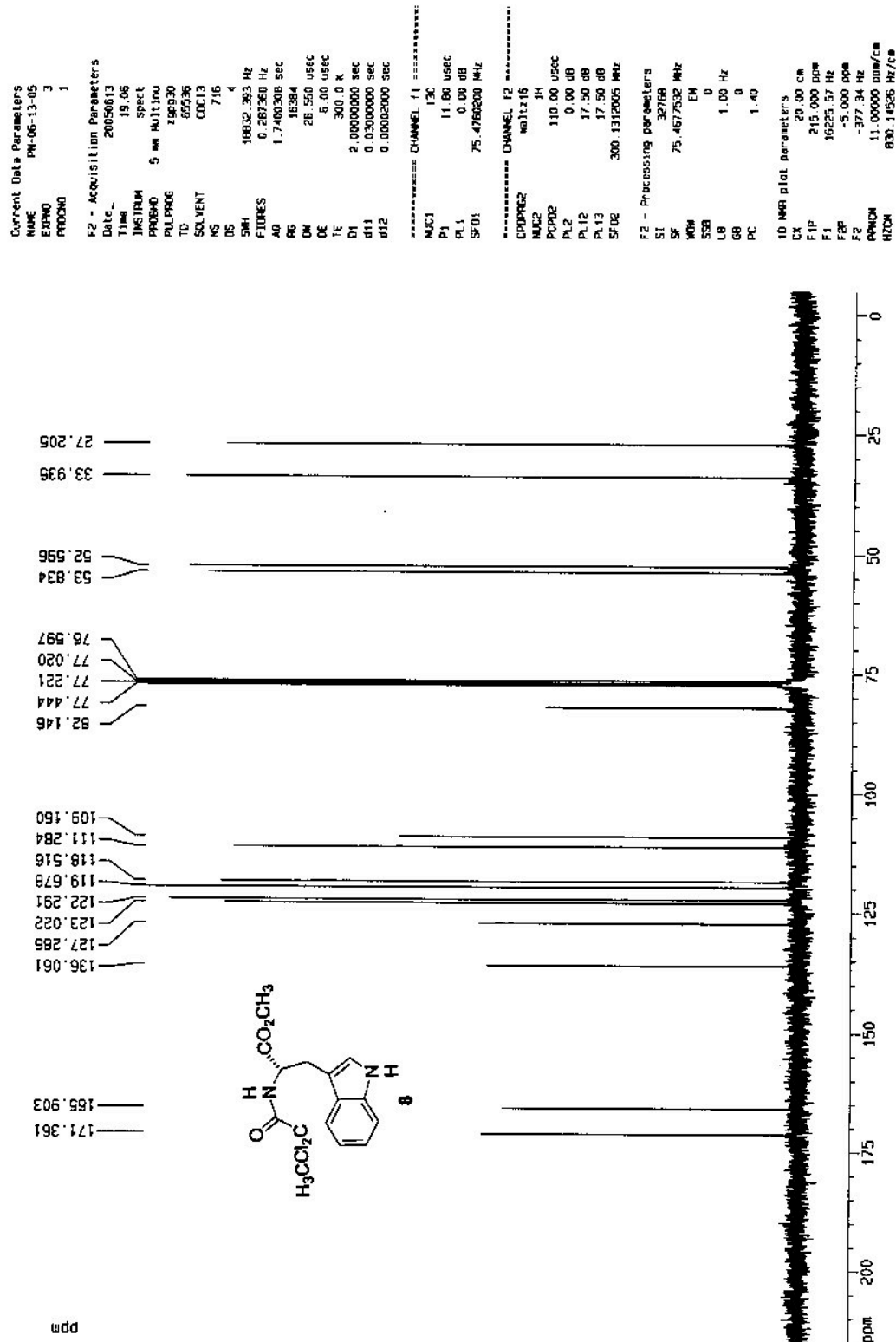
(±)-Cyclic Urea **18**. To an ice-cooled solution of cyclic urea **SM7** (103 mg, 0.28 mmol) in a 10:1 mixture of THF and H₂O (5.5 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (127 mg, 0.56 mmol). The reaction mixture was stirred in an ice bath for 1 h and then at room temperature for 14 h. The resulting dark yellow solution was concentrated to dryness. CH₂Cl₂ (10 mL) was added to the dark red solid residue followed by a 0.1 M aq. NaOH solution (10 mL). The precipitate was filtered off

and washed with CH₂Cl₂ (10 mL). The organic layer of the filtrate was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 25 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (100% EtOAc) to afford the desired product **18** as a yellow solid (55 mg, 47% over steps). mp 276 °C (dec.); IR (film) 3408, 1691, 1634 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 12.32 (s, 1H), 8.19 (s, 1H), 7.37 (dd, *J* = 7.2, 0.9 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 6.9 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 1H), 6.44 (s, 1H), 6.02 (s, 1H), 4.89 (d, *J* = 8.6 Hz, 1H), 3.53 (q, *J* = 7.2 Hz, 1H), 3.11 (d, *J* = 8.6 Hz, 1H), 2.76 (d, *J* = 9.1 Hz, 1H), 1.45 (s, 9H), 1.40 (d, *J* = 7.1 Hz, 3H); ¹³C NMR (300 MHz, DMSO-d₆) δ 188.7, 161.5, 156.9, 136.7, 134.7, 133.2, 123.1, 122.6, 121.2, 114.2, 110.7, 78.4, 62.4, 61.4, 49.3, 46.8, 28.4, 19.9; LRMS(ESI) *m/z* (relative intensity) 407.2 (100%, M+Na⁺); HRMS (ESI) *m/z* calcd for [C₂₀H₂₄N₄O₄Na]⁺: 407.1696, found 407.1699.

