© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 1

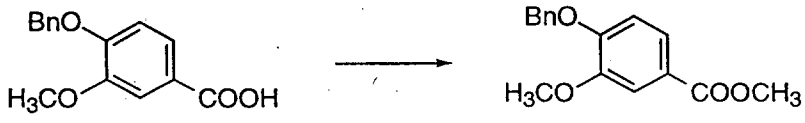
SUPPORTING MATERIAL

A Novel Route to Pyrrolo[2,1-c][1,4]Benzodiazepine-5-ones (PBDs). Formal Total Synthesis of (±)-DC-81

By Tiansheng Wang, Alfred S. Lui and Ian S. Cloudsdale

Experimental Section

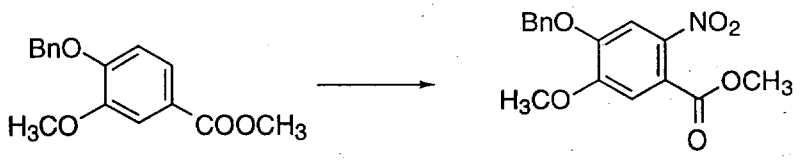
N-allylisatoic anhydride **5a** was purchased from Maybridge. Reagents and solvents were used as received from commercial suppliers. TLC was performed on pre-coated silica gel 60 F_{254} plates from Merck using reagent-grade solvents. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh). ^{1}H-NMR were performed at 300 MHz and ^{13}C NMR at 75 MHz in $CDCl_3$ unless otherwise specified. Chemical shifts are in ppm downfield from internal tetramethylsilane. IR spectra were recorded on a Perkin-Elmer 1600 FT IR spectrometer. Mass spectra were recorded on a HP 5989B spectrometer. HRMS were performed by Mass Spectrometry Facility of University of California, Berkeley. Elemental analyses were conducted by Galbraith Laboratories, Inc.



6 7

Methyl 4-benzyloxy-3-methoxybenzoate (7): A suspension containing 4-benzyloxy-3-methoxybenzoic acid **6** (14.69 g, 56.88 mmol), potassium carbonate (15.7 g, 114 mmol) and methyl iodide (5.3 ml, 85.5 mmol) in acetone (300 ml) was heated under reflux for 3 h. After filtration and washing with dichloromethane, the combined filtrates were concentrated under vacuum to a residue,

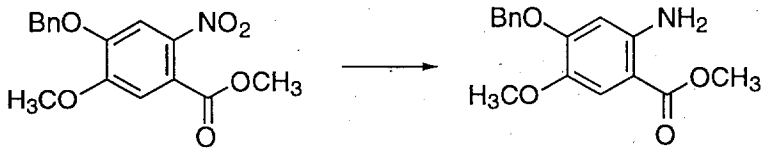
which was re-dissolved in dichloromethane (200 ml). The resulting solution was washed with water (2 x 50 ml), dried (Na_2SO_4) and concentrated. The residue was triturated with methanol to afford 7 (9.07 g, 58.6%) as white solid. Mp. 80.5-82°C (MeOH); TLC (SiO_2, hexane/ethyl ether, 1:1) R_f = 0.55; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.62-7.32 (m, 7 H), 6.89 (d, J = 8.4 Hz, 1 H), 5.20 (s, 2 H), 3.92 (s, 3 H), 3.87 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.77, 152.07, 149.11, 136.33, 128.59, 128.00, 127.17, 123.32, 122.96, 112.47, 70.74, 56.02, 51.89; API-TIS m/z: 272 (M). Cacl for $C_{16}H_{16}O_4$: C 70.58; H 5.92. Found: C 70.29; H 5.77.



7 8

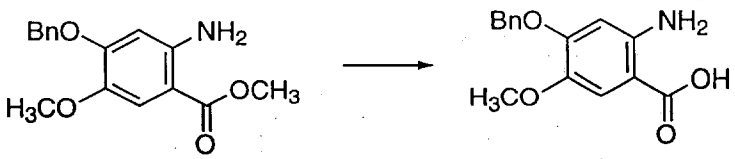
Methyl 4-benzyloxy-5-methoxy-2-nitrobenzoate (8): To a solution of methyl ester 7 (8.76 g, 32.17 mmol) in dichloromethane at -25°C (dry ice/carbon tetrachloride bath) was added a fresh prepared mixture consisting of tin (IV) chloride (40 ml of 1M in dichloromethane solution, 40 mmol) and fuming nitric acid (2.14 ml, 51 mmol) in 3 min. The resulting mixture was kept at -20°C for 10 min, Water (100 ml) was added to the reaction and the mixture was separated. The aqueous phase was extracted by ethyl acetate (2 x 80 ml) and the combined organic phases were washed with brine and dried under sodium sulfate. Concentration under vacuum then gave a residue that was triturated with methanol to generate **8** as a white solid (8.43 g, 82.6%). Mp. 126-127°C (needles from MeOH); TLC (SiO_2, hexane/ethyl ether, 1:1) R_f = 0.32; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1 H), 7.63-7.34 (m, 5 H), 7.08 (s, 1 H), 5.21 (s, 2 H), 3.98 (s, 3 H), 3.91 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.30, 153.08, 149.38, 140.97, 135.13, 128.82, 128.55, 127.51, 121.97, 111.06, 108.95, 71.44, 56.61, 53.21;

API-TIS m/z: 317 (M). Anal. Cacl. for $C_{16}H_{15}NO_6$: C 60.57; H 4.77; N 4.41. Found: C 60.47; H 4.59; N 4.38.



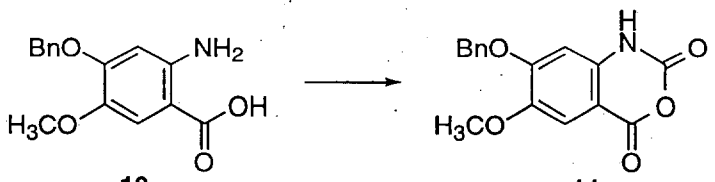
8 9

Methyl 2-amino-4-benzyloxy-5-methoxybenzoate (9): To a solution of **8** (6.34 g, 19.98 mmol) in dichloromethane (100 ml) and methanol (50ml) was added nickel (II) chloride hexahydrate (1.5 g, 6.3 mmol). Sodium borohydride (2.5 g, 66 mmol) was then added in portions to the reaction at 0-5°C in 30 min. The solvents were evaporated under vacuum and to the resulting residue was added cold 2 N hydrochloric acid (100 ml). The mixture was extracted with ethyl acetate (3 x 80 ml). After washing with brine (30 ml) and drying (Na_2SO_4), the organic layer was evaporated under vacuum. Recrystalization of the residue gave **9** as an amorphous solid (5.50 g, 95.8%). Mp. 128-128.5°C (needles from MeOH); TLC (SiO_2, hexane/ethyl ether, 1:1) $R_f = 0.41$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.42-7.30 (m, 5 H), 7.34 (s, 1 H), 6.15 (s, 1 H), 5.49 (b s, 2 H), 5.11 (s, 2 H), 3.84 (s, 3 H), 3.82 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.07, 153.91, 146.85, 140.81, 136.14, 128.59, 127.98, 127.05, 113.10, 102.27, 101.01, 70.35, 56.51, 51.29; API-TIS m/z: 288 (M). Anal. Cacl. for $C_{16}H_{17}NO_4$: C 66.89; H 5.96; N 4.87. Found: C 66.70; H 5.69; N 4.81.

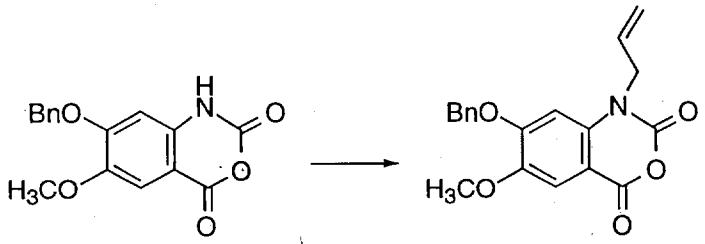


9 10

2-Amino-4-benzyloxy-5-methoxybenzoic acid (10): A solution of **9** (4.88 g, 16.98 mmol) in 2 N sodium hydroxide (60 ml) and methanol (60 mL) was heated at reflux for 1 h. Methanol was removed by a rotary evaporator and the aqueous residue was acidified to pH 2 with cold concentrated hydrochloric acid. Filtration and washing with water then gave the acid **10** as solid (4.55 g, 98.0%). Mp. 190-193°C (MeOH); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.84-7.45 (m, 5H), 7.37 (s, 1H), 7.09 (s, 1H), 5.22 (s, 2H), 3.82 (s, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 167.67, 152.42, 143.82, 136.93, 136.11, 128.57, 128.25, 128.18, 113.41, 108.90, 105.13, 69.86, 55.97; API-TIS m/z: 274 (M+1).

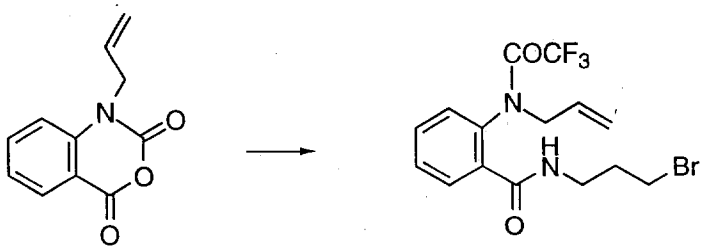


7-Benzyloxy-6-methoxyisatoic anhydride (11): A suspension of the acid **10** (2.88 g, 10.54 mmol) in 2N sodium hydroxide (30 ml) was warmed to a clear solution and then cooled to room temperature. A 20% phosgene-toluene solution (15 ml) was then added. After stirring at room temperature for 2 h, the reaction was filtered and the resulting solid was washed with 2% methanol in water (20 ml). Drying under vacuum then gave **11** as an tan solid (2.5 g, 81.1%). Mp. 234-235°C (acetonitrile-ether); ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.74 (s, 1 H), 7.58-7.52 (m, 5H), 7.39 (s, 1H), 6.86 (s, 1H), 5.31 (s, 2H), 3.93 (s, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 159.35, 155.40, 147.32, 145.80, 137.47, 135.56, 128.52, 128.27, 128.07, 108.84, 101.41, 99.01, 70.25, 55.93; API-TIS m/z: 300 (M+1).



11 5b

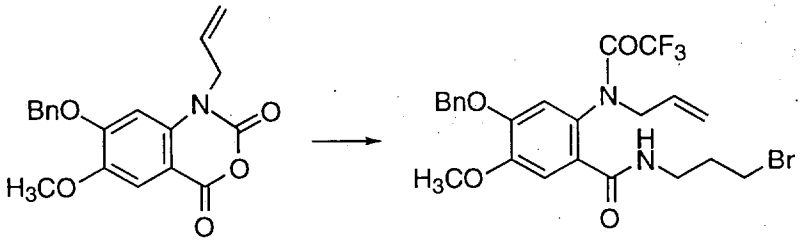
N-Allyl-7-benzyloxy-6-methoxyisatoic anhydride (5b): To a solution of **11** (2.00 g, 6.68 mmol) in N,N-dimethyl acetamide (30 ml) was added sodium hydride (0.245 g, 10.2 mmol) in 3 min. The resulting solution was stirred at room temperature for 30 min. Allyl bromide (1.05 ml, 12.1 mmol) was added. After stirring at room temperature for 12 h, water (60 ml) was added. The mixture was extracted with dichloromethane (3 x 20 ml). The combined extracts were washed with brine and dried. Removal of solvent under vacuum gave the residue, which was washed with small amount of ether to afford **5b** as white solid (1.98 g, 87.3%). Mp. 148-149°C (ethyl acetate-hexane); TLC (SiO_2, hexane / ethyl ether, 1:1) $R_f = 0.10$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.49 (s, 1 H), 7.41-7.35 (m, 5 H), 6.54 (s, 1 H), 5.82-5.70 (m, 1 H), 5.27 (s, 2 H), 5.19 (d, J = 10.4 Hz, 1 H), 5.11 (d, J = 17.2 Hz, 1 H), 4.52 (d, J = 4.9 Hz, 2 H), 3.95 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.21, 155.61, 148.15, 146.50, 137.17, 135.10, 130.18, 128.98, 128.56, 126.87, 118.37, 110.37, 103.55, 99.65, 71.38, 56.42, 47.23; API-TIS m/z: 340 (M+1); Anal. Cacl for $C_{19}H_{17}NO_5$: C 67.25; H 5.05; N 4.13. Found: C 67.10; H 4.93; N 4.01.



5a 13a

2-(Allyl-trifluoroacetyl-amino)-N-(3-bromopropyl)-benzamide (13a) : To a solution of N-allylisatoic anhydride (2.03 g, 10 mmol) in 20 ml acetonitrile was added triethylamine (2.7 ml, 20 mmol), followed by 3-bromopropylamine hydrobromide (3.0g, 13.7 mmol). After stirring at room temperature for 5 h, the reaction was evaporated under vacuum and the residue was purified by flash chromatography (SiO_2, hexane/ethyl ether, 3:1) to give 2.869 g of allylaminobenzamide **12**. During the condensation of the purified fractions, a new, nonpolar spot gradually appeared on TLC. Therefore it was immediately acetylated as follows. The purified product was dissolved in 70 ml dichloromethane and triethylamine (1.5 mmol, 10.8 mmol) was added. To the ice-cooled reaction was added dropwise trifluoroacetic anhydride (1.48 ml, 10.5 mmol). After stirring at 0°C for 5 min, the reaction was washed with water and the aqueous phase was extracted with dichloromethane (2 X 10 ml). The combined organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (SiO_2, hexane / ethyl ether, 1:1) to afford 3.1154 g of the **13a** as a white solid (79.2% over 2 steps). TLC (SiO_2, hexane/ethyl ether, 1:1) $R_f = 0.26$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 7.1 and 1.6 Hz, 1 H), 7.52-7.41 (m, 2 H), 7.21 (d, J = 7.4 Hz, 1 H), 6.93 (br t, J = 5.4 Hz, 1 H), 5.89-5.76 (m, 1 H), 5.17 (d, *J* = 10.0 Hz, 1 H), 5.09 (d, *J* = 17.1 Hz, 1 H), 4.74 (dd, *J* = 14.6 and 5.6 Hz, 1H), 3.87 (dd, *J* = 14.6 and 7.6 Hz, 1 H), 3.52 (br d, *J* = 6.6 Hz, 2 H), 3.44 (t, *J* = 6.5 Hz, 2 H), 2.13 (t, *J* = 6.6 Hz, 2 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.66, 156.21 (q, J = 35 Hz, **CO**-CF_3), 136.55, 133.90, 130.81, 130.58, 130.48, 129.31, 128.00, 119.73, 116.07 (q, J = 287 Hz, CF_3), 54.74, 38.34, 31.68, 30.48; IR (film) υ_{max}: 3346, 2934, 1697, 1650, 1599, 1534, 1488, 1450, 1303, 1195, 1152, 931, 757 cm^{-1}; MS m/z (rel intens) 395 (3), 393 (3), 325 (3), 323 (2), 314 (1), 313 (7), 297 (2), 295 (3), 281 (7), 280 (26), 279 (10), 278 (25), 265 (2), 263 (2), 256 (17), 153 (7), 251 (7), 244 (4), 243 (21), 228 (2), 226 (1), 217 (2), 216 (10), 215 (9), 199 (12), 186 (14), 172 (14), 171 (38), 168 (5), 160 (7), 159 (19), 158 (100), 157 (36), 147 (7), 146 (52), 144 (11), 142 (6), 132 (16), 131 (18), 130 (42),

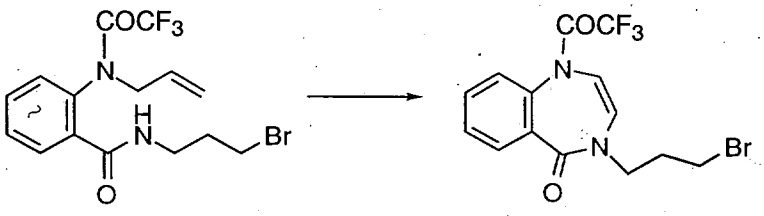
129 (8), 118 (11), 105 (17), 104 (14), 103 (18), 102 (11); Anal. Cacl. for $C_{15}H_{16}BrF_3N_2O_2$: C 45.82; H 4.10; N 7.12; Br 20.32; F 15.11. Found: C 46.09; H 4.22; N 7.32; Br 20.09; F 15.03.



5b **13b**

2-(Allyl-trifluoroacetyl)-amino-4-benzyloxy-N-3-(bromopropyl)-5-methoxy-benzamide (13b): To a solution of **5b** (0.339g, 1.0 mmol) and triethylamine (0.18 ml, 1.3 mmol) in dichloromethane (5 ml) was added 3-bromopropylamine hydrobromide (0.259 g, 1.2 mmol). After stirring at room temperature for 2 h, additional triethylamine (0.18 ml) and 3-bromopropylamine hydrobromide (0.259 g) were added. After 2 h, the TLC (SiO_2, ethyl acetate/hexane, 1:1) indicated that most of the **5b** had been consumed. The solvents were evaporated and the residue was partitioned between water (30 ml) and dichloromethane (50 ml). The separated organic layer was dried and concentrated in vacua. The crude product was dissolved in dichloromethane (5ml) and cooled to 0°C. Triethylamine (0.21 ml, 1.5 mmol) and triflouroacetic anhydride (0.2 ml, mmol) were added. After 10 min, the reaction was warmed to room temperature and concentrated under vacuum. The residue was dissolved in dichloromethane (30 ml) and washed with water (15 ml). Drying (Na_2SO_4) and evaporating gave the crude product which was purified by flash chromatography (SiO_2, ethyl acetate / hexane 1:2) to generate **13b** as an oil (0.31 g, 58%). TLC (SiO_2, ethyl acetate / hexane, 1:1) $R_f = 0.60$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37-28 (m, 5 H), 7.11 (s, 1 H), 6.62 (s, 1 H), 6.31 (t, J = 6.4 Hz, 1 H), 5.71-5.62 (m, 1 H), 5.25-4.92 (m, 4 H), 4.72 (dd, J = 14.4 and 5.6 Hz, 1 H), 3.93 (s, 3H), 3.78 (dd, J = 14.4 and 7.8

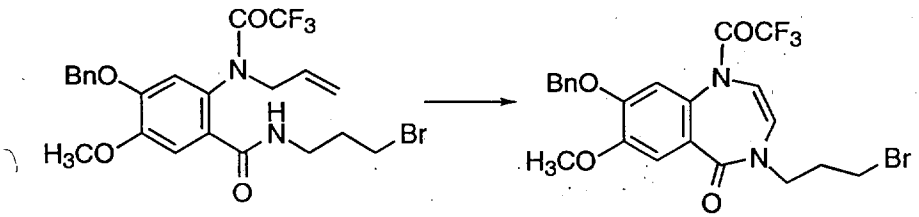
Hz, 1 H), 3.56-3.43 (m, 4 H), 2.16-2.04 (m, 2 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.23, 156.34 (q, J = 35 Hz, **C**OCF_3), 149.55, 149.03, 135.61, 130.62, 129.57, 128.54, 127.48, 127.00, 126.47, 120.00, 116.16 (q, J = 287 Hz, CF3), 116.15, 110.84, 70.99, 56.14, 54.91, 38.52, 31.75, 30.74; IR (film) υ_{max}: 3350, 3066, 3014, 2940, 1694, 1650, 1601, 1504, 1454, 1354, 1269, 1204, 1150, 1038, 1020, 915, 871, 755, 698 cm^{-1}; MS m/z (rel intens) (CI) 531 (19), 529 (20), 489 (3), 477 (5), 452 (4), 451 (16), 450 (29), 449 (100), 439 (3), 409 (15), 392 (6), 379 (18), 359 (27), 132 (8), 115 (48), 114 (17); Anal. Cacl for $C_{23}H_{24}BrF_3N_2O_4$: C 52.19; H 4.57; N 5.29. Found: C 52.32; H 4.86; N 5.27.