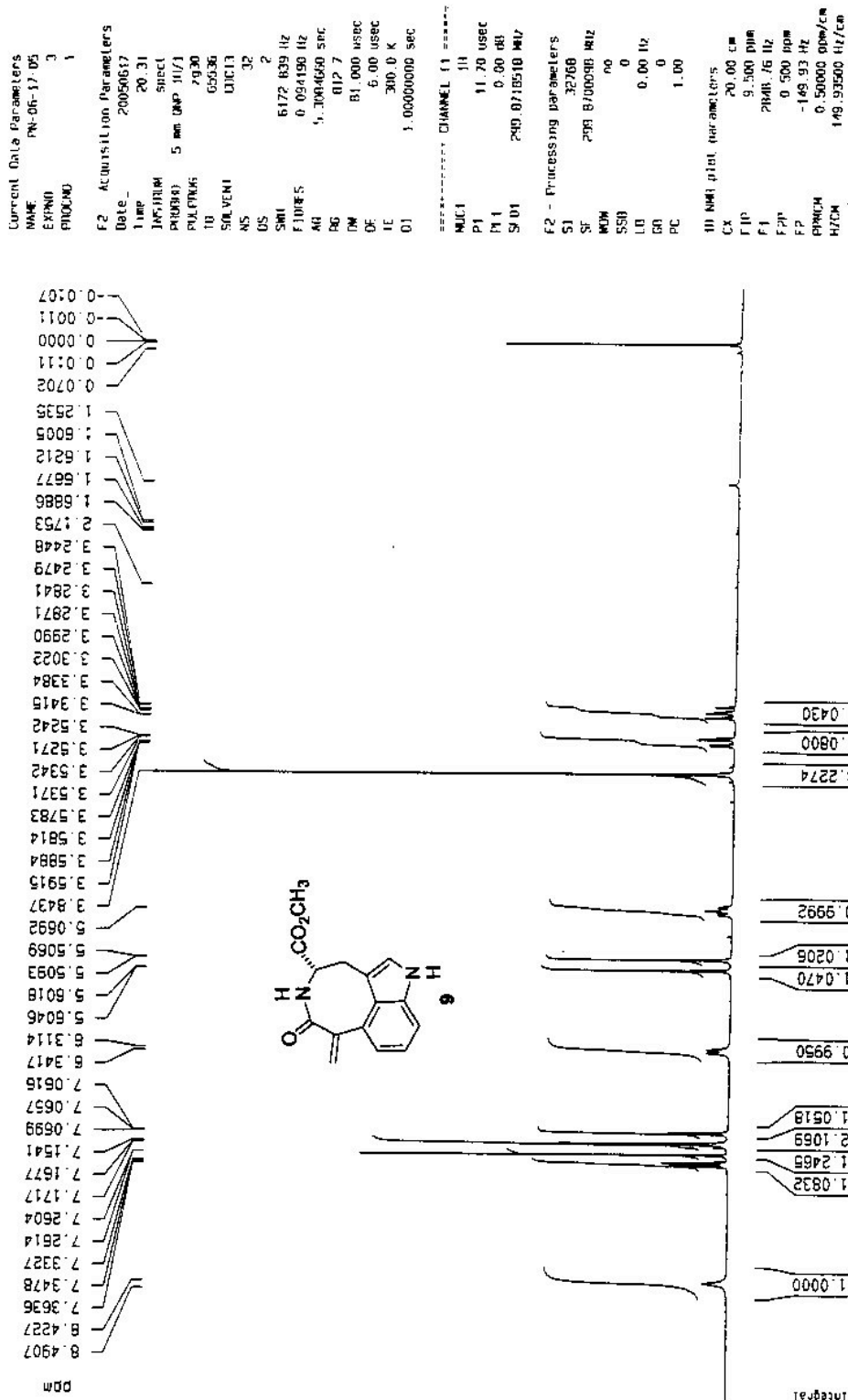
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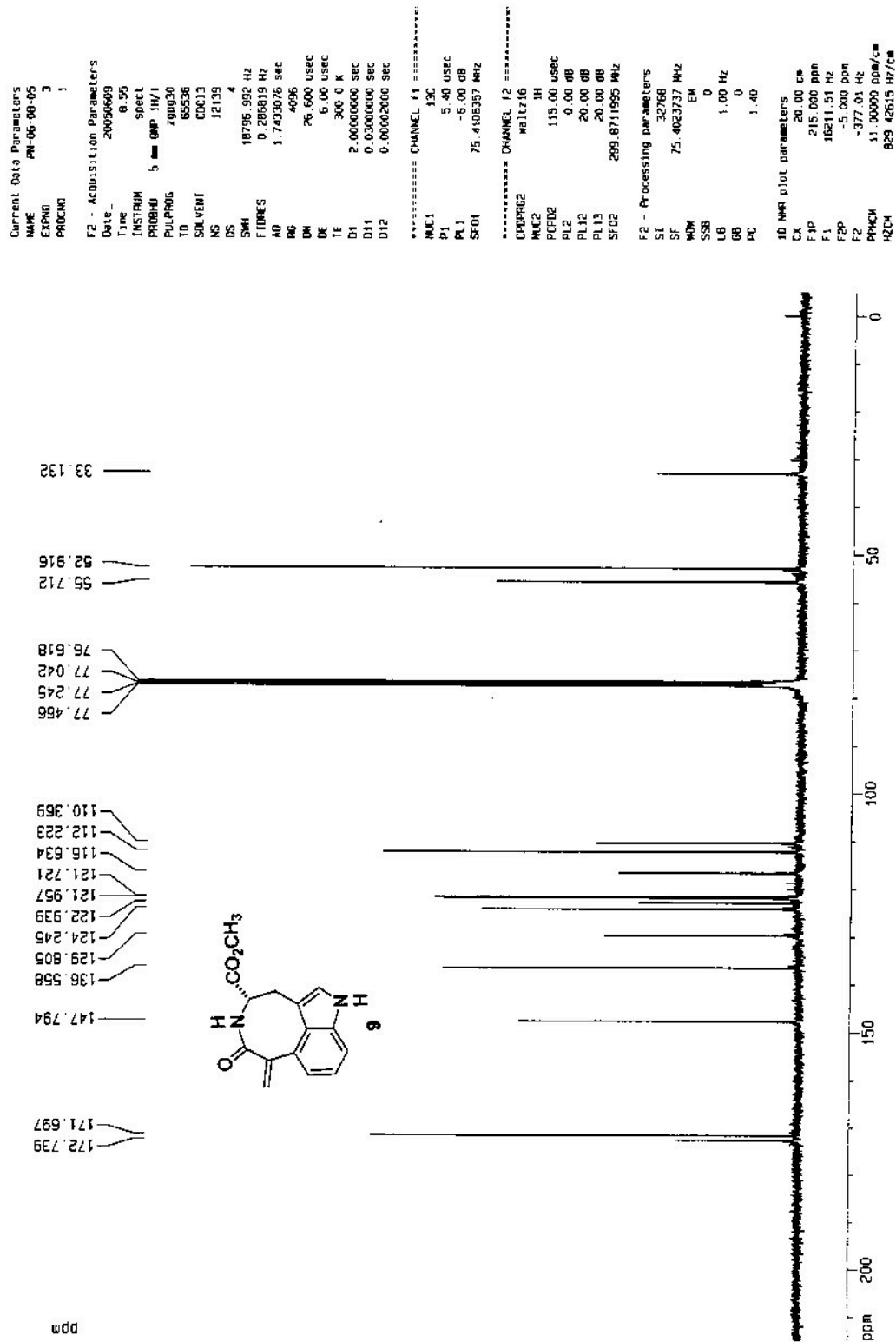
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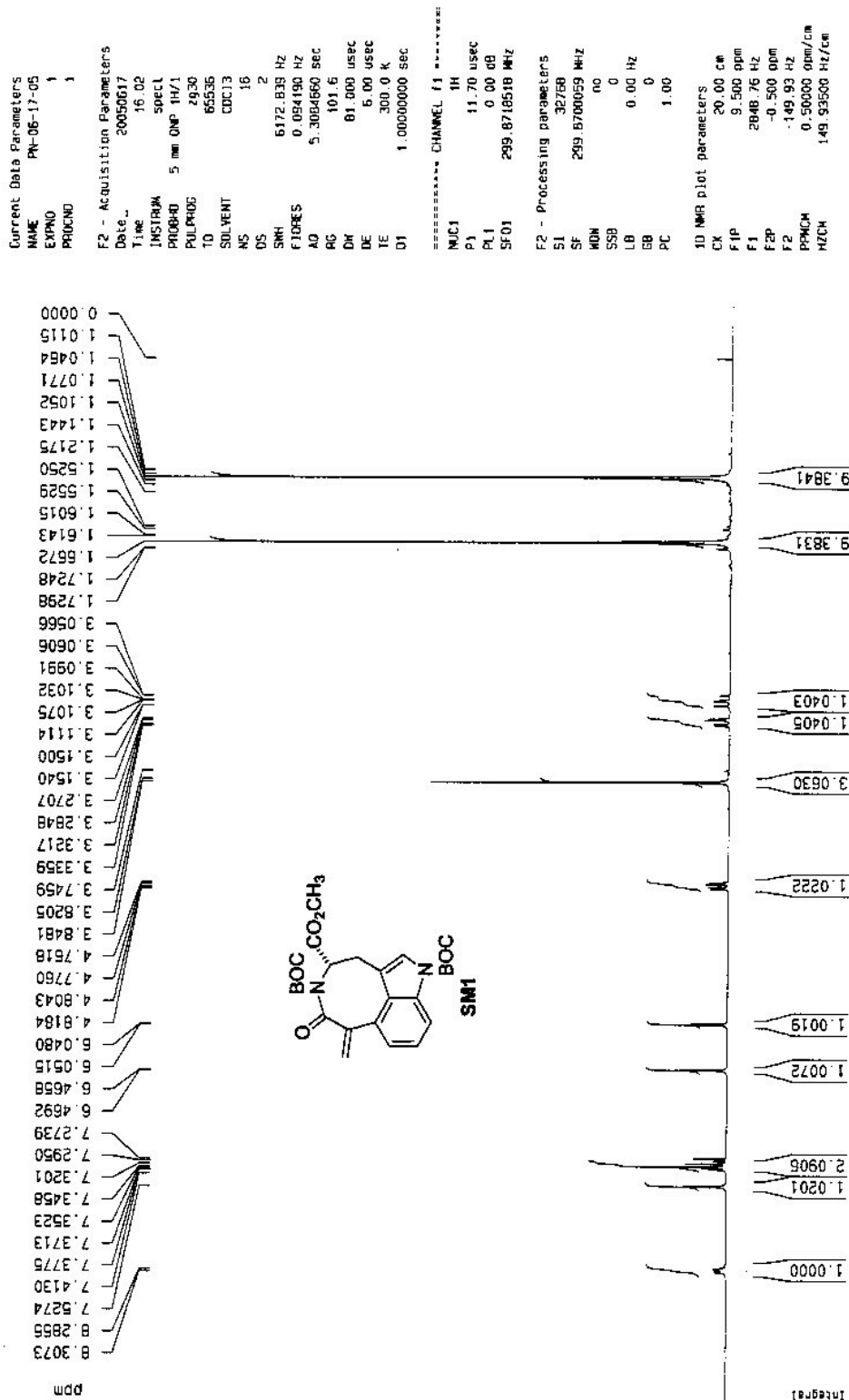
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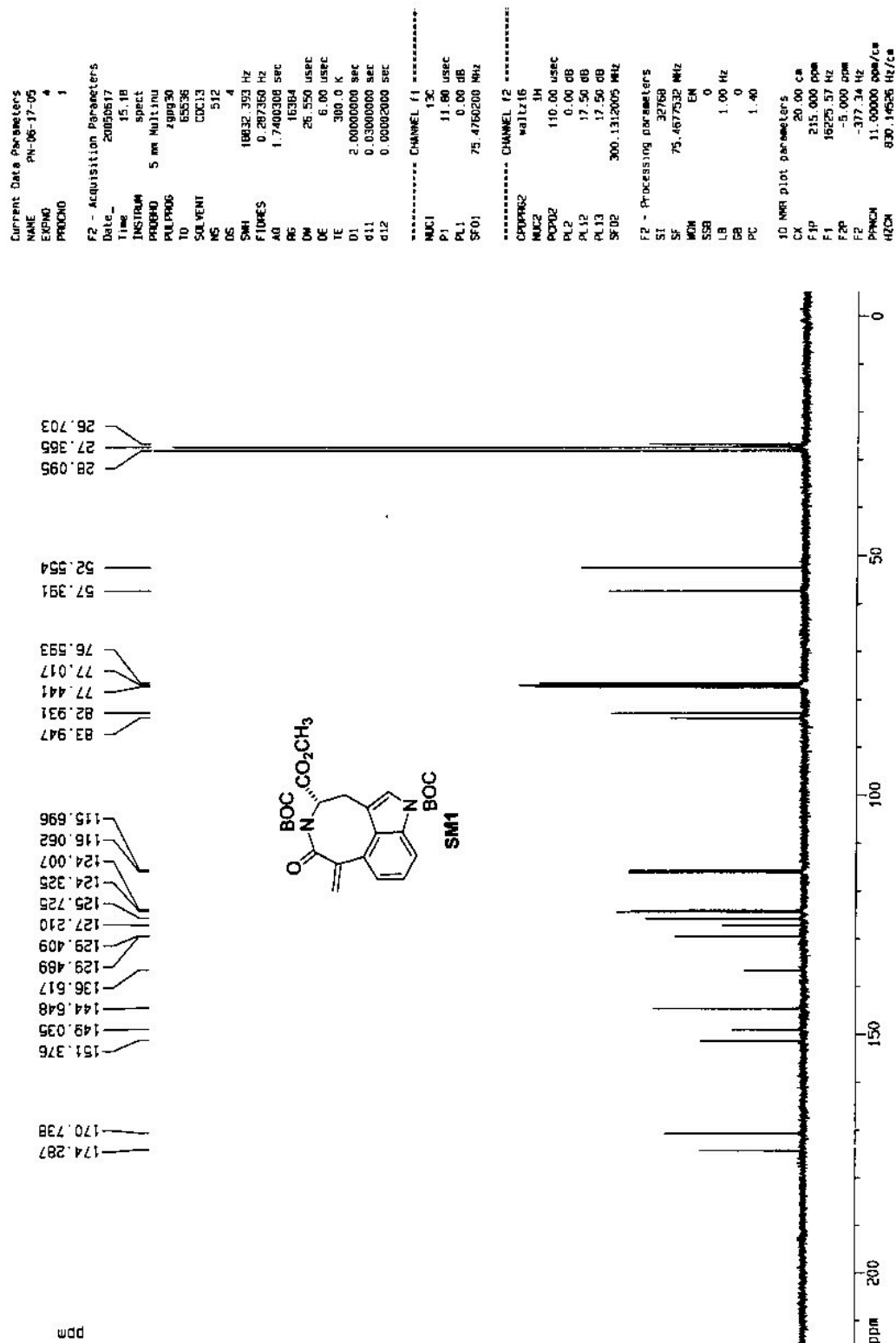
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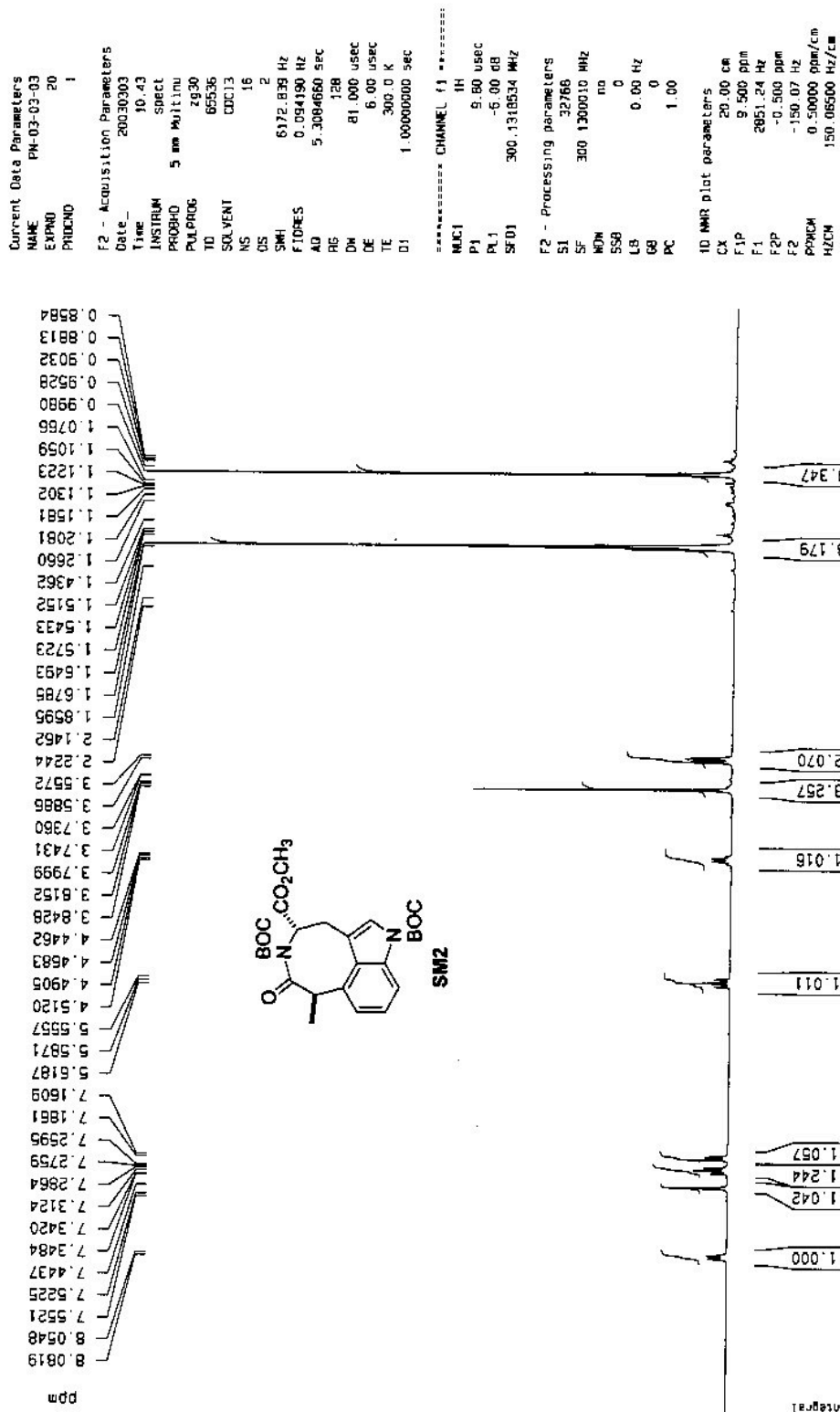
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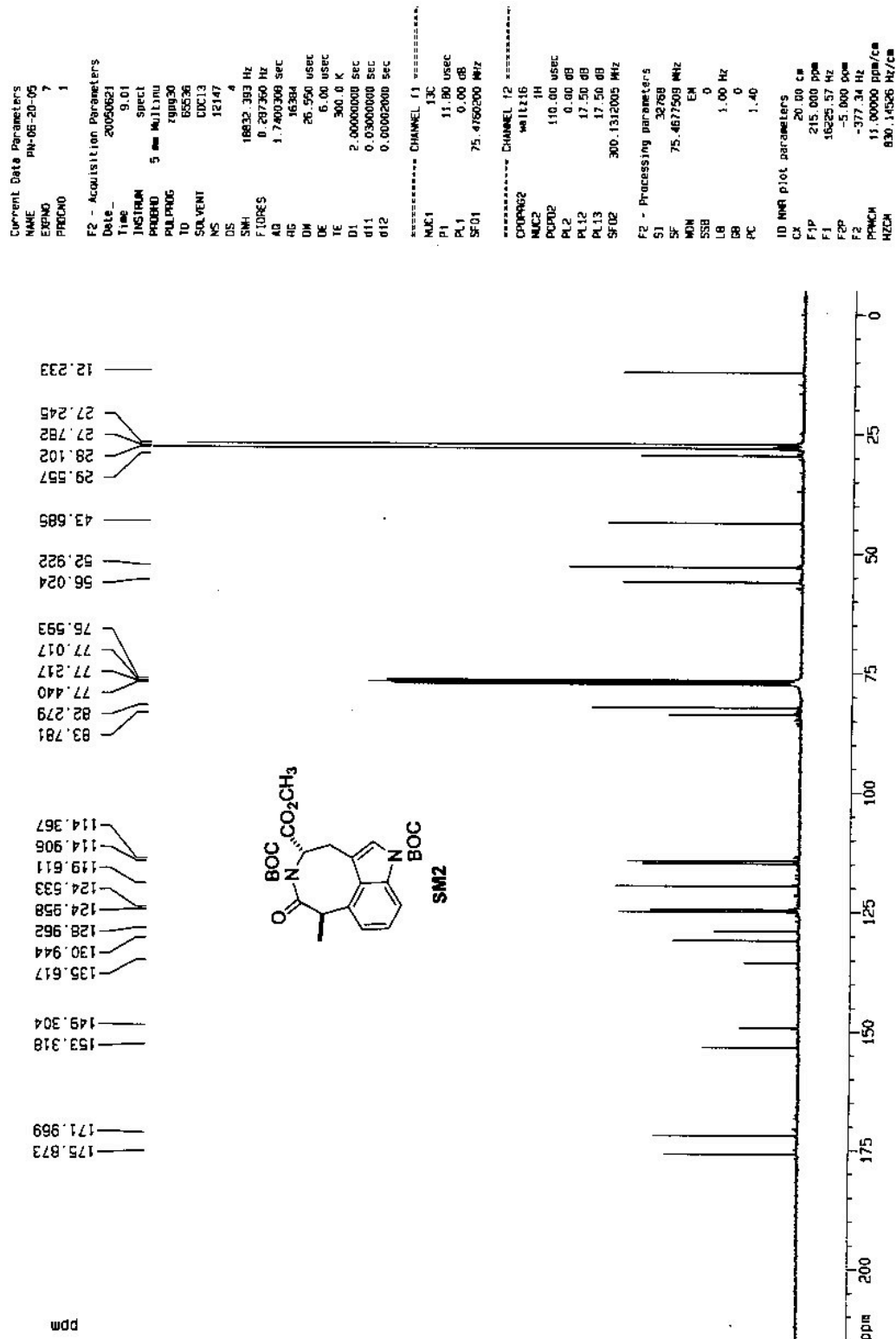
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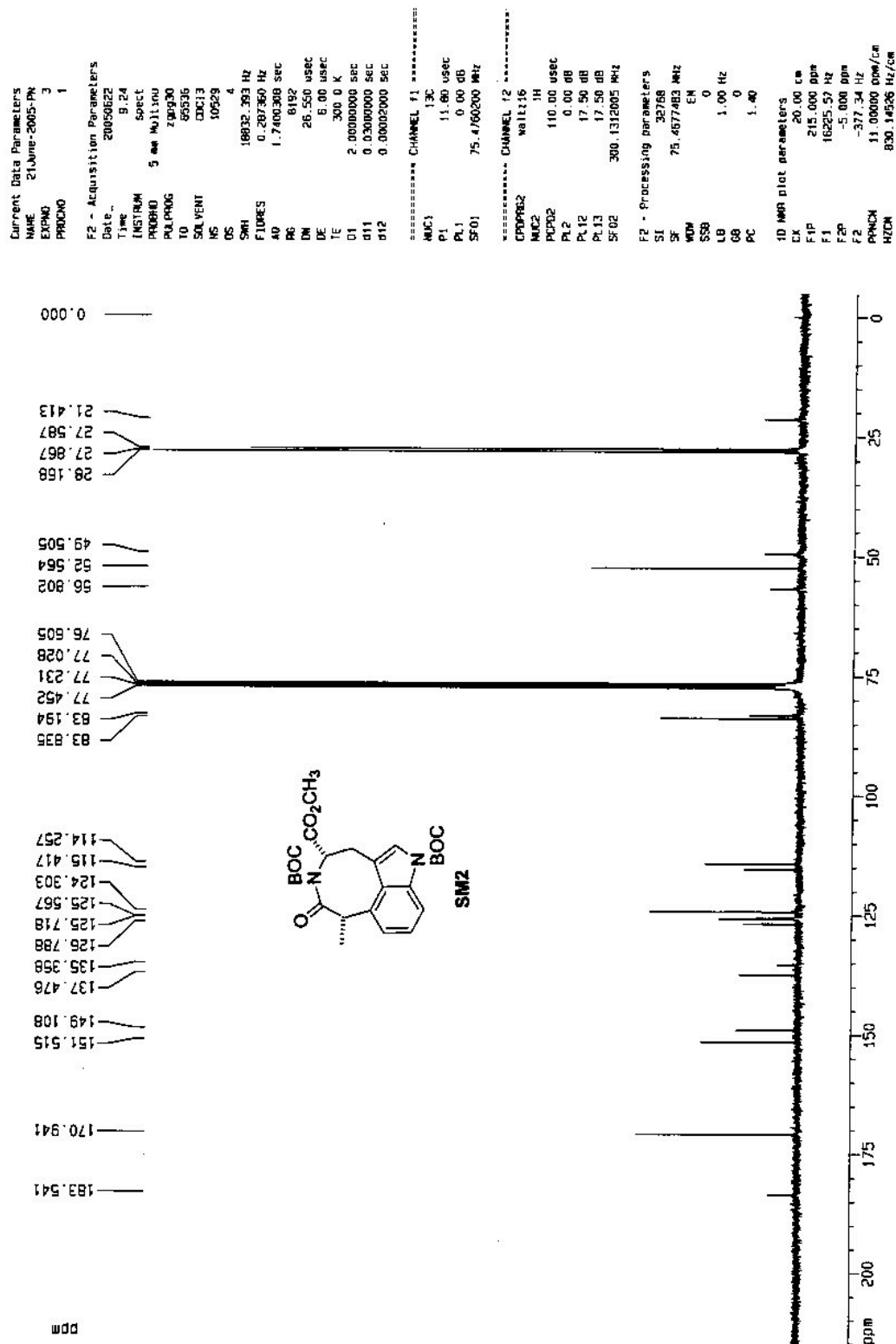


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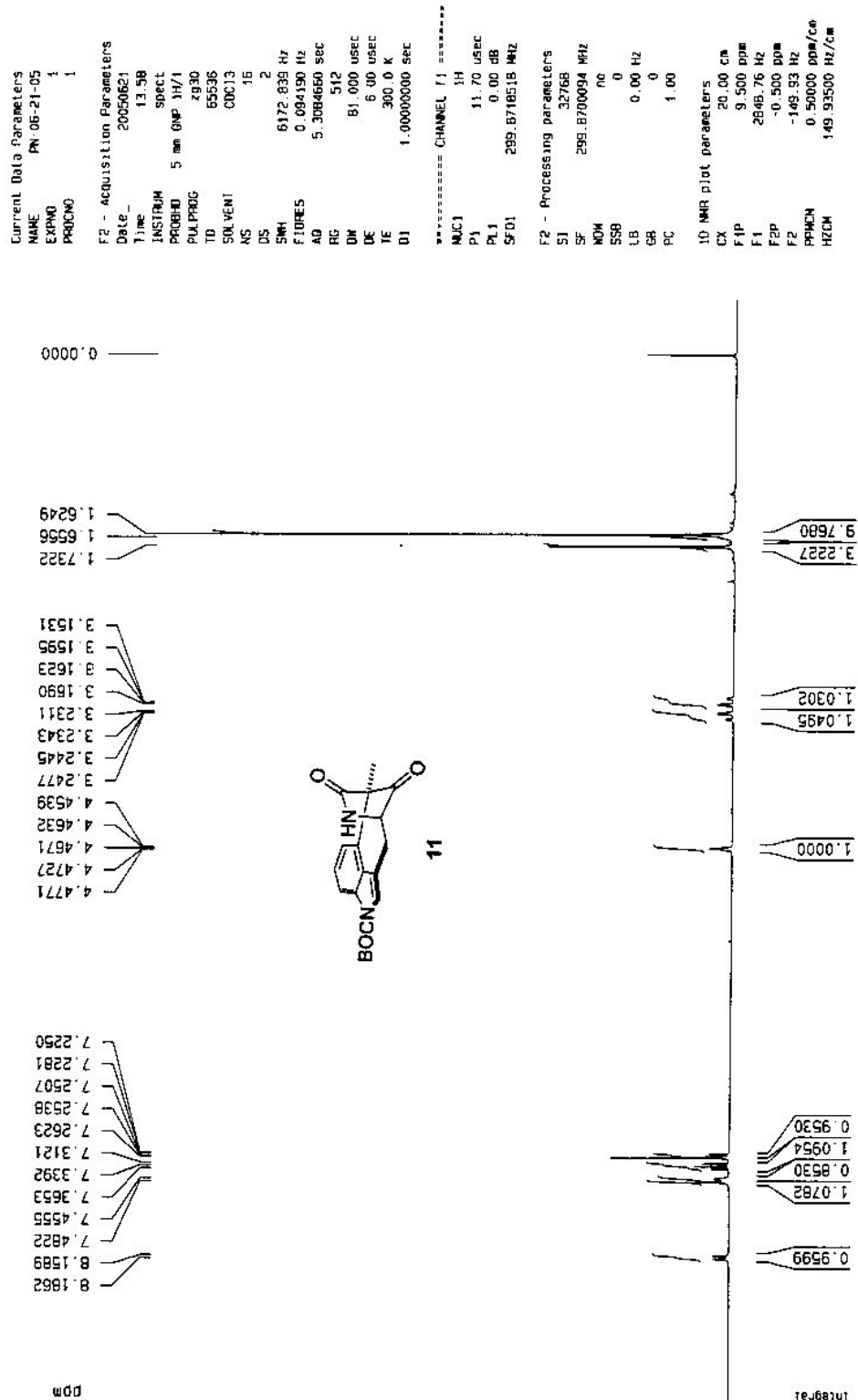




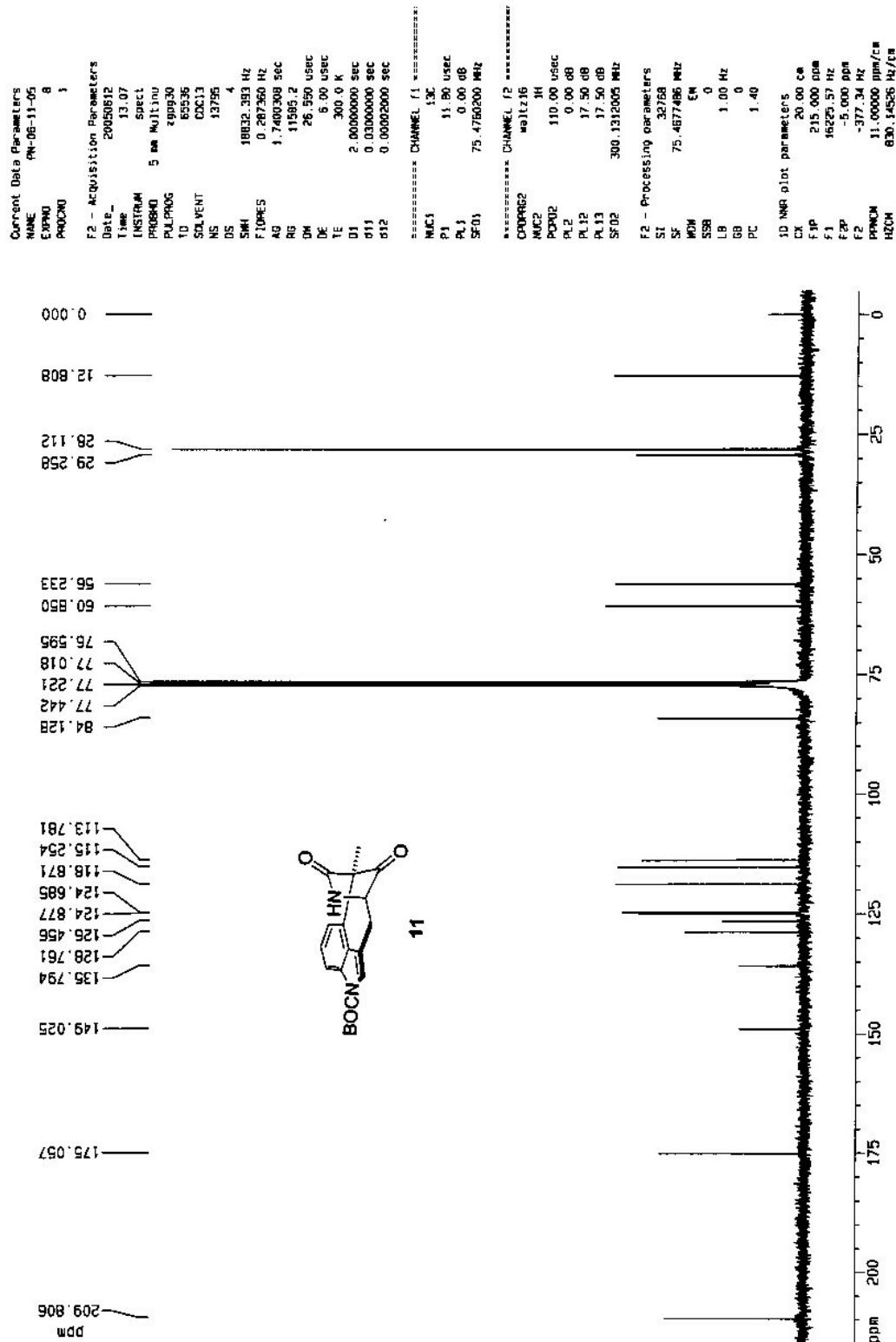
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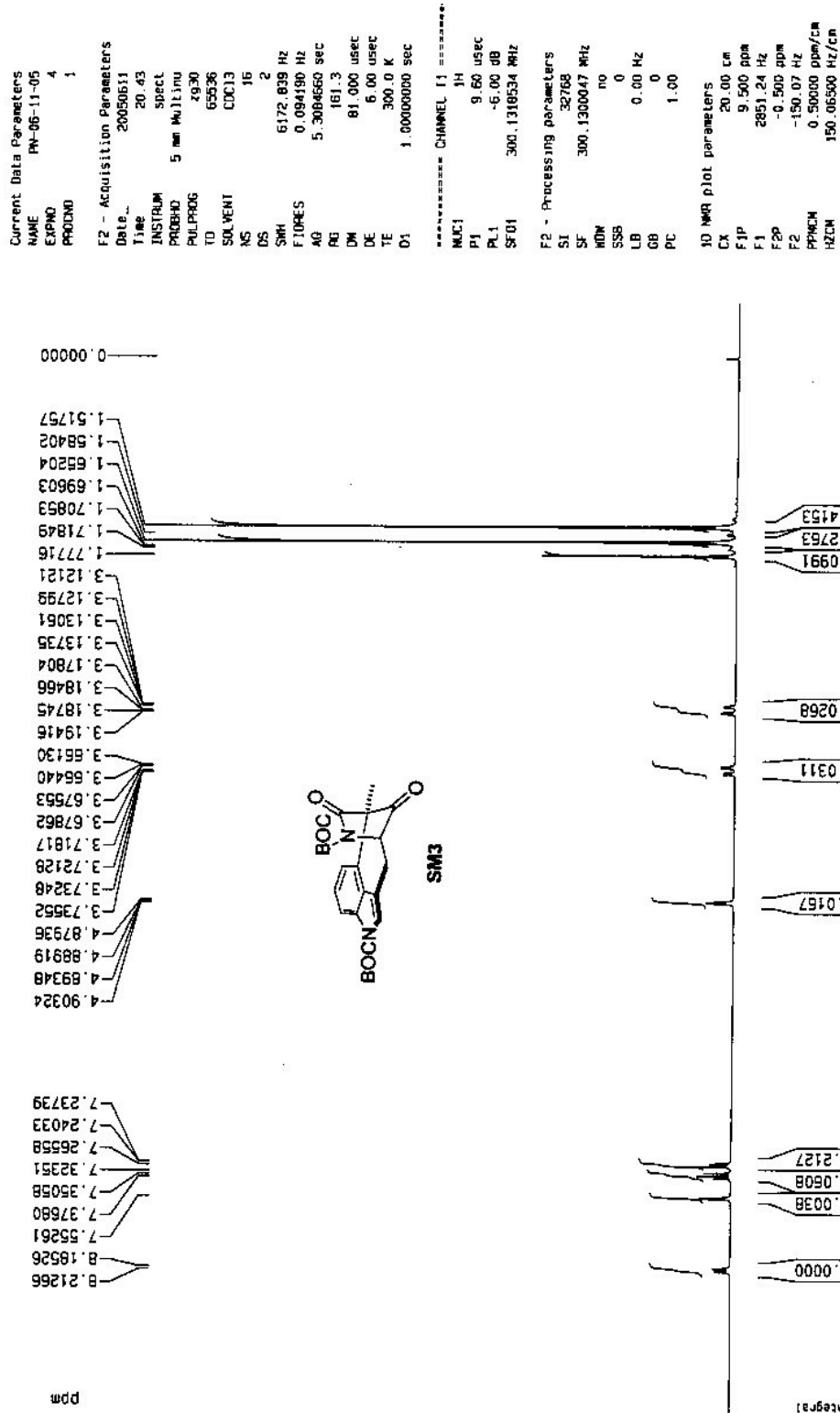
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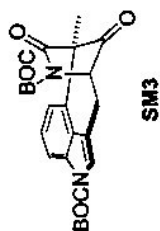
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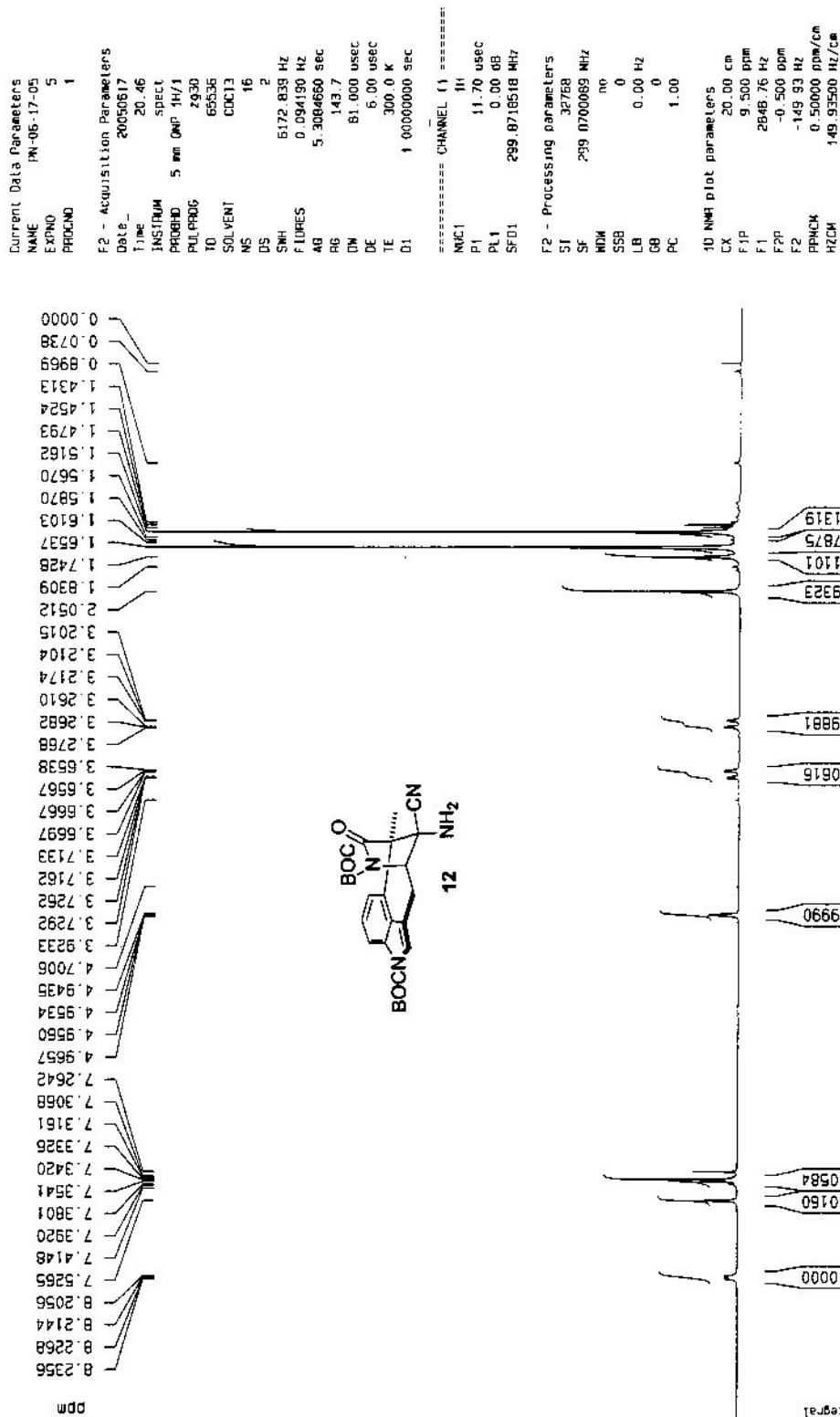
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PPMCH 11.00000 ppm/cm
NUCH 630.14526 Hz/cm

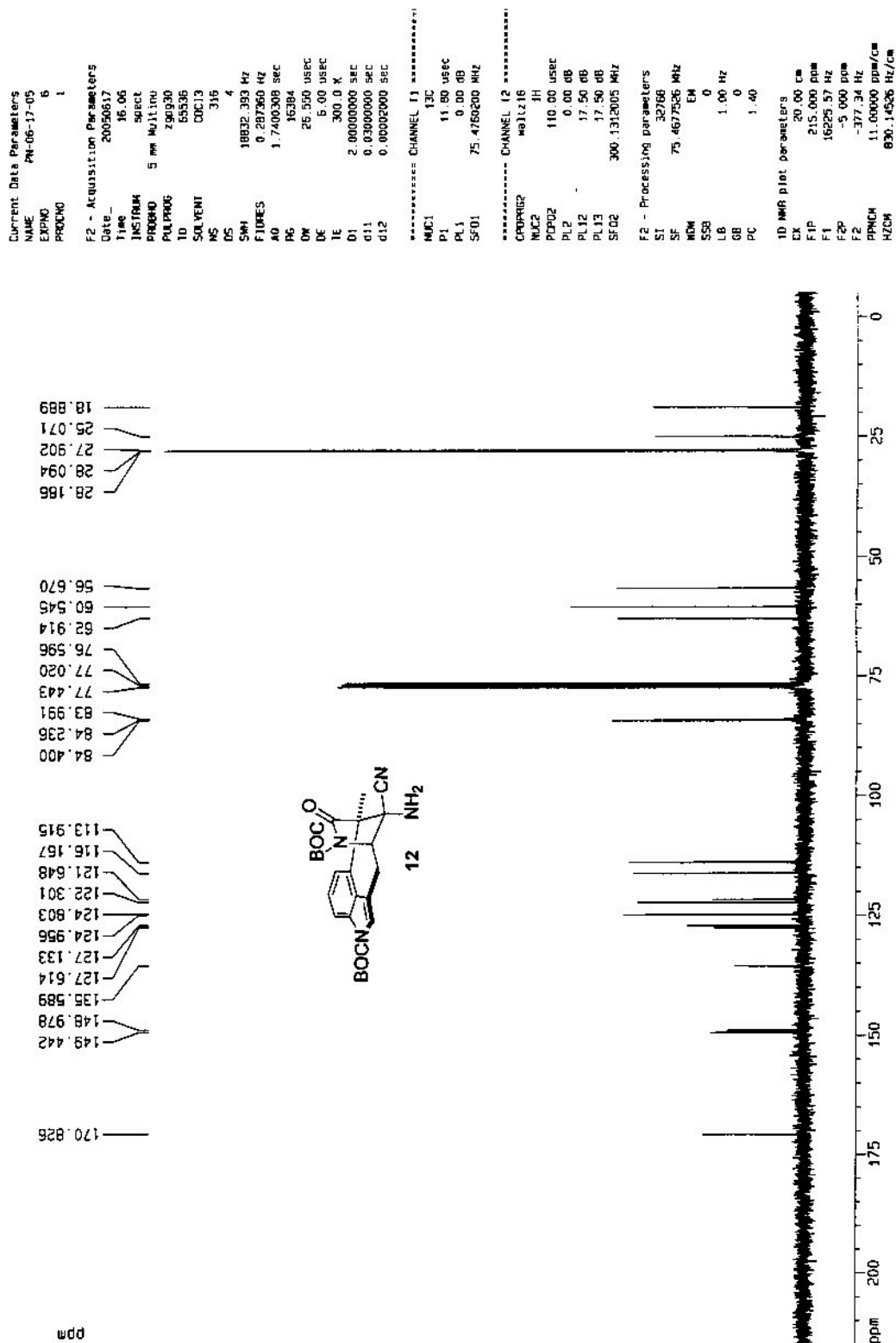
ppm
207.575
170.608
149.312
148.998
135.776
127.577
126.271
124.890
124.745
118.849
115.545
113.206
84.350
84.210
77.441
77.017
76.592
64.757
59.055
28.081
27.913
26.940
13.420