13a **15a**

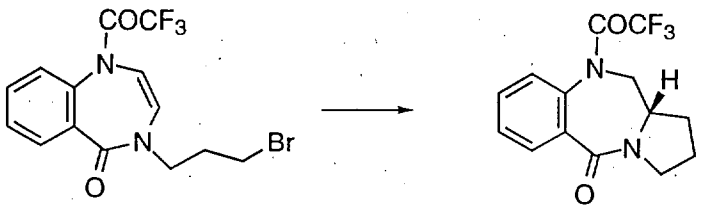
4-(3-Bromopropyl)-1-trifluoroacetyl-1, 4-dihydrobenzo[e][1,4]diazepin-5-one (15a): Ozone was bubbled through a solution containing **13a** (2.5778 g, 6.56 mmol) in dichloromethane (60 ml) and methanol (10 ml) at –78°C until a blue color persisted for 5 min. After bubbling with nitrogen for 5 min, dimethyl sulfide (0.53 ml, 7.2 mmol) was added and the reaction was warmed from –78°C to room temperature in 2 h. The solvents were removed under vacuum and the residue was dissolved in dichloromethane (100 ml). Washing with water, drying (Na_2SO_4) and evaporation then gave the crude hemi-aminal which was dissolved in benzene (45 ml). After addition of camphorsulfonic acid (0.2 g) and connection to a Dean-Stark trap, the benzene solution was refluxed overnight. Evaporation followed by purification by flash column (SiO_2, ethyl ether / hexane, 1:1) then afforded pure **15a** as a viscous oil (1.7144 g, 69.3%), TLC (SiO_2, hexane/ethyl ether, 1:1) R_f= 0.35; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, J = 7.8 and 1.3 Hz, 1 H), 7.59 (td, *J* = 7.7 and 1.5 Hz, 1 H), 7.45 (br t, *J* = 7.5 Hz, 1 H), 7.31 (br d, *J* = 7.9 Hz, 1 H), 6.44 and 6.39 (br s, 1 H), 6.14 (d, J = 5.6 Hz, 1 H), 4.31-4.10 (m, 1

H), 3.54-3.44 (m, 3 H), 2.28-2.20 (m, 2 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.22, 155.20 (q, J = 36 Hz, **C**OCF_3), 141.29, 132.74, 132.10, 129.88, 129.46, 128.50, 125.61, 116.95, 115.94 (q, J = 286 Hz, CF_3), 47.79, 31.12, 30.03; IR (film) υ_{max}: 3084, 1719, 1648, 1602, 1578, 1455, 1407, 1306, 1280, 1230, 1203, 1113, 1084, 923, 885, 746 cm^{-1}; MS m/z (rel intens) 379 (4), 378 (26), 377 (6), 376 (26), 361 1), 359 (1), 331 (1), 329 (1), 310 (10), 309 (63), 308 (13), 307 (64), 298 (4), 297 (23), 281 (11), 279 (10), 265 (4), 242 (4), 229 (38), 200 (4), 187 (27), 171 (6), 146 (6), 145 (9), 144 (21), 143 (5), 133 (10), 132 (100), 130 (5), 123 (16), 121 (16), 117 (10), 116 (10), 104 (10), 103 (10), 89 (9), 77 (22), 76 (16), 69 (9), 51 (4);Anal. Cacl for $C_{14}H_{12}BrF_3N_2O_2$: C 44.58; H 3.21; N 7.43; Br 21.19; F 15.11. Found: C 44.46; H 3.31; N 7.61; Br 21.05; F 15.03.



8-Benzyloxy-4-(3-bromopropyl)-7-methoxy-1-trifluoroacetyl-1,4-dihydrobenzo[e] 1,4]diazepin-5-one (15b): The process for **15a** was repeated, starting from 0.1464 g (0.28 mmol) of **13b**, 0.064 g product **15b** was obtained (45.1%), TLC (SiO_2, ethyl ether/hexane, 1:1) R_f=0.31; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.45-7.31 (m, 6 H), 6.81 (s, 1 H), 6.32 (br s, 1 H), 6.09 (d, J = 5.4 Hz, 1 H), 5.19 (d, J = 12.1 Hz, 1 H), 5.08 (d, J = 12.1 Hz, 1 H), 4.29-4.11 (m, 1 H), 3.91 (s, 3 H), 3.49-3.13 (m, 3 H), 2.26-2.18 (m, 2 H); IR (film) υ_{max}: 2937, 1711, 1643, 1604, 1515, 1454, 1418, 1265, 1227, 1198, 1153, 1063, 1026, 871, 751 cm^{-1}; MS m/z (rel intens) 515 (25), 514 (98), 513 (29), 512 (100), 497 (2), 495 (3), 446 (17), 445 (65), 444 (18), 443 (69), 435 (3), 434 (12), 433 (29), 432 (8), 423 (8), 417 (8), 415 (7), 401 (9), 399 (8), 395 (6), 393 (6), 365 (8), 355 (10), 354 (11), 353 (15), 352 (10), 325 (7), 298 (7), 296 (8),

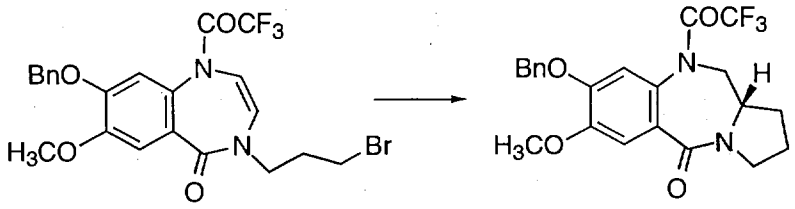
274 (9), 268 (11), 246 (25), 189 (13), 178 (20), 177 (12), 176 (21), 175 (19), 147 (28), 123 (29), 121 (37) ; EI-HRMS m/z cacd for $C_{22}H_{20}BrF_3N_2O_4$ (M^+) 512.0558 and 514.0538, found 512.0564 and 514.0542.



15a **16a**

10-Trifluoroacetyl-1,2,3,10,11,11a-hexahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-5-one (16a): A solution containing the benzodiazepinone **15a** (1.00 g, 2.65 mmol), tributyltin hydride (0.655 ml, 3.31 mmol) and AIBN (0.20 g) in benzene (177ml) was degassed with argon for 5 min and then refluxed for 2 h. After cooling and adding more tributyltin hydride (0.6 ml) and AIBN (0.2 g), the reflux was continued for another 2 h. Cooling and evaporation then gave a residue which was purified by flash chromatography (SiO_2, 1:1 hexane/ethyl acetate) to afford 0.7145 g of **15** as a white solid (90.3%), mp 154-155°C; TLC (SiO_2, hexane /ethyl acetate, 1:1) Rf = 0.17; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.84-7.81 (m, 1H), 7.56-7.53 (m, 2H), 7.27-7.24 (m, 1H), 4.41 (t, J = 12.6 Hz, 1 H), 3.83-3.72 (m, 2 H), 3.61-3.55 (m, 1 H), 3.51 (dd, J = 12.8 and 4.7Hz, 1 H), 2.18-2.02 (m, 3 H), 1.88-1.85 (m, 1 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 165.95, 157.74, (q, J = 36 Hz, **C**O**C**F_3), 135.04, 134.33, 131.48, 129.91, 129.50, 127.85, 115.94 (q, J = 286 Hz, CF3), 55.79, 54.41, 46.12, 28.20, 23.09; IR (film) υ_{max}: 2978, 2880, 1698, 1650, 1602, 1488, 1458, 1413, 1355, 1201, 1157, 1120, 1010, 898, 776, 757, 719, 698 cm^{-1}; MS m/z (rel intens) 299 (M+1, 1), 298 (M, 6), 279 (1), 270 (3), 230 (6), 229 (29), 216 (4), 201 (7), 187 (7), 186 (48), 166 (2), 160 (6)146 (3), 133 (10), 132 (100), 116 (2), 105 (6), 104 (7), 90 (5), 83

(34), 77 (23), 70 (39), 51 (5); Anal. Cacl for $C_{14}H_{13}F_3N_2O_2$: C 56.38; H 4.39; N 9.39. Found: C 56.01; H 4.40; N 9.31.

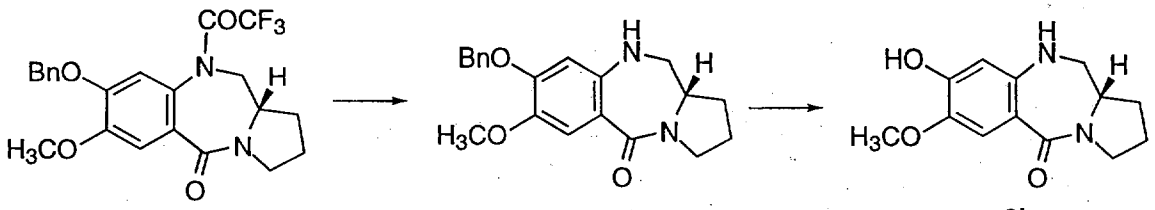


15b **16b**

8-Benzyloxy-7-methoxy-10-trifluoroacetyl-1,2,3,10,11,11a-hexahydro-benzo[e] pyrrolo[1,2-a] [1,4] diazepin-5-one (16b): A solution containing the bicyclic bromide **15b** (0.084 g, 0.16 mmol), tributyltin hydride (0.057 ml, 0.0.29 mmol) and AIBN (5 mg) in benzene (13 ml) was degassed with argon for 5 min, and then heated to reflux for 2 h. After cooling and evaporation, the residue was purified by flash chromatography (SiO_2, ethyl acetate/hexane 2.5:1) to afford pure product as a white solid (0.065 g, 91%). Mp 199-200°C (ether/hexane); TLC (SiO_2, hexane/ethyl acetate, 1:3) R_f = 0.34; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.41-7.30 (m, 5 H), 7.28 (s, 1 H), 6.72 (s, 1 H), 5.13 (s, 2 H), 4.34 (t, *J* = 12.6 Hz, 1 H), 3.93 (s, 3 H), 3.79-3.70 (m, 2 H), 3.57-3.48 (m, 1 H), 3.43 (dd, *J* = 12.8 and 4.8 Hz, 1 H), 2.12-1.97 (m, 3 H), 1.84-1.79 (m,1 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.19, 157.31 (q, *J* = 36 Hz, **COCF$_3$**), 150.25, 149.84, 135.67, 128.64, 128.02, 127.79, 127.25, 127.12, 115.95 (q, *J* = 286 Hz, CF_3), 113.24, 111.56, 71.31, 56.16, 56.04, 54.70, 46.19, 28.38, 23.14; IR (film) υ_{max}: 2956, 2878, 1698, 1642, 1603, 1515, 1454, 1430, 1381, 1280, 1197, 1158, 1044, 1002, 875, 753, 698, cm^{-1}; MS m/z (rel intens) 435 (M+1, 3), 434 (M, 10), 365 (2), 343 (1), 315 (1), 190 (1)176 (1), 175 (1), 149 (1), 122 (2), 105 (3), 92 (9), 91 (100), 89 (1); EI-HRMS m/z cacd for $C_{22}H_{21}F_3N_2O_4$ (M^+) 434.1453, found 434.1463.

16a 3a

1,2,3,10,11,11a-hexahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-5-one (3a): The trifluoroacetamide **16a** (0.7145 g, 2.40 mmol) was dissolved in methanol (10 ml) and water (2 ml). After addition of potassium carbonate (0.5 g), the reaction was stirred at room temperature overnight. Evaporation gave a white residue, which was washed three times with water and dried under vacuum to afford pure product **3a** (0.466g, 96.2%) as a white solid. Mp 175.5-177°C; TLC (SiO_2, 5% methanol in dichloromethane) R_f = 0.37; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.1 Hz, 1 H), 7.17 (t, *J* = 7.6 Hz, 1 H), 6.74 (t, *J* = 7.5 Hz, 1 H), 6.57 (d, *J* = 8.1 Hz, 1 H), 4.54 (d, *J* = 6 Hz, 1 H), 3.89-3.77 (m, 2 H), 3.70-3.61 (m, 1 H), 3.52 (dd, *J* = 12.4 and 6.8 Hz, 1 H), 3.27 (dd, *J* = 11.8 and 10.3 Hz, 1 H), 2.27-2.13 (m, 1 H), 1.96-1.76 (m, 2 H), 1.71-1.62 (m, 1 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.79, 145.65, 132.87, 131.73, 118.67, 117.88, 117.47, 57.01, 52.98, 48.09, 30.68, 22.77; IR (film) υ_{max}: cm^{-1}; MS m/z (rel intens): 203 (M+1, 21), 202 (M, 100), 173 (2), 146 (2), 134 (5), 133 (46), 132 (23), 117 (3), 106 (4), 105 (41), 104 (44), 92 (4); Anal. Cacl for $C_{12}H_{14}N_2O$: C 71.26; H 6.98; N 13.85 . Found: C 70.95; H 7.03; N 13.83.