PN5_P162_purified



PN5_P162_purified



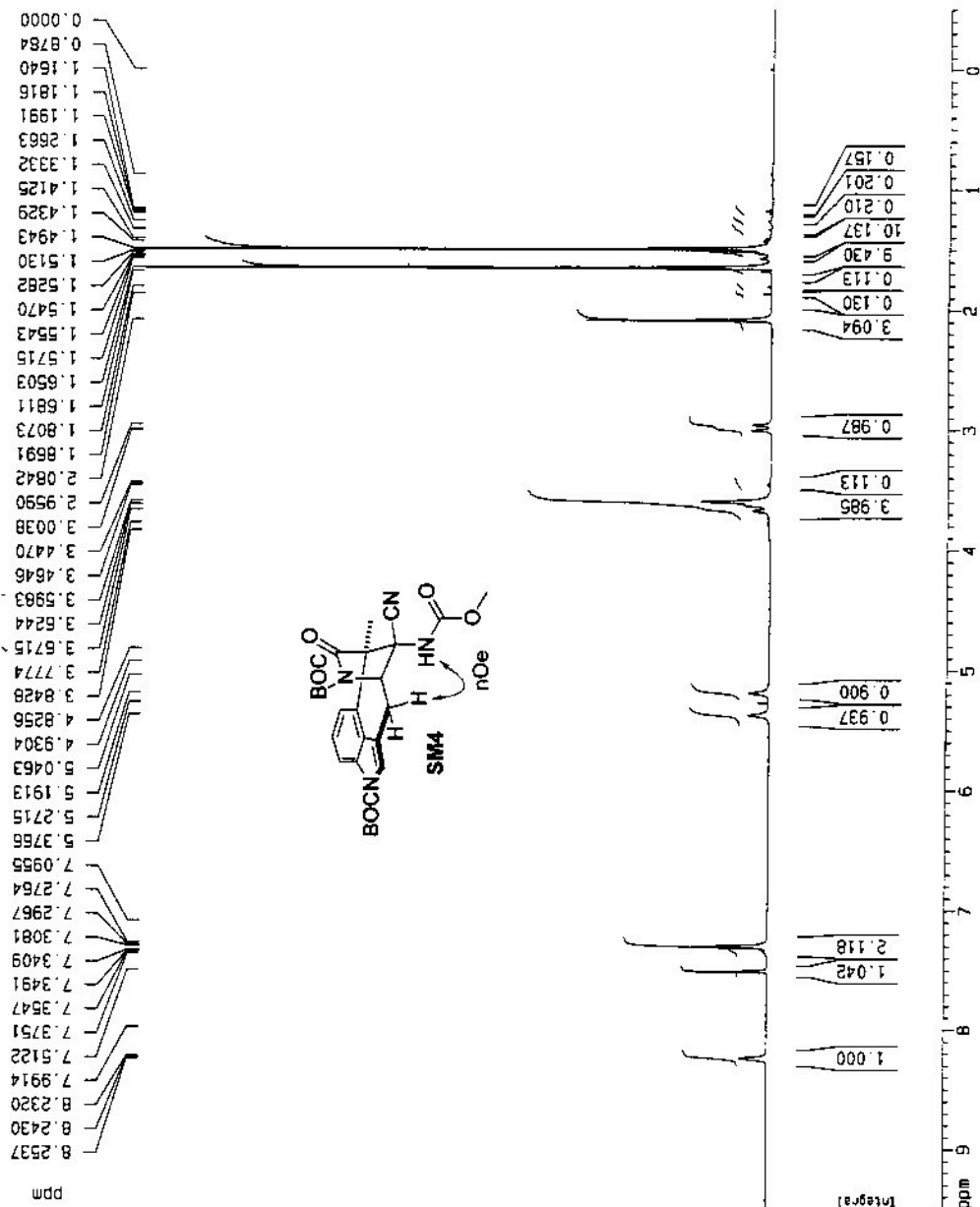
Current Data Parameters
NAME PN-07-02-04
EXPNO 11
PROCNO 1

F2 - Acquisition Parameters
Date_ 20040702
Time 10:02
INSTRUM spect
PROBHD 5 mm BBI 1H-B
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1
DS 0
SMH B27B 146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 16
DN 50.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.0000000 sec
D12 0.0000040 sec

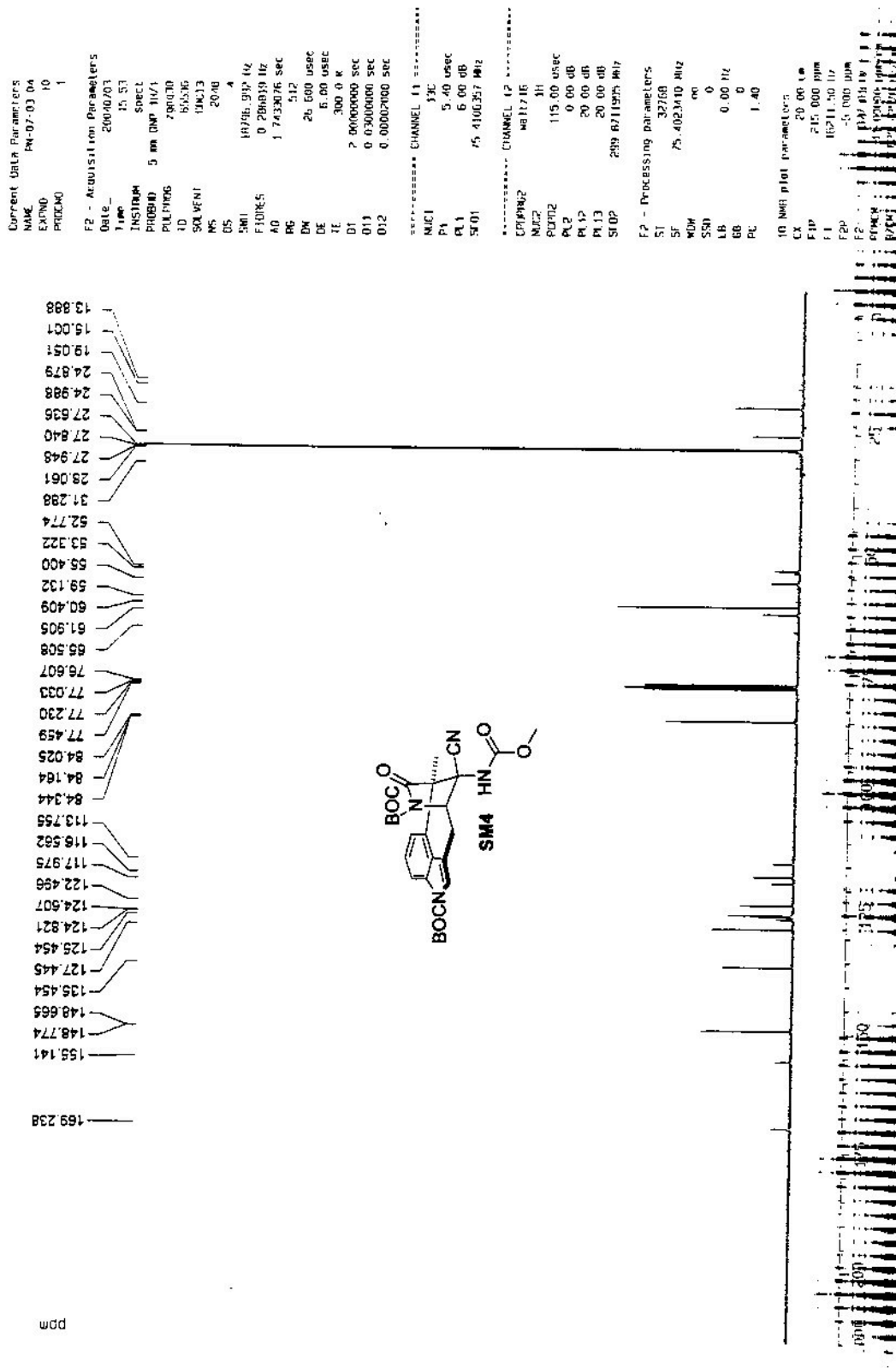
===== CHANNEL f1 =====
NUC1 1H
P1 7.00 usec
PL1 0.00 dB
SF01 400.1314289 MHz

F2 - Processing parameters
SI 32768
SF 400.1259890 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

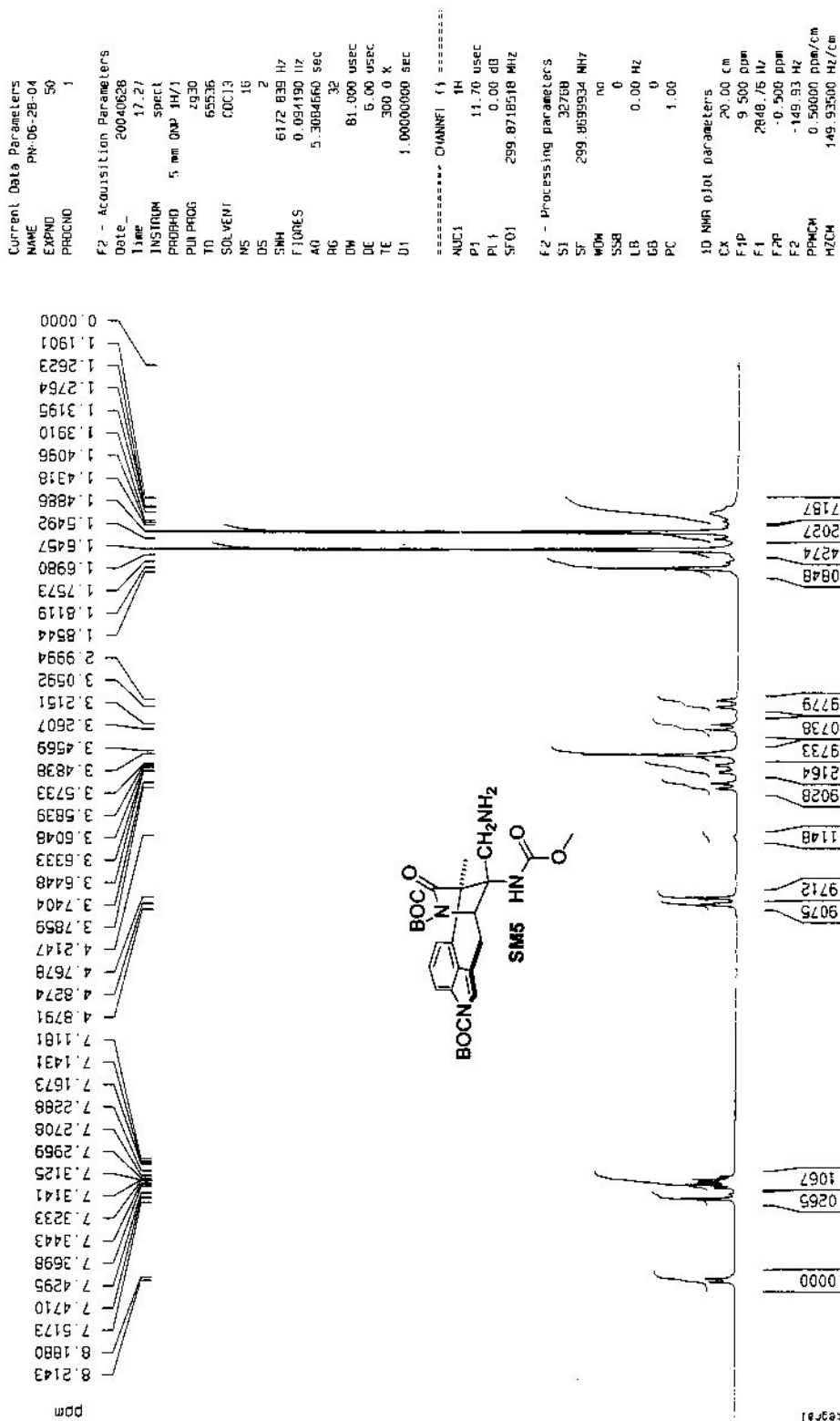
1D NMR plot parameters
CX 20.00 cm
FIP 9.500 ppm
F1 35001.23 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.50000 ppm/cm
HZCM 200.06498 Hz/cm