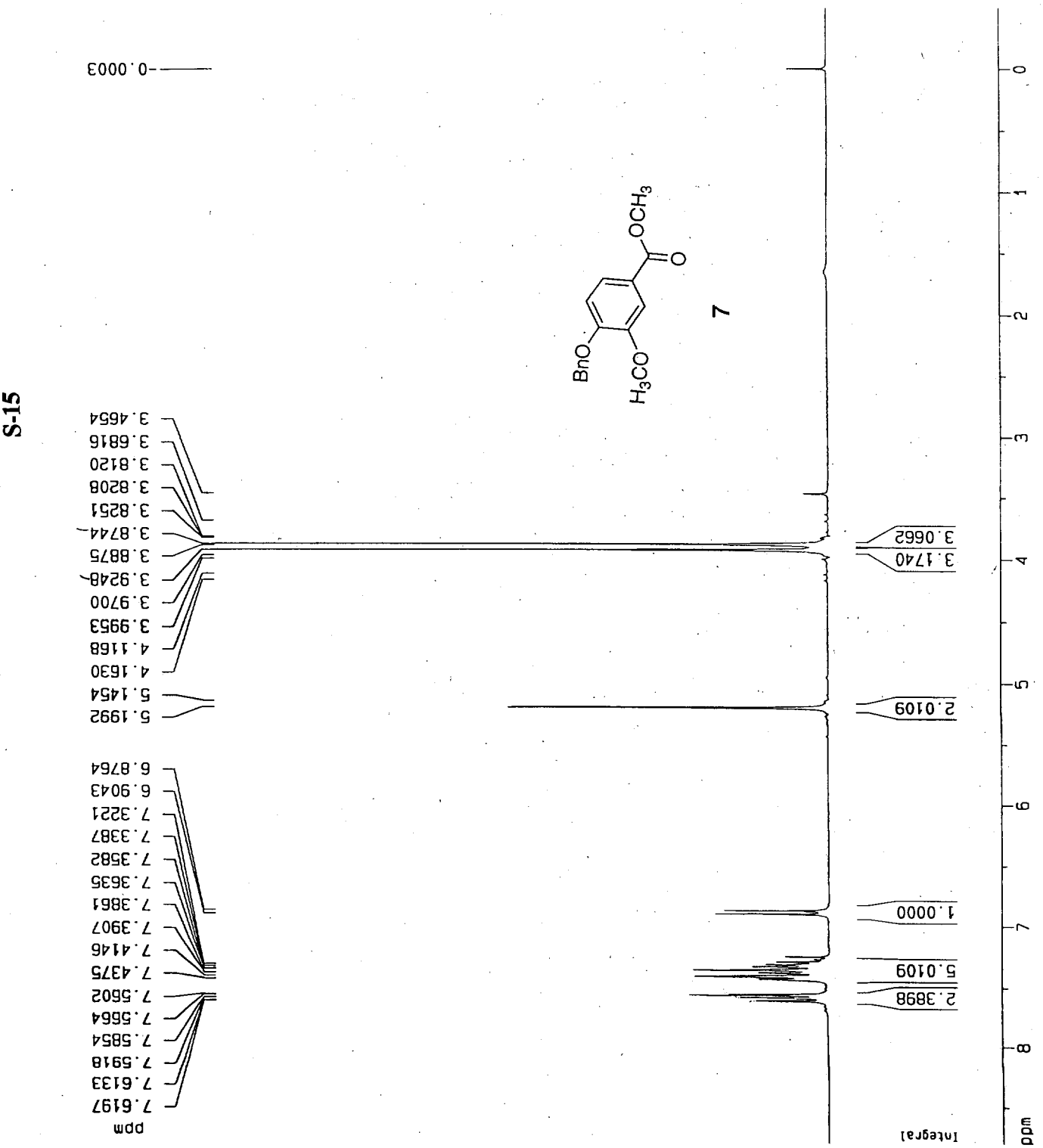


8-Hydroxy-7-methoxy-1,2,3,10,11,11a-hexahydro-benzo[e]pyrrolo[1,2-a][1,4] diazepin-5-one (3b): To tricyclic compound **16b** (0.1245 g, 0.29 mmol) in acetonitrile (9 ml) and water (2 ml) was added potassium carbonate (0.3 g). After stirring at room temperature overnight, the solvents were removed under vacuum. Water (50 ml) was added and the resulting suspension was extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried (Na_2SO_4) and evaporated to give the secondary amine **17** (0.0918 g, 94.7%) as a single spot in TLC as a white solid, which was used directly for next step. TLC (SiO_2, 4% methanol in dichloromethane) $R_f = 0.40$; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.60 (s, 1 H), 7.36-7.25 (m, 5 H), 6.07 (s, 1 H), 4.99 (s, 2 H), 4.53 (d, J = 6.0 Hz, 1 H), 3.81 (s, 3 H), 3.79–3.65 (m, 2 H), 3.60 (dd, J = 12 and 7 Hz, 1 H), 3.43 (dd, J = 11.8 and 7 Hz, 1 H), 3.11 (dd, J = 11.8 and 9 Hz, 1 H), 2.18-2.10 (m, 1 H), 1.90-1.55 (m, 3 H) ; ^{13}C-NMR (75 MHz, $CDCl_3$) 166.25, 151.63, 141.79, 141.43, 136.47, 128.45, 127.81, 127.12, 115.19, 110.24, 102.53, 70.36, 57.66, 56.22, 52.62, 48.33, 30.76, 22.72.

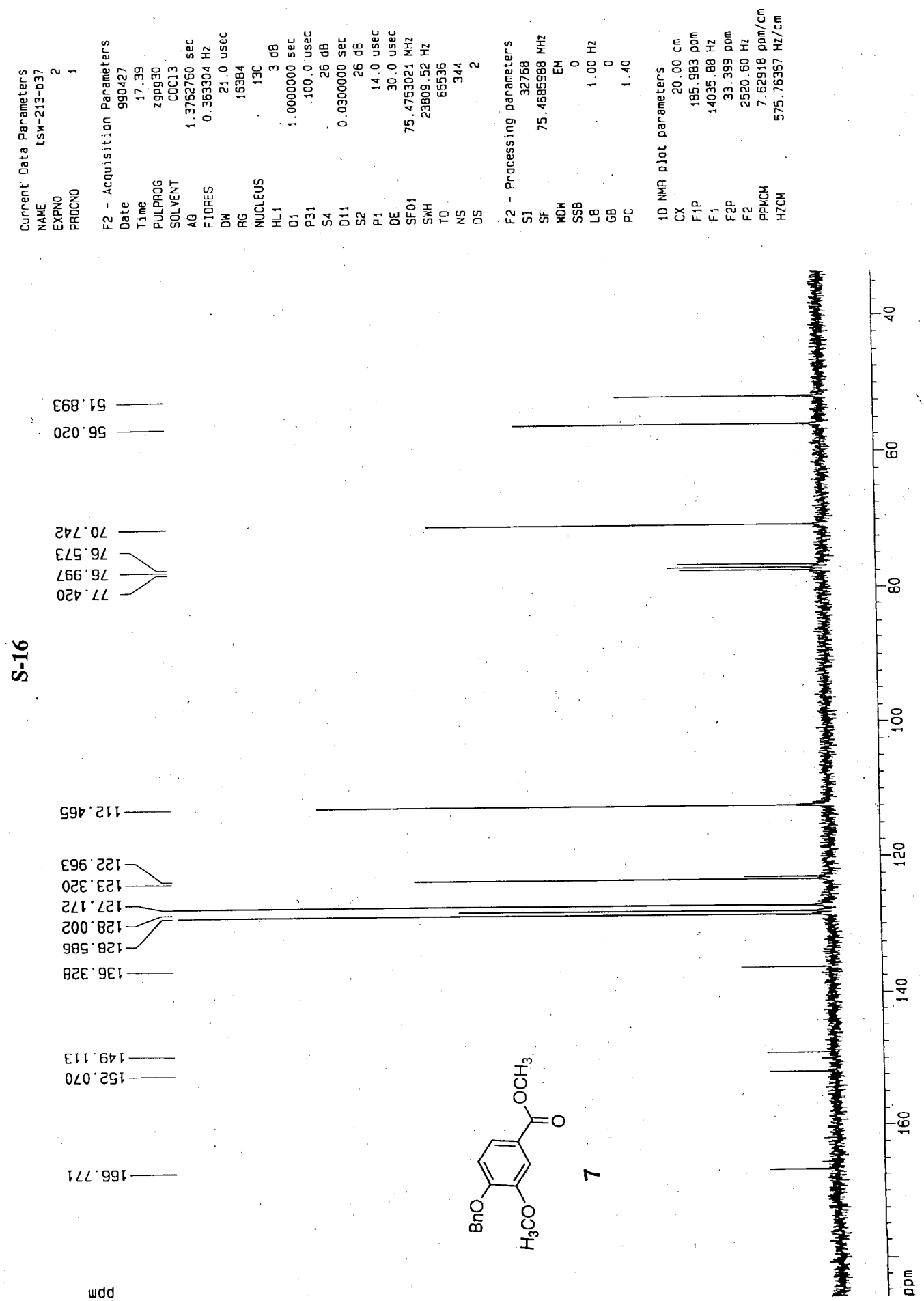
The crude amine **17** was dissolved in methanol (5 ml). After addition of 10% palladium on carbon (10 mg) and ammonium formate (0.3 g), the suspension was heated to reflux for 1 h. The reaction was cooled, filtrated through celite and washed with methanol-dichloromethane (1:2). Evaporation gave the residue which was absorbed on silica gel and was chromatographic (SiO_2, 4% methanol in dichloromethane) to afford pure **3b** as a white solid (0.0523 g, 53.9% over 2 steps). Mp 248-250°C (methanol); TLC (SiO_2, 4% methanol in dichloromethane) $R_f = 0.20$; ^{1}H-NMR (300 MHz, methanol-d_4) δ 7.29 (s, 1 H), 6.08 (s, 1 H), 3.74 (s, 3 H), 3.64 (dd, J = 7.2 and 5 Hz, 1 H), 3.56-3.49 (m, 1 H),

3.23 (br s, 1 H), 3.45 (dd, J = 12.7 and 1.7Hz, 1 H), 3.04 (dd, J = 12.7 and 8.8 Hz, 1 H), 2.20-2.12 (m, 1 H), 1.89-1.61 (m, 3 H); ^{13}C-NMR (75 MHz, methanol-d_4) δ 169.54, 152.76, 145.10, 142.18, 116.04, 110.22, 105.42, 59.90, 57.13, 54.09, 31.92, 31.07, 24.06; CI MS: 249 (M+1); MS m/z (rel intens) 248 (M, 100); EI HRMS Cacd for $C_{13}H_{16}N_2O_3$: M^+, 248.1161, found 248.1160.

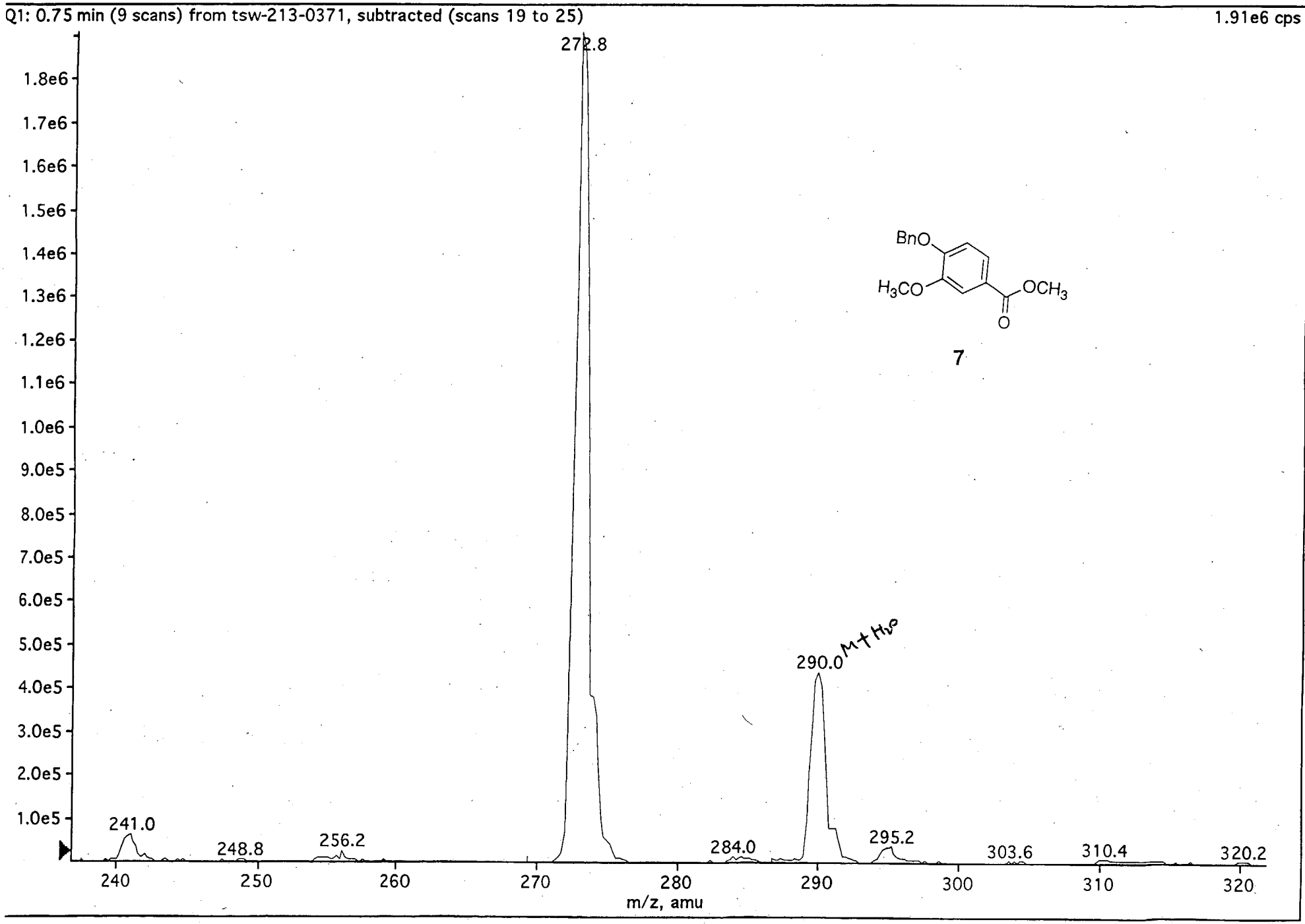
© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 15



© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 16



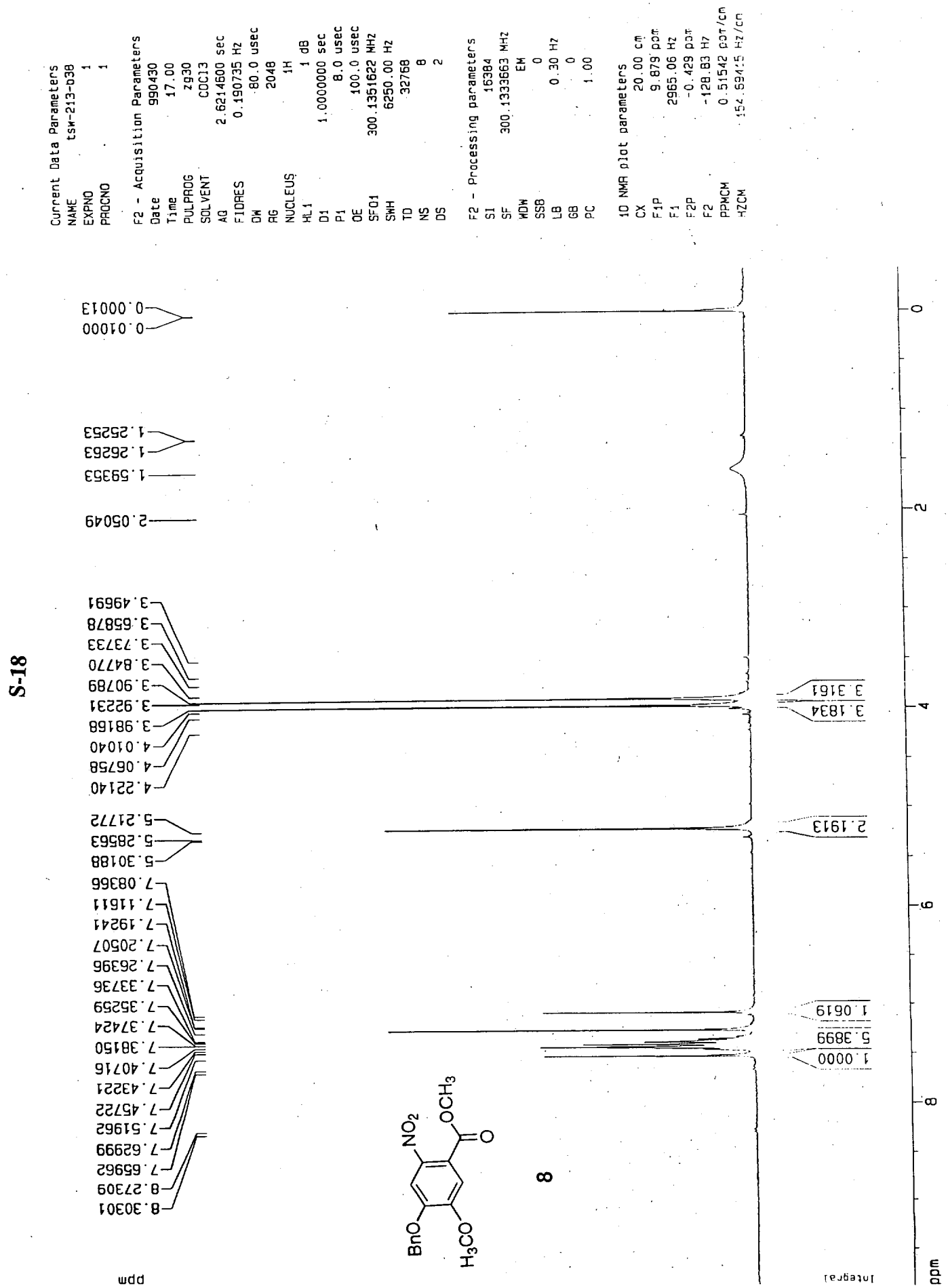
riod 1, Expt. 1; Mass range: 100.0 to 1000.0 by 0.2 amu; Dwell: 1.0 ms; Pause: 5.0 ms
q. Time: Fri, Aug 13, 1999 at 06:20:11 PM; Exp. Comment: Default Comment.