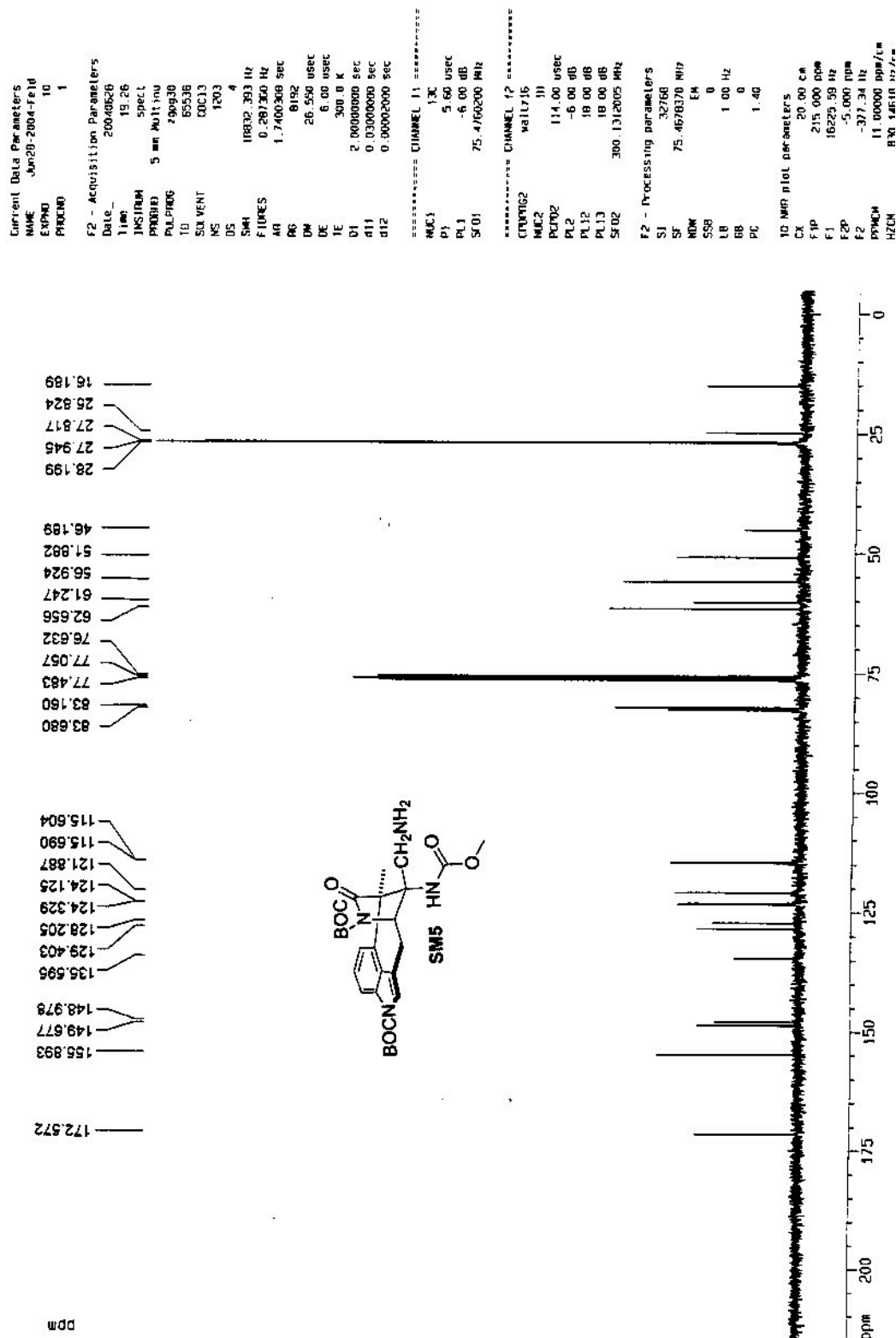
PN4_p97_purified

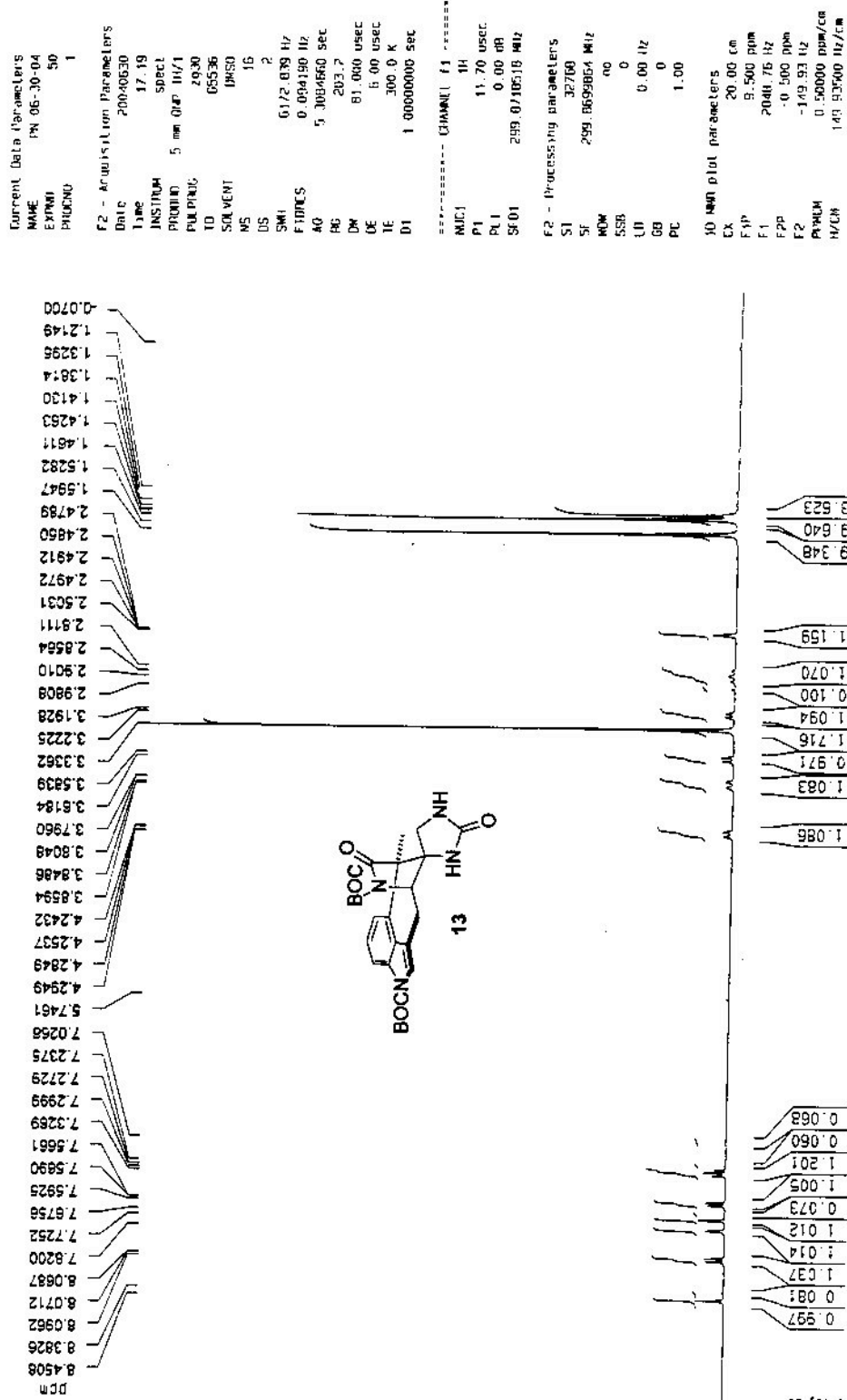


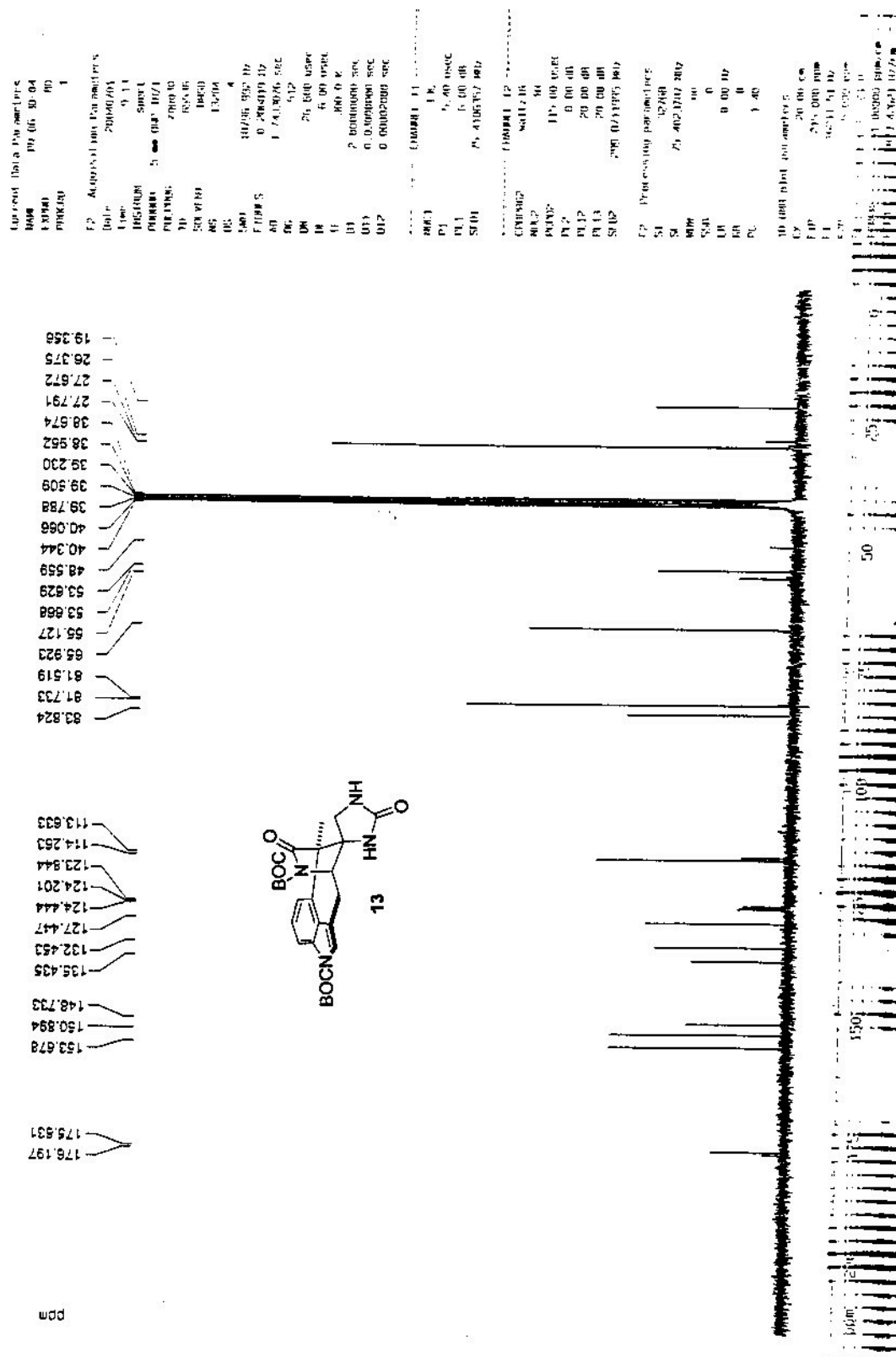
PN4_p9f_crude



PM4_p91_crude







PN5_P154_Purified_B

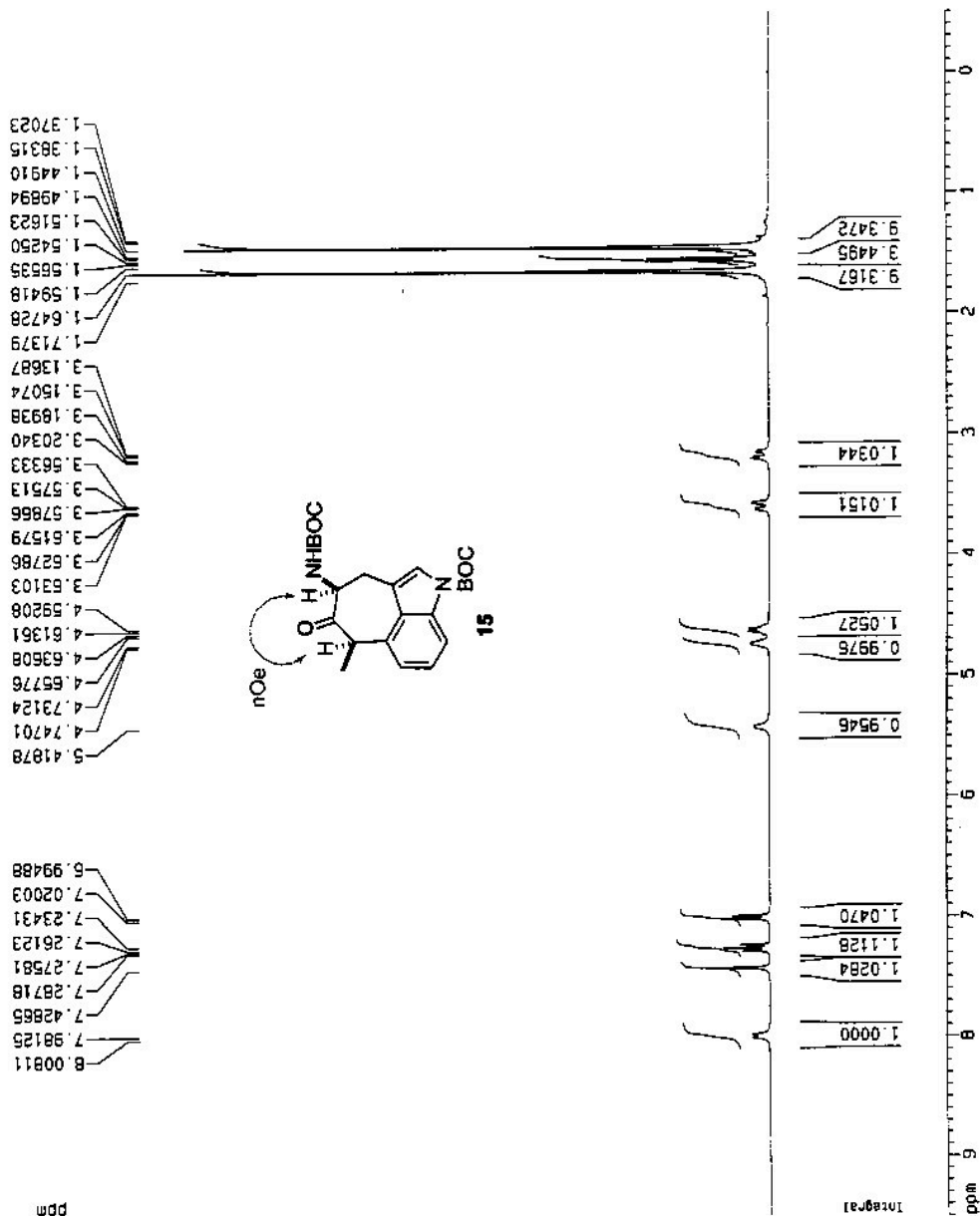
Current Data Parameters
NAME PN-05-08-05
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20050608
Time 19.52
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.094190 Hz
AQ 5.3084660 sec
RG 35.9
QM 81.000 usec
DE 6.00 usec
TE 300.0 K
D1 1.0000000 sec

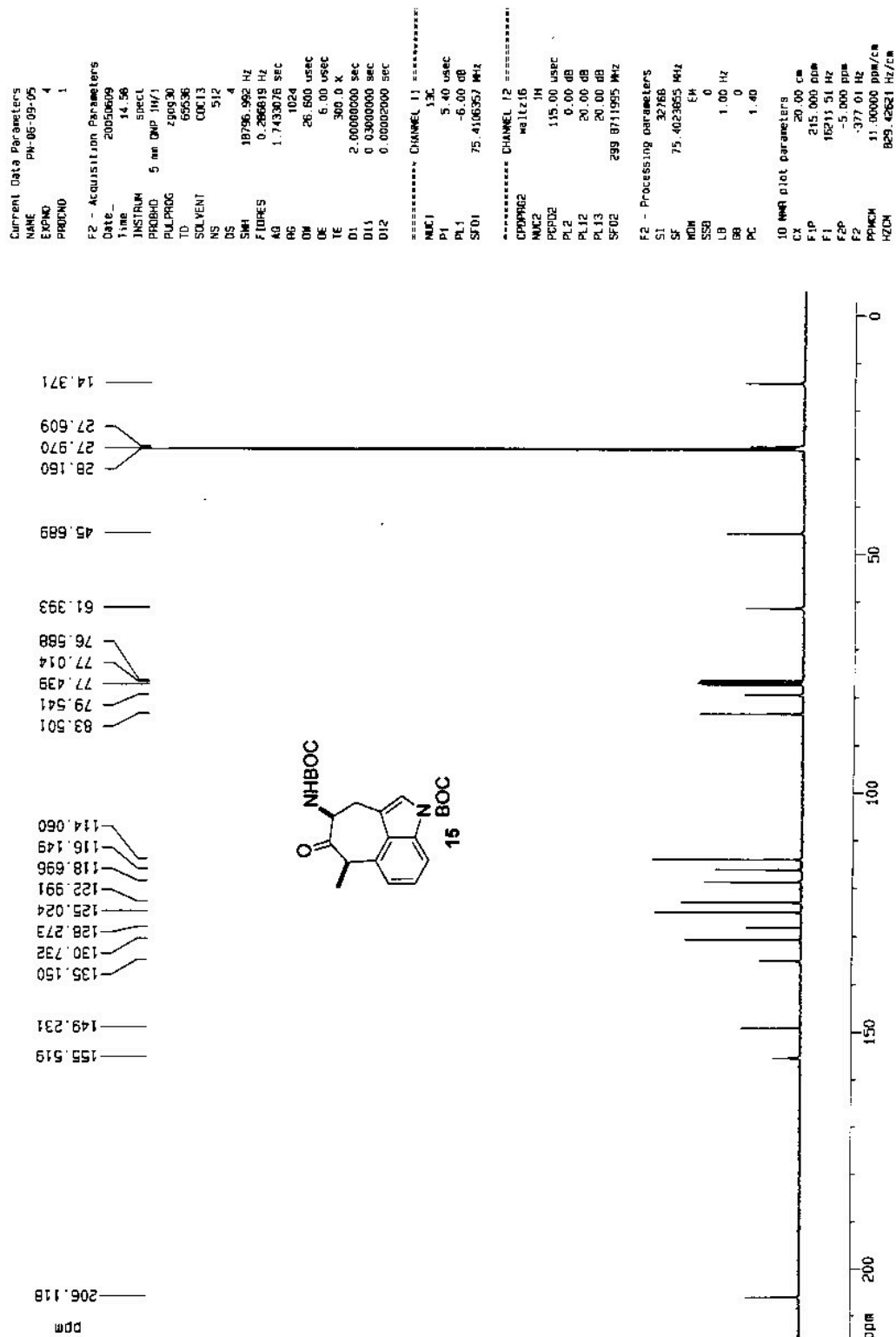
===== CHANNEL f1 =====
NUC1 1H
P1 11.70 usec
PL1 0.00 dB
SFO1 299.871518 MHz

F2 - Processing parameters
SI 32768
SF 299.870048 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

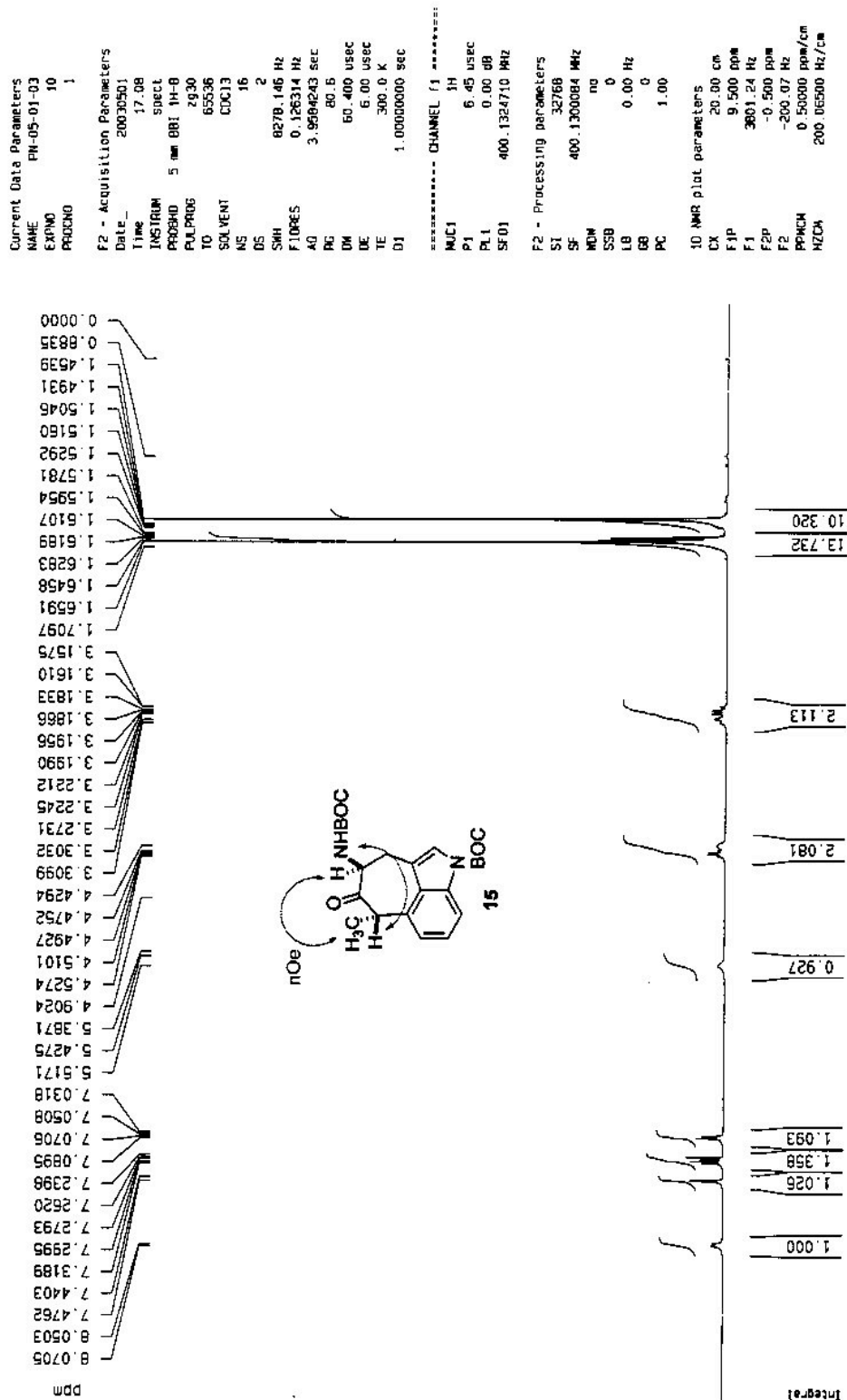
1D NMR plot parameters
CX 20.00 cm
F1P 9.500 ppm
F1 2848.76 Hz
F2P -0.500 ppm
F2 -149.93 Hz
PPM0 0.0000 ppm/cm
HZ0 149.93500 Hz/cm