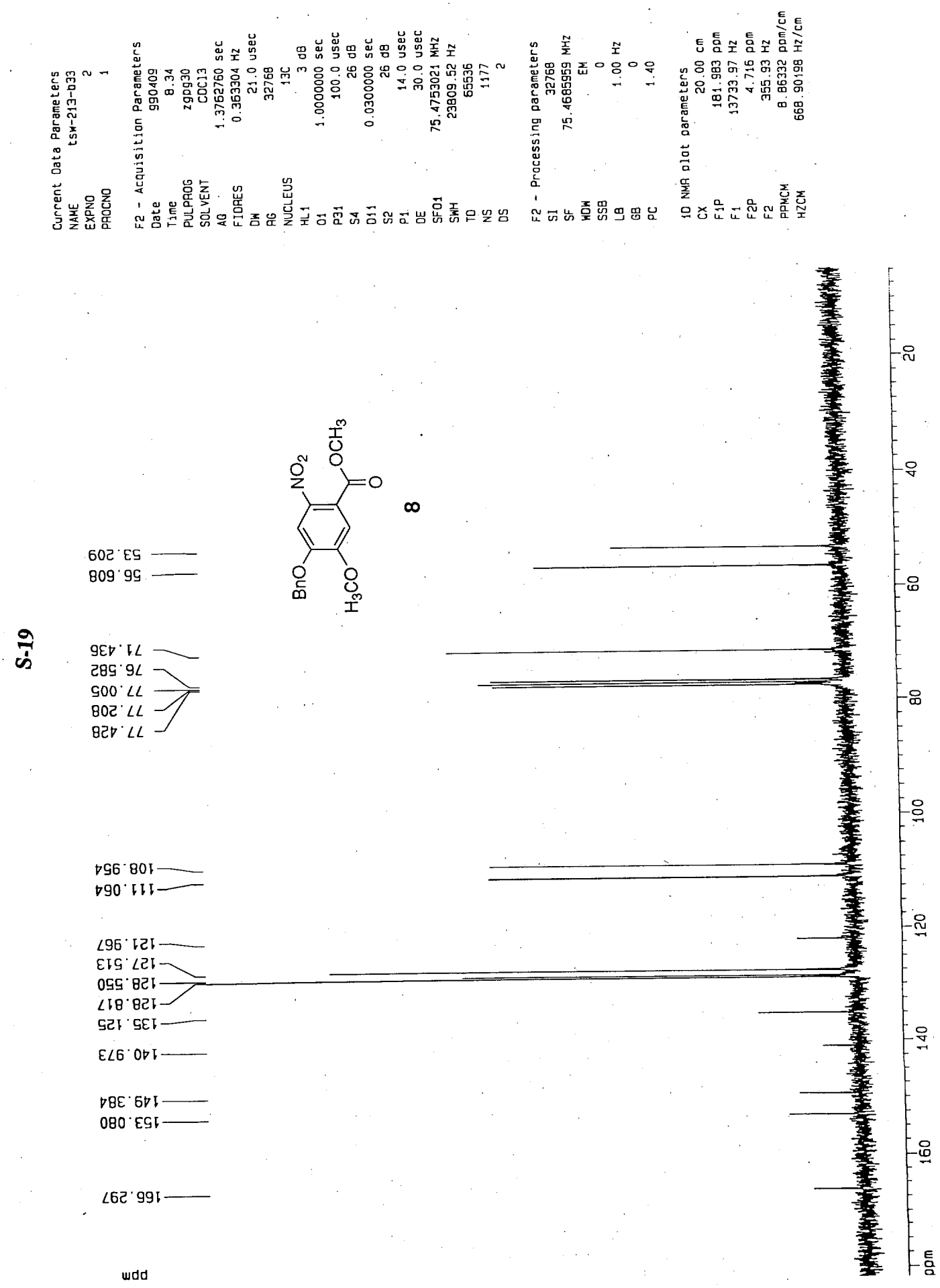
7

© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 17

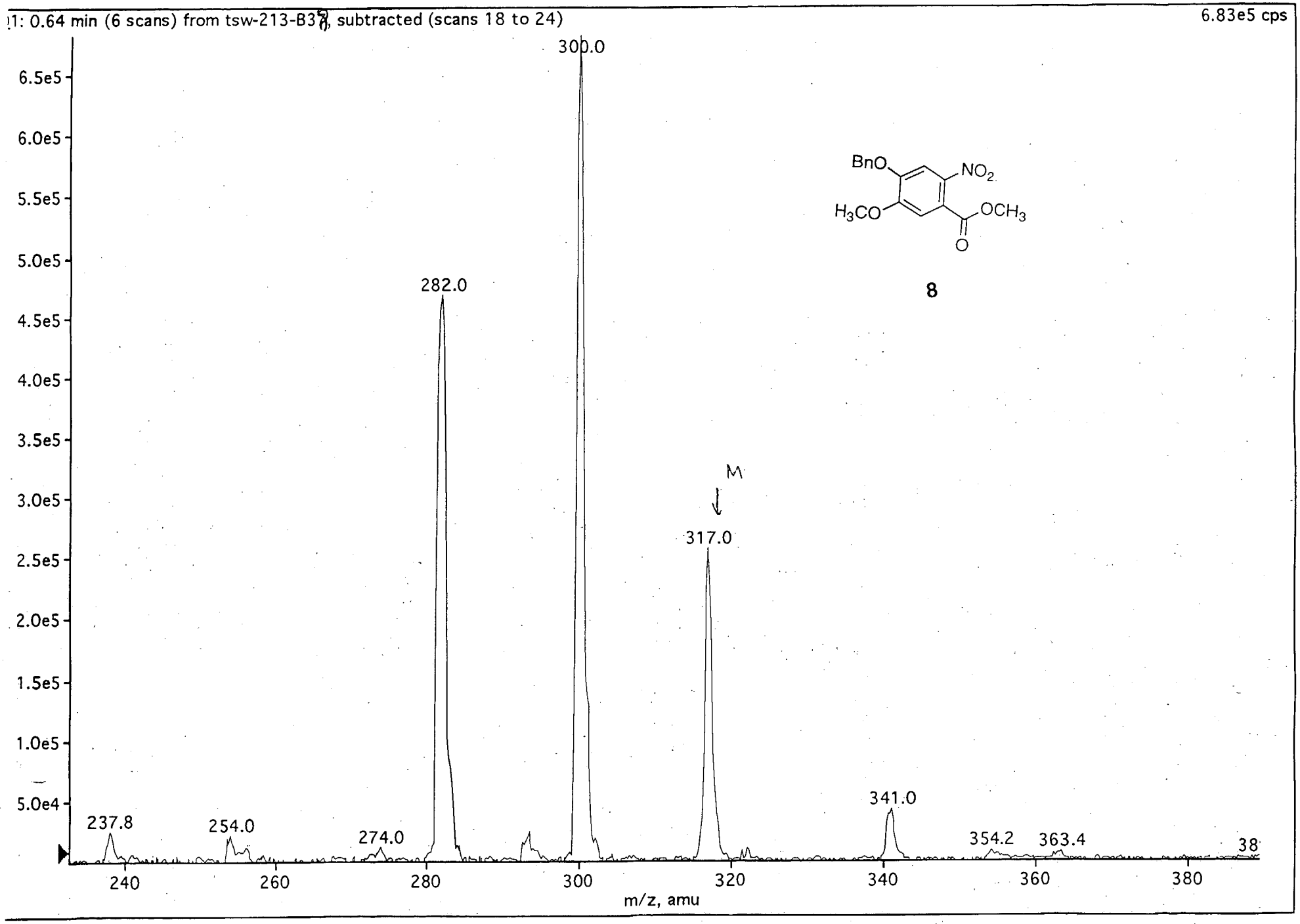
© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 18



© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 19



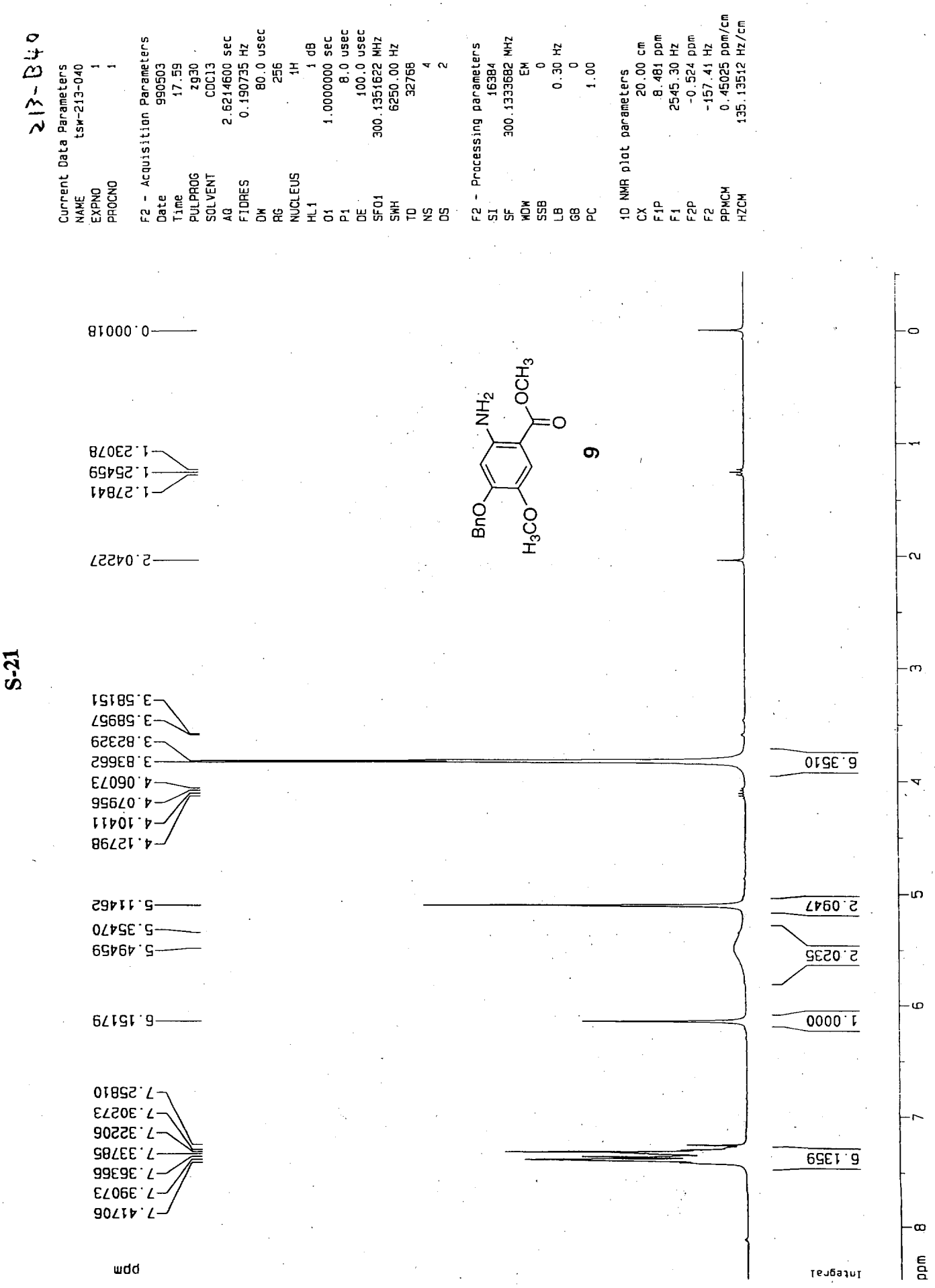
-213-B37 (tsw TSW-213-B37)
od 1, Expt. 1; Mass range: 100.0 to 1000.0 by 0.2 amu; Dwell: 1.0 ms; Pause: 5.0 ms
. Time: Fri, Apr 23, 1999 at 03:30:01 PM; Exp. Comment: Default Comment.