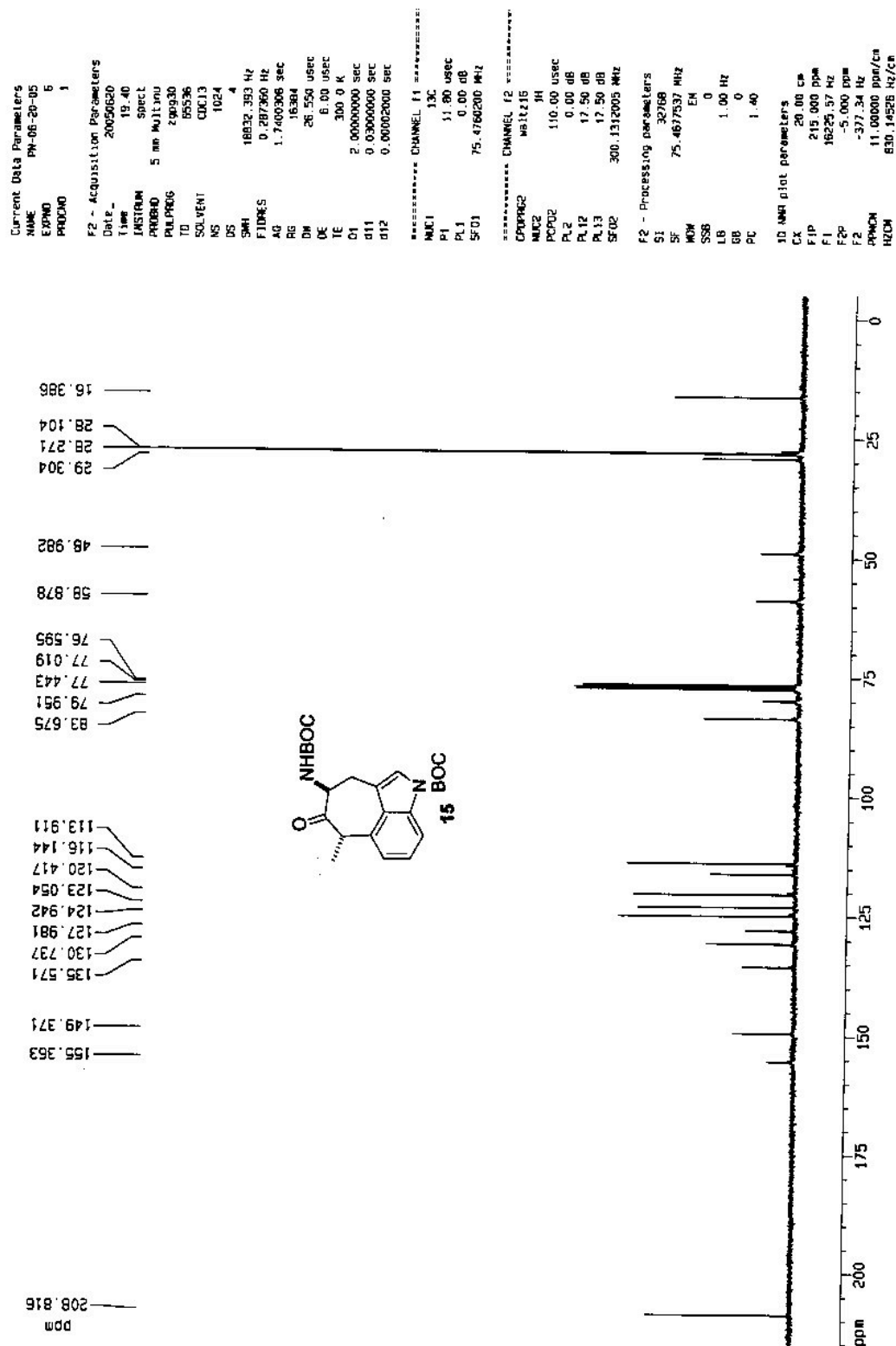
PN5_P154_purified_B



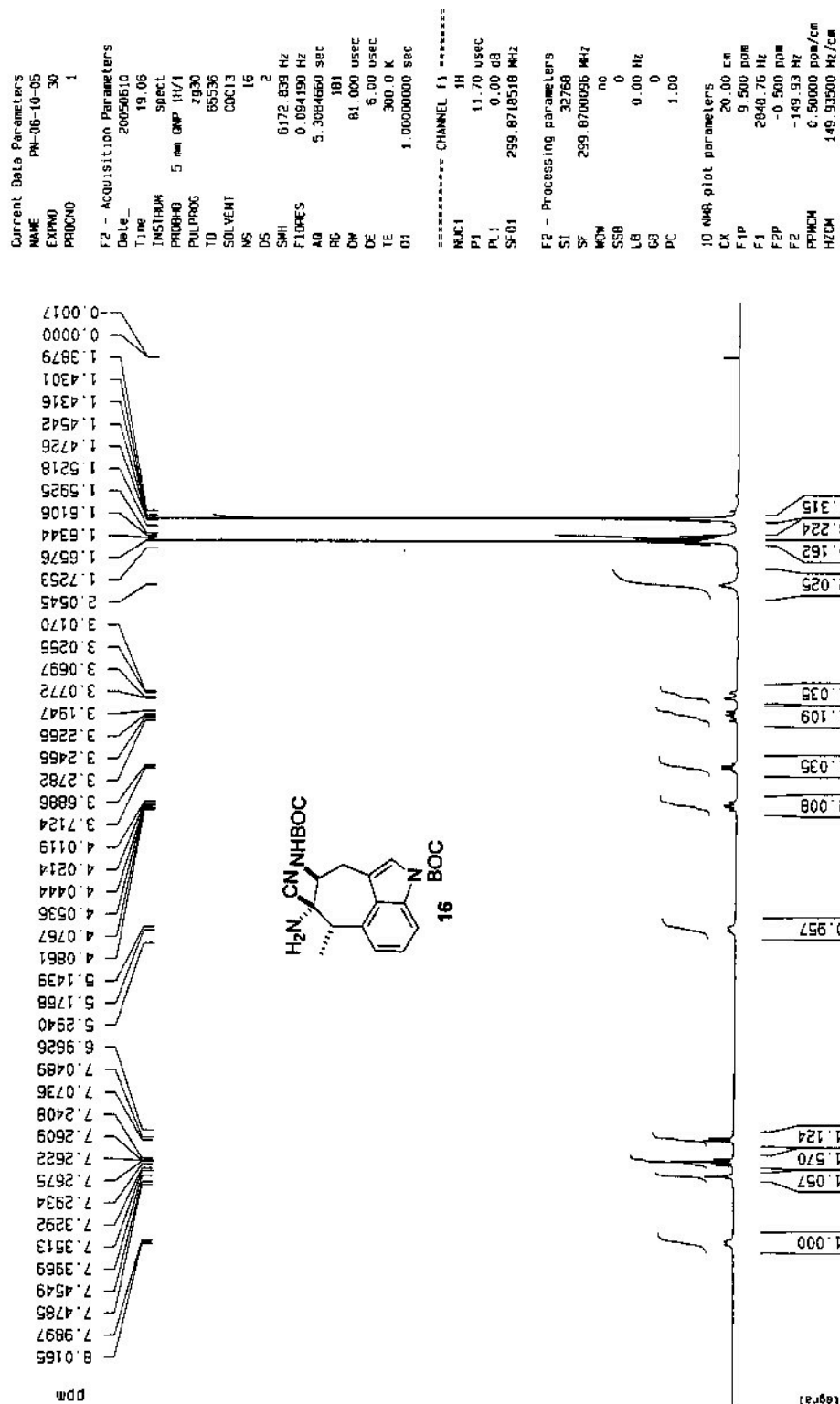
PN2_P125_purified_1



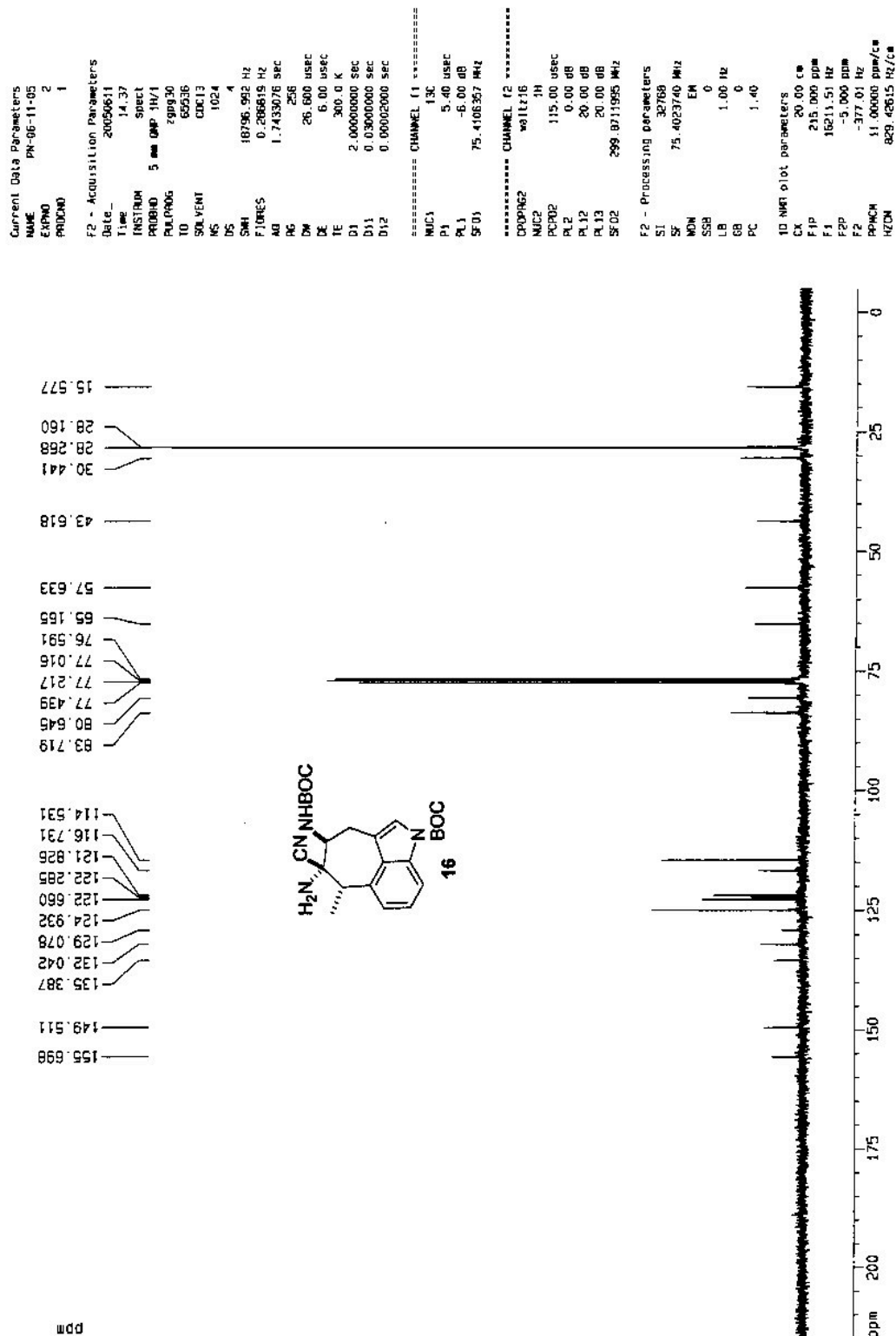
PN5_P154_purified_A



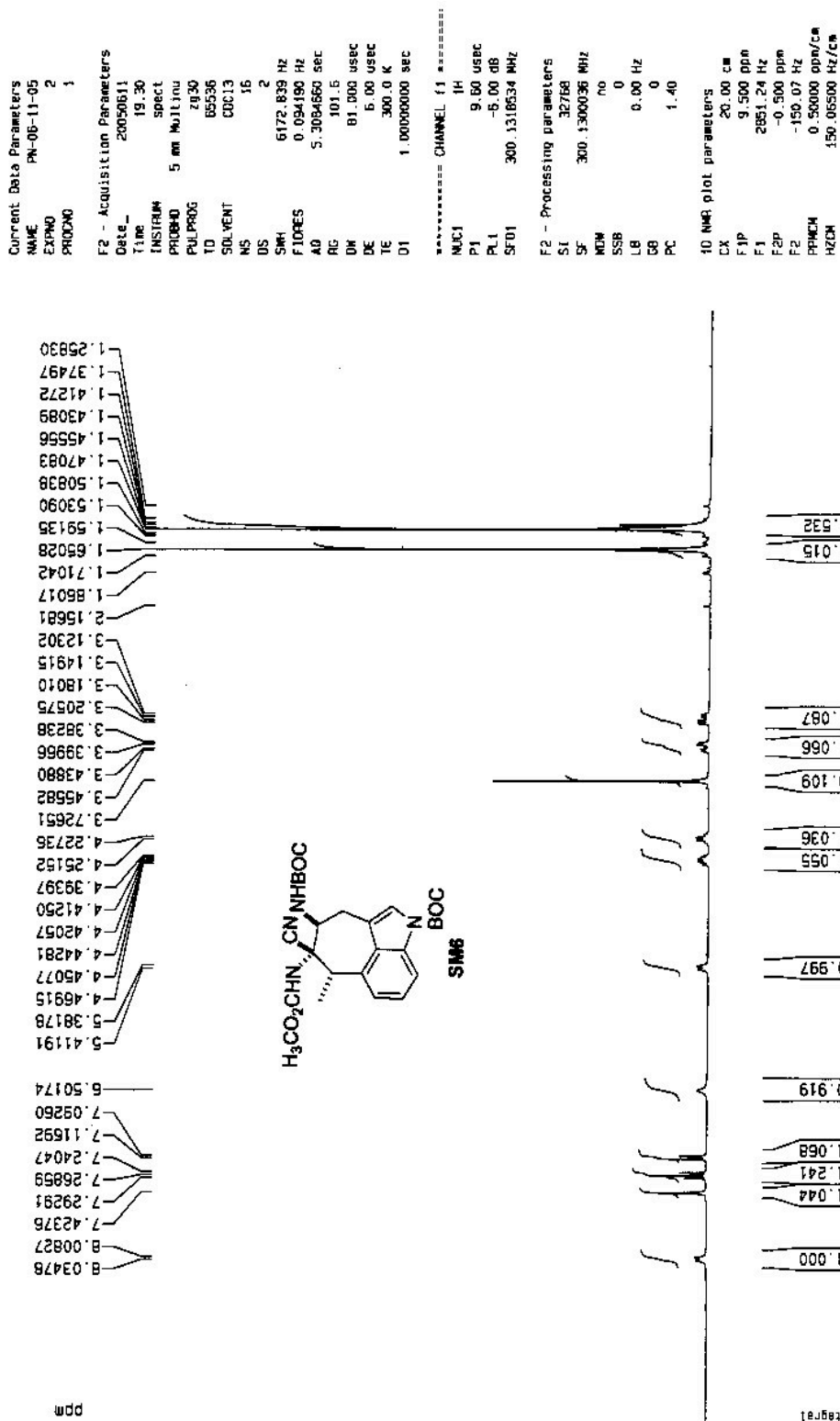
PN5_P156_purified



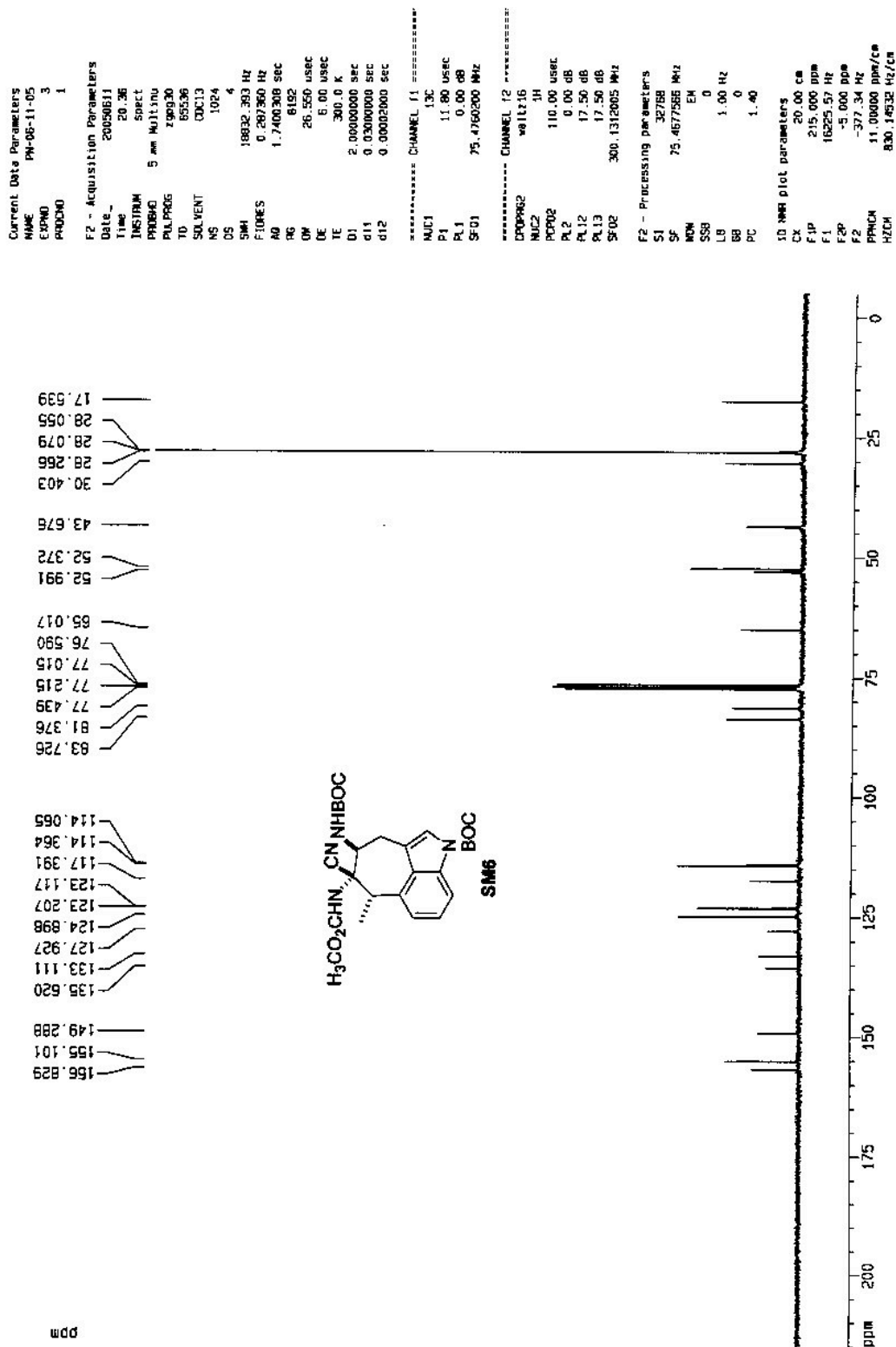
PNS_P156_purified

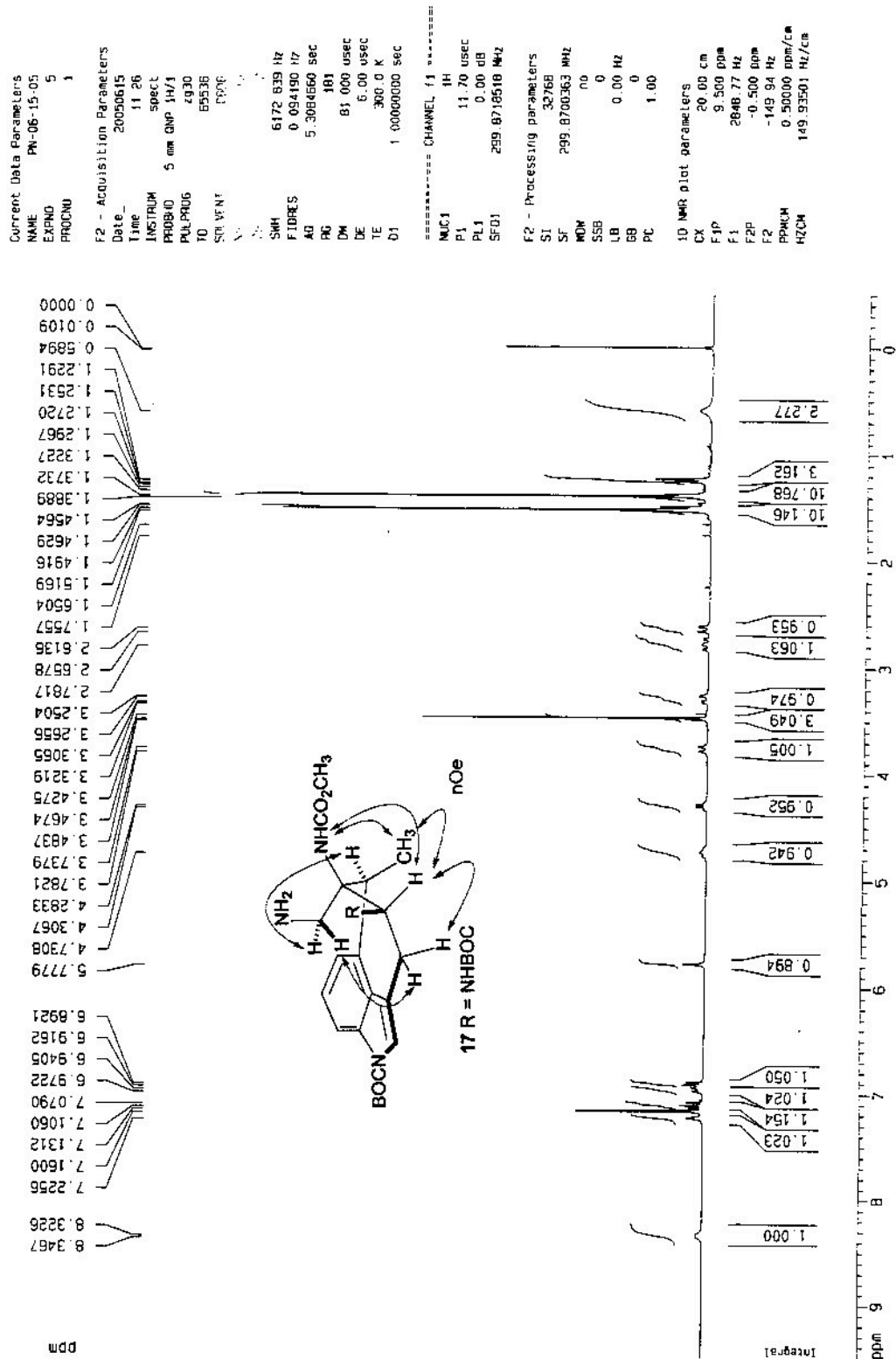


PN5_P157_purified

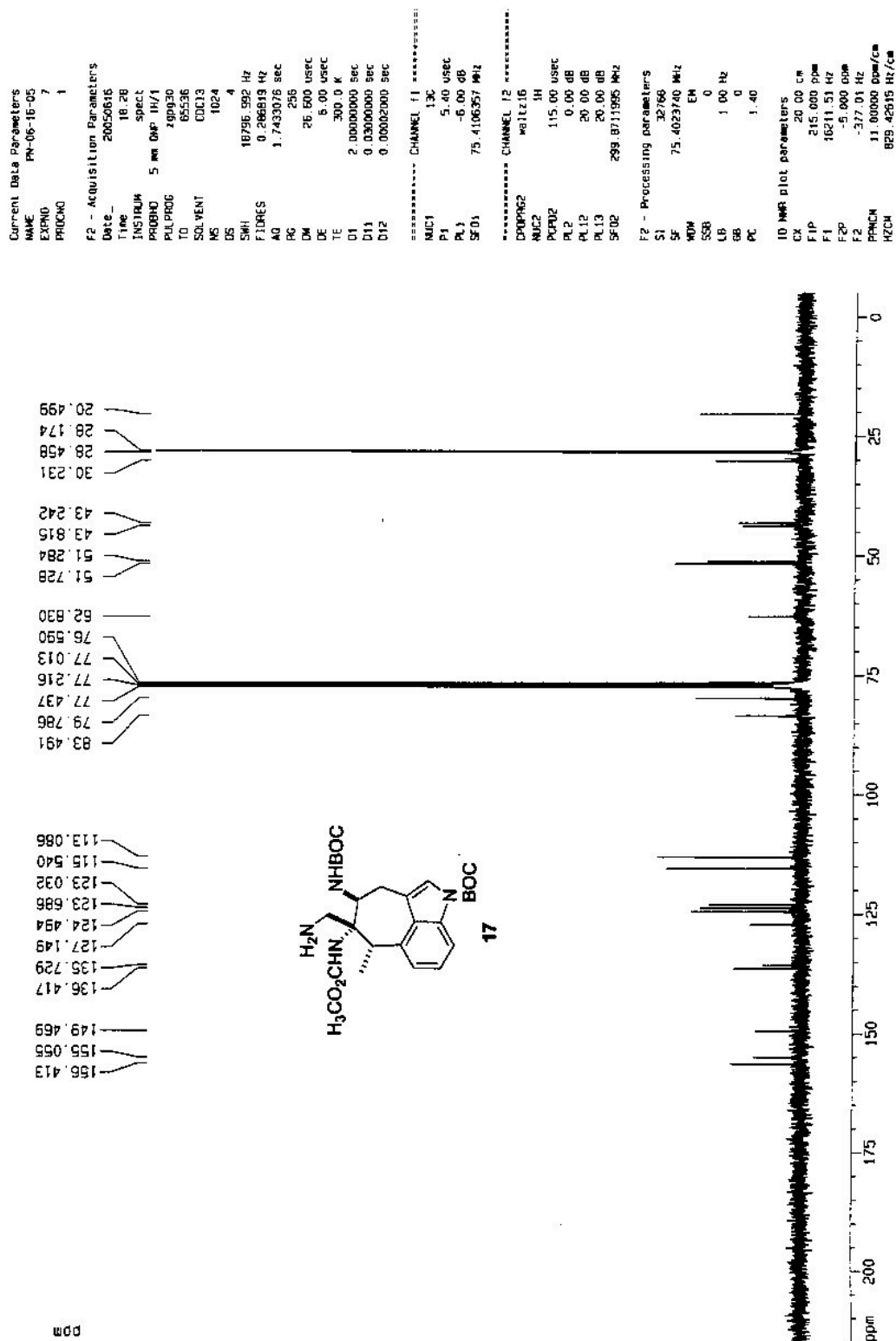


PW5_P157_purified

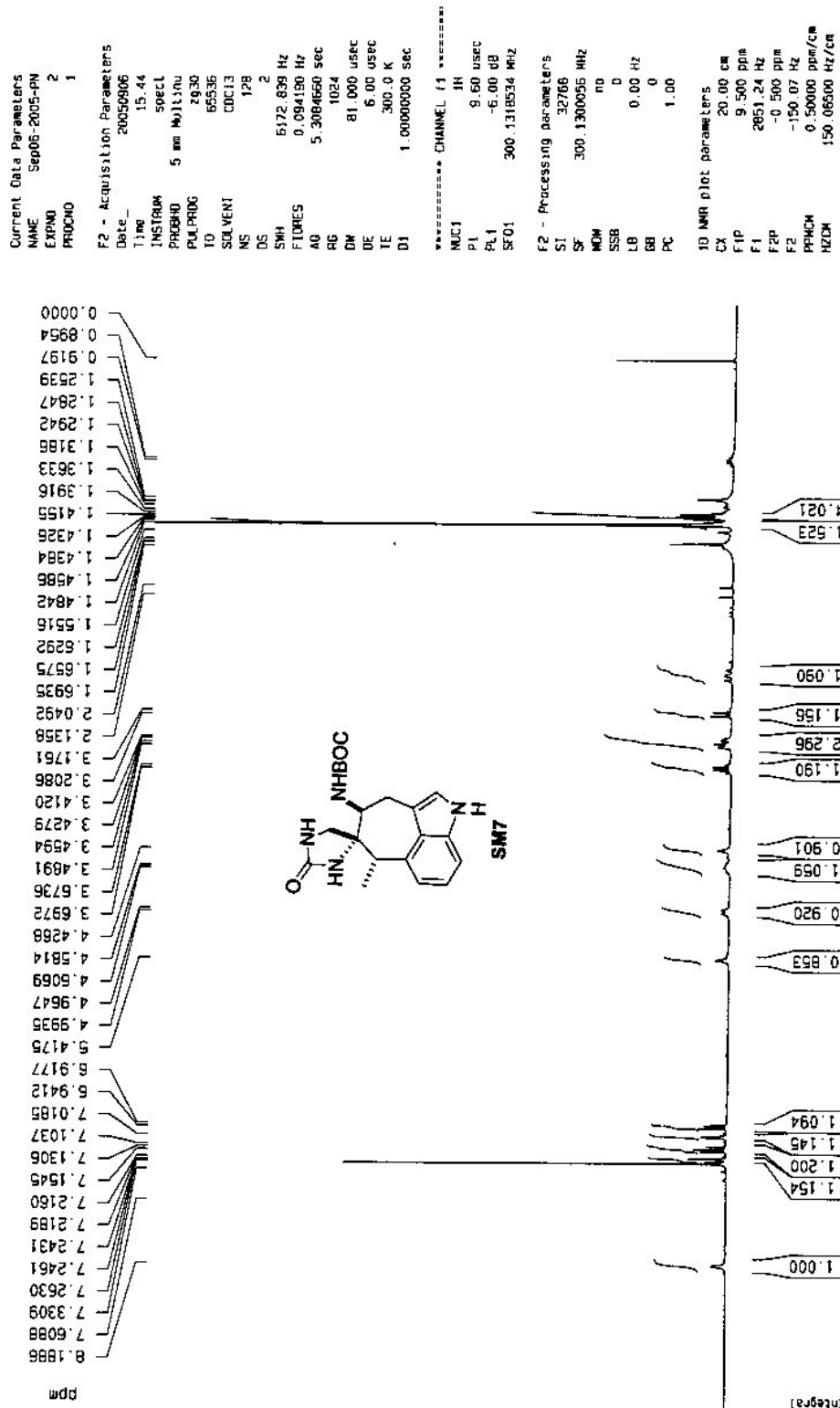




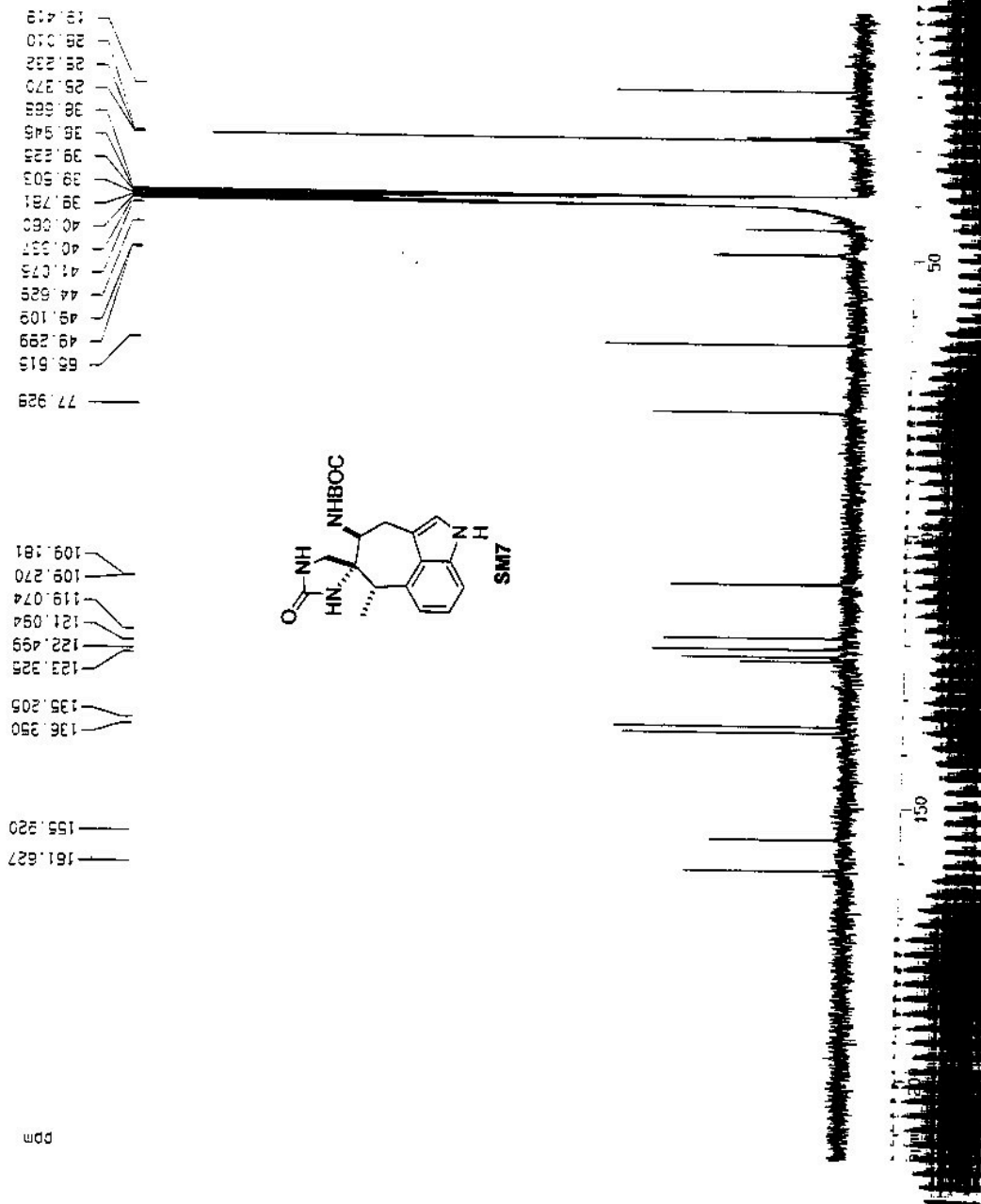
PNS_P159_purified



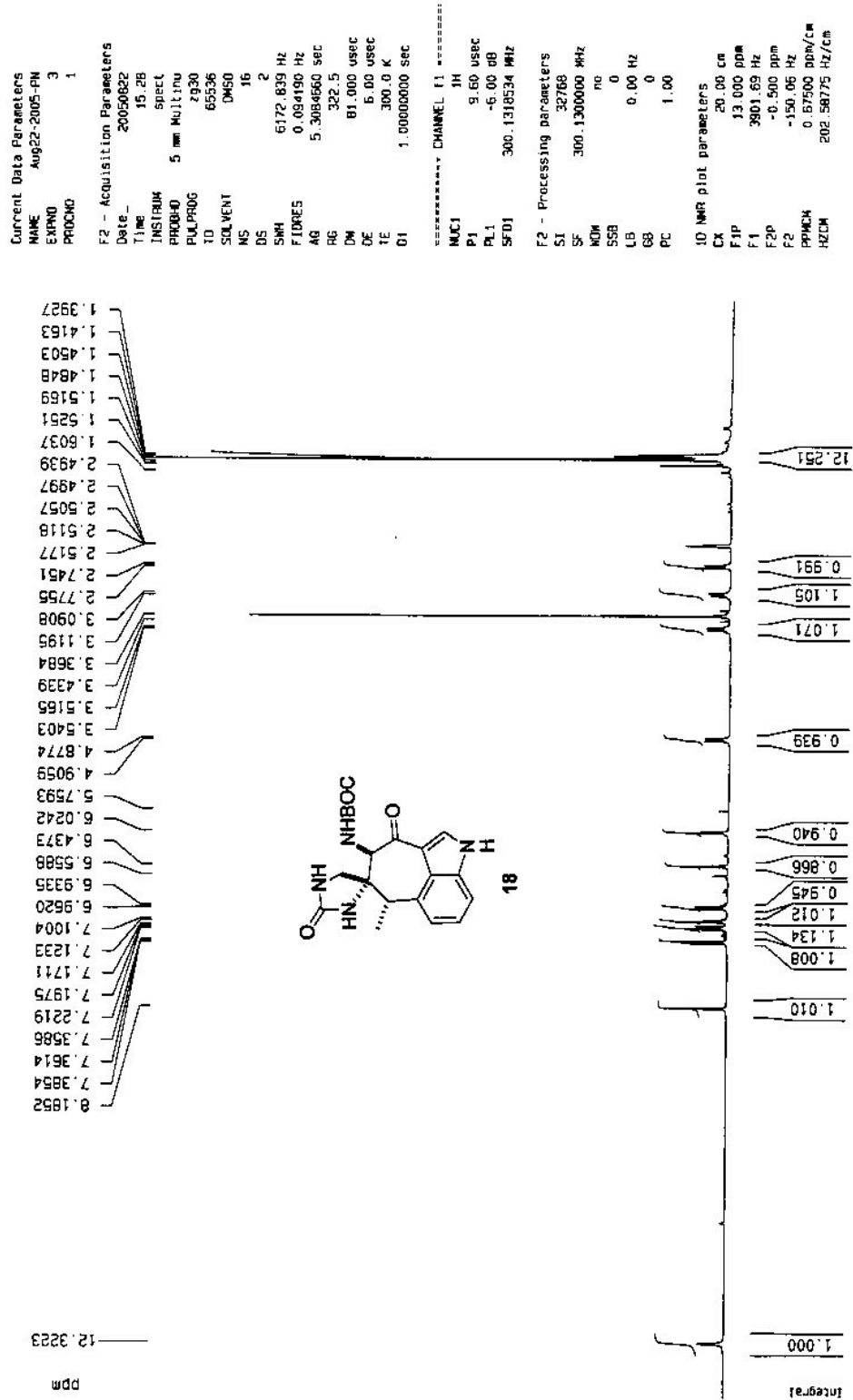
PM5_P264

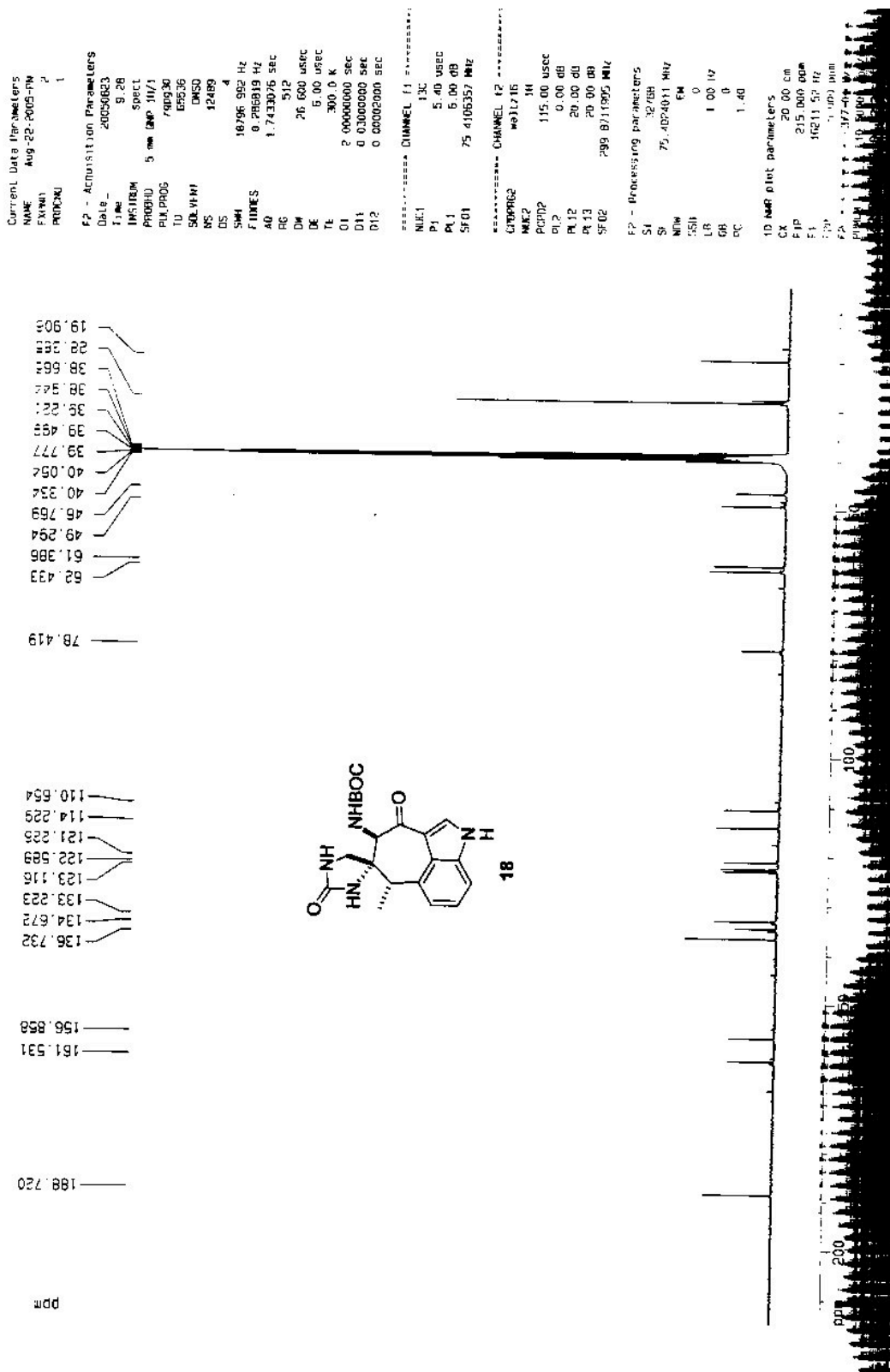


PM5_P26.4



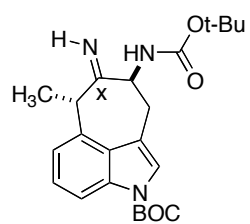
PN5_P248_purified in DMSO



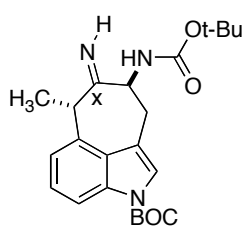
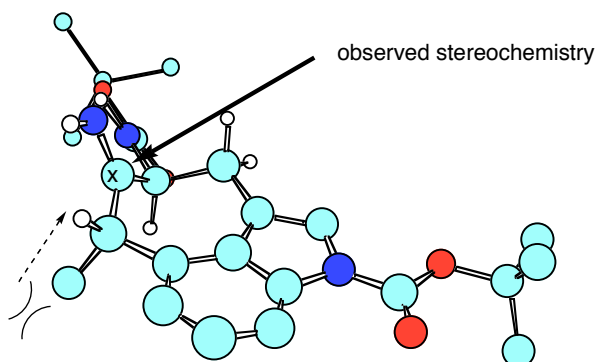


Macromodel 9.0 calculations (MMFF parameter set)

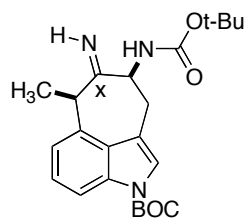
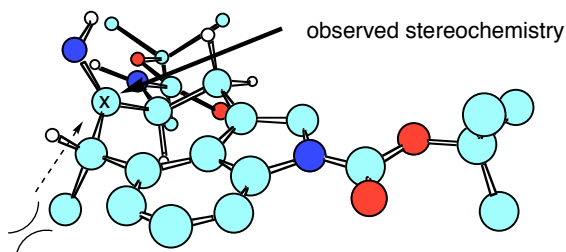
10000-step directed Monte Carlo search about all rotatable bonds. Each minima shown was found over 450 times.



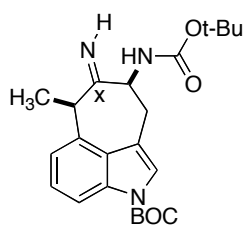
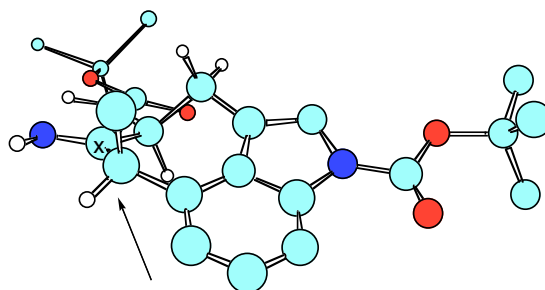
0.0 Kcal/mol



2.8 Kcal/mol



3.0 Kcal/mol



3.6 Kcal/mol