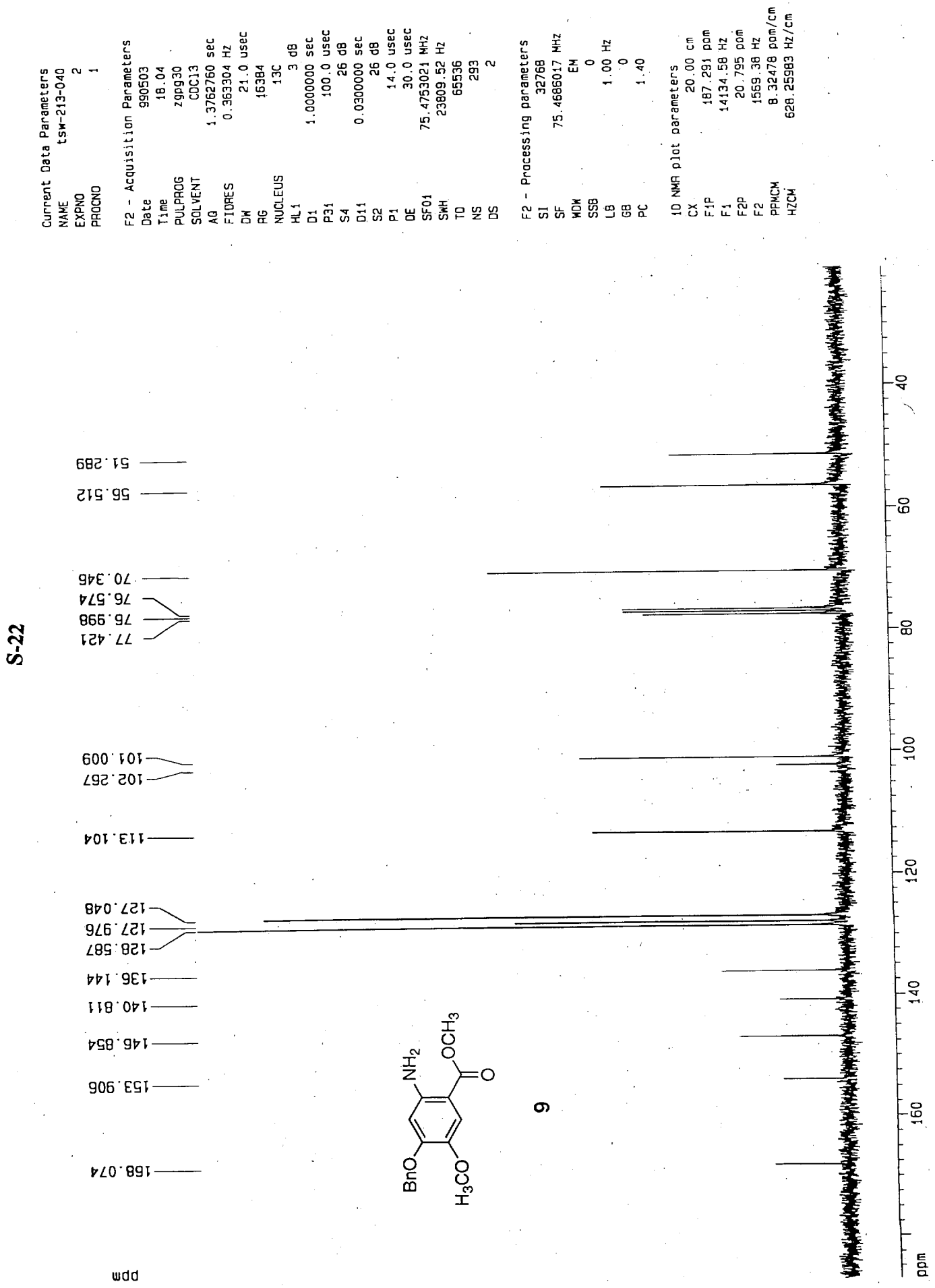
8

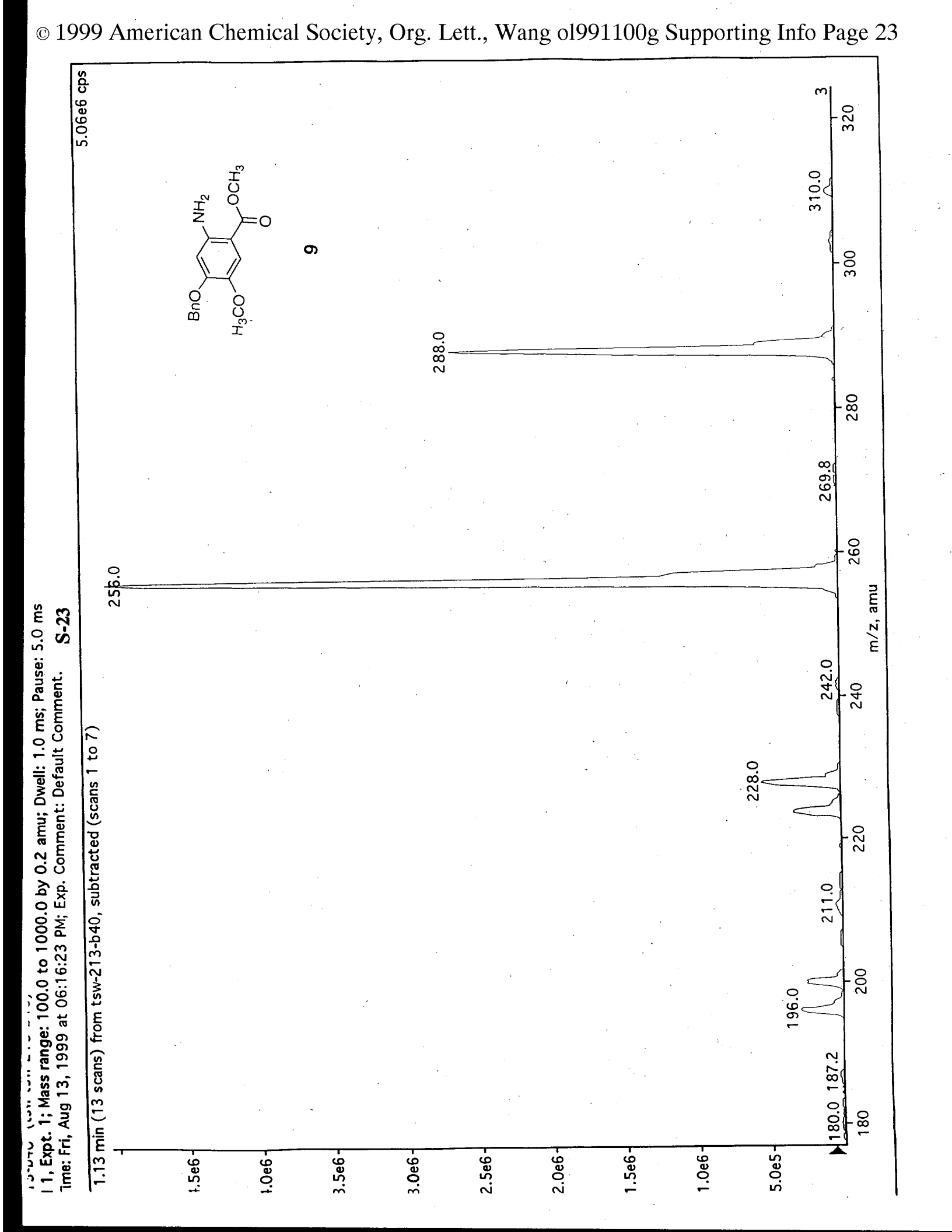
© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 20

© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 21

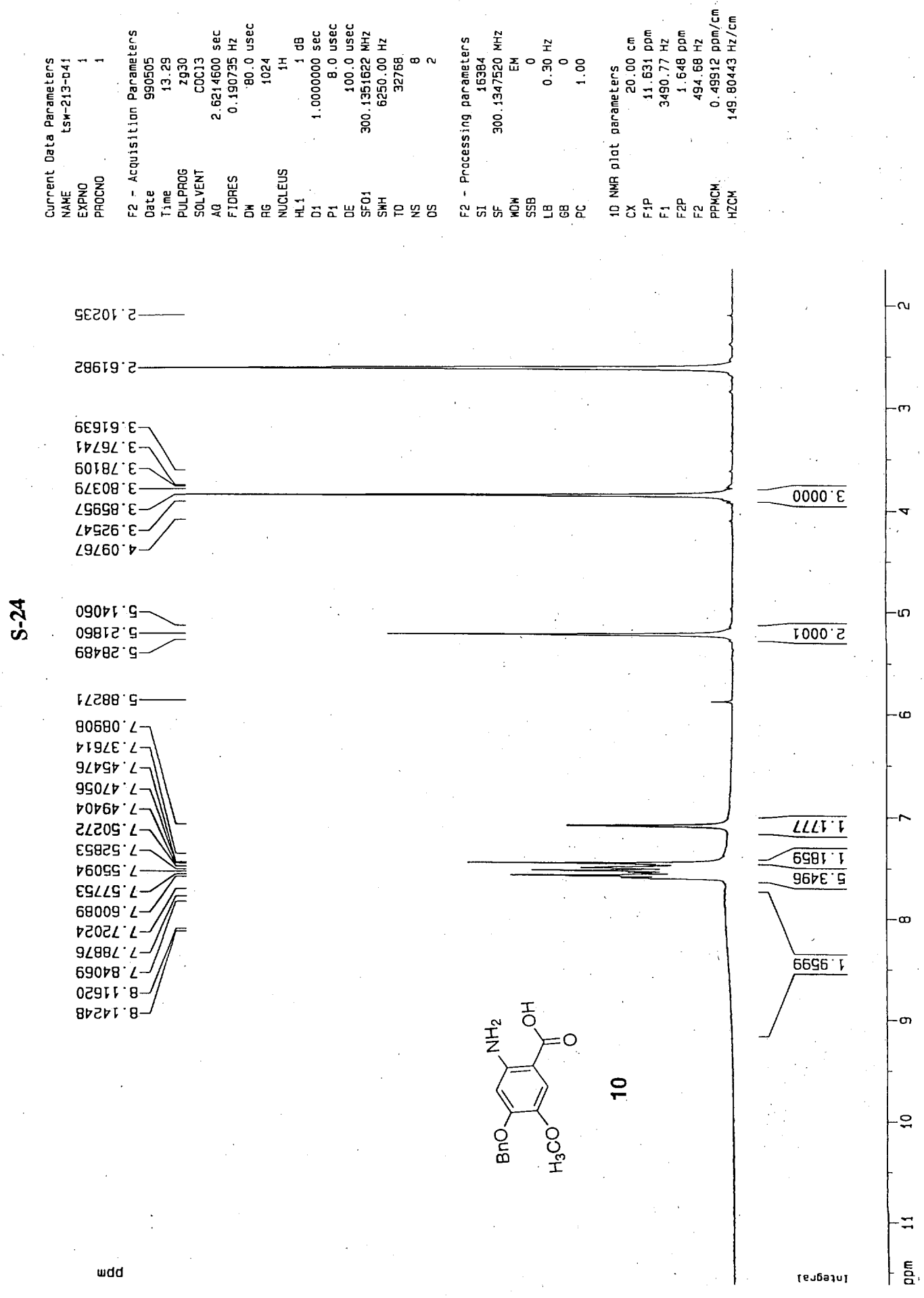


© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 22

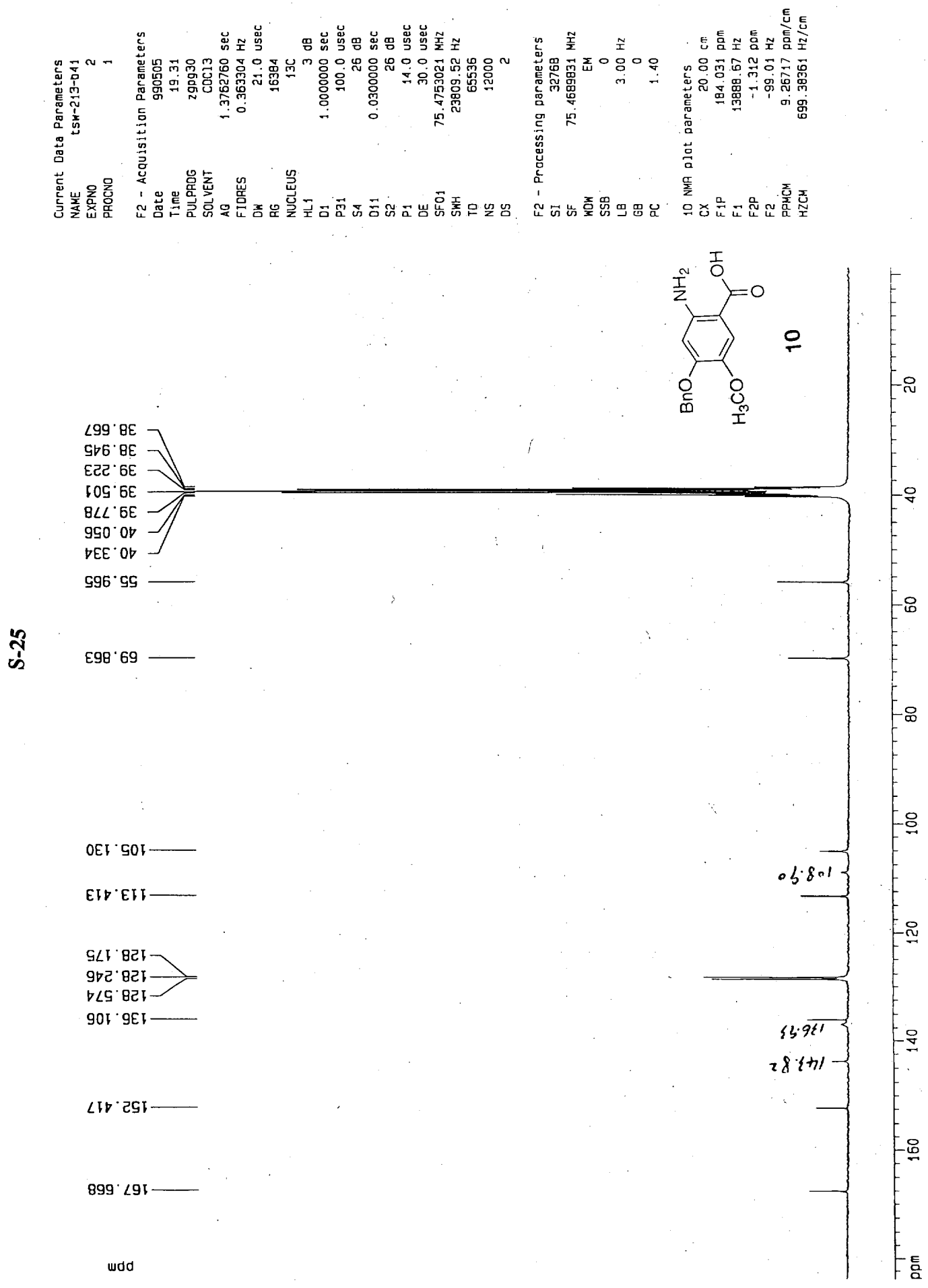


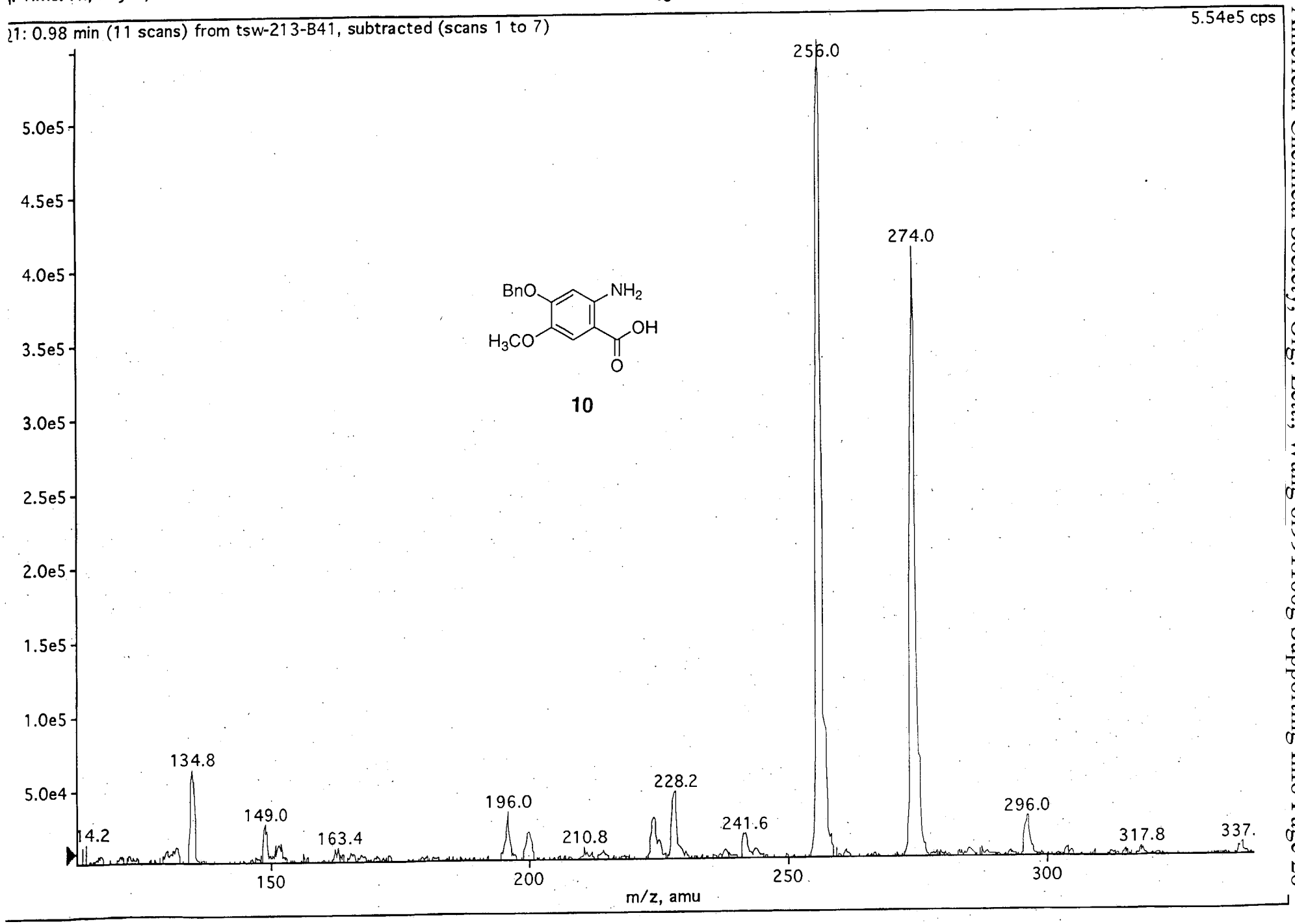

I 1, Expt. 1; Mass range: 100.0 to 1000.0 by 0.2 amu; Dwell: 1.0 ms; Pause: 5.0 ms
Time: Fri, Aug 13, 1999 at 06:16:23 PM; Exp. Comment: Default Comment.
S-23
1.13 min (13 scans) from tsw-213-b40, subtracted (scans 1 to 7)
5.06e6 cps
NH2
OCH3
O
BnO
H3CO
9
256.0
288.0
310.0
269.8
242.0
228.0
211.0
196.0
187.2
180.0
m/z, amu

© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 24



© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 25

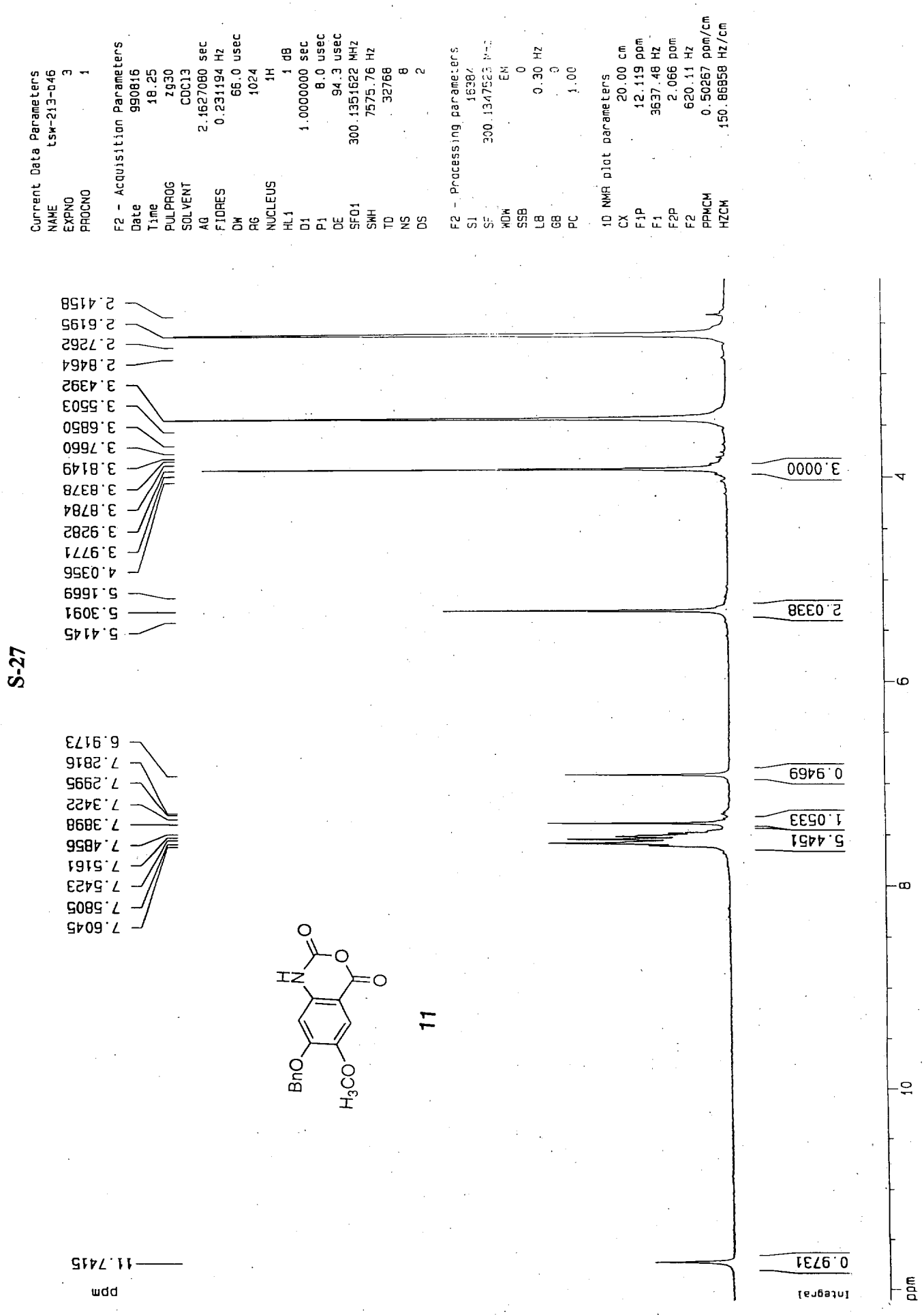




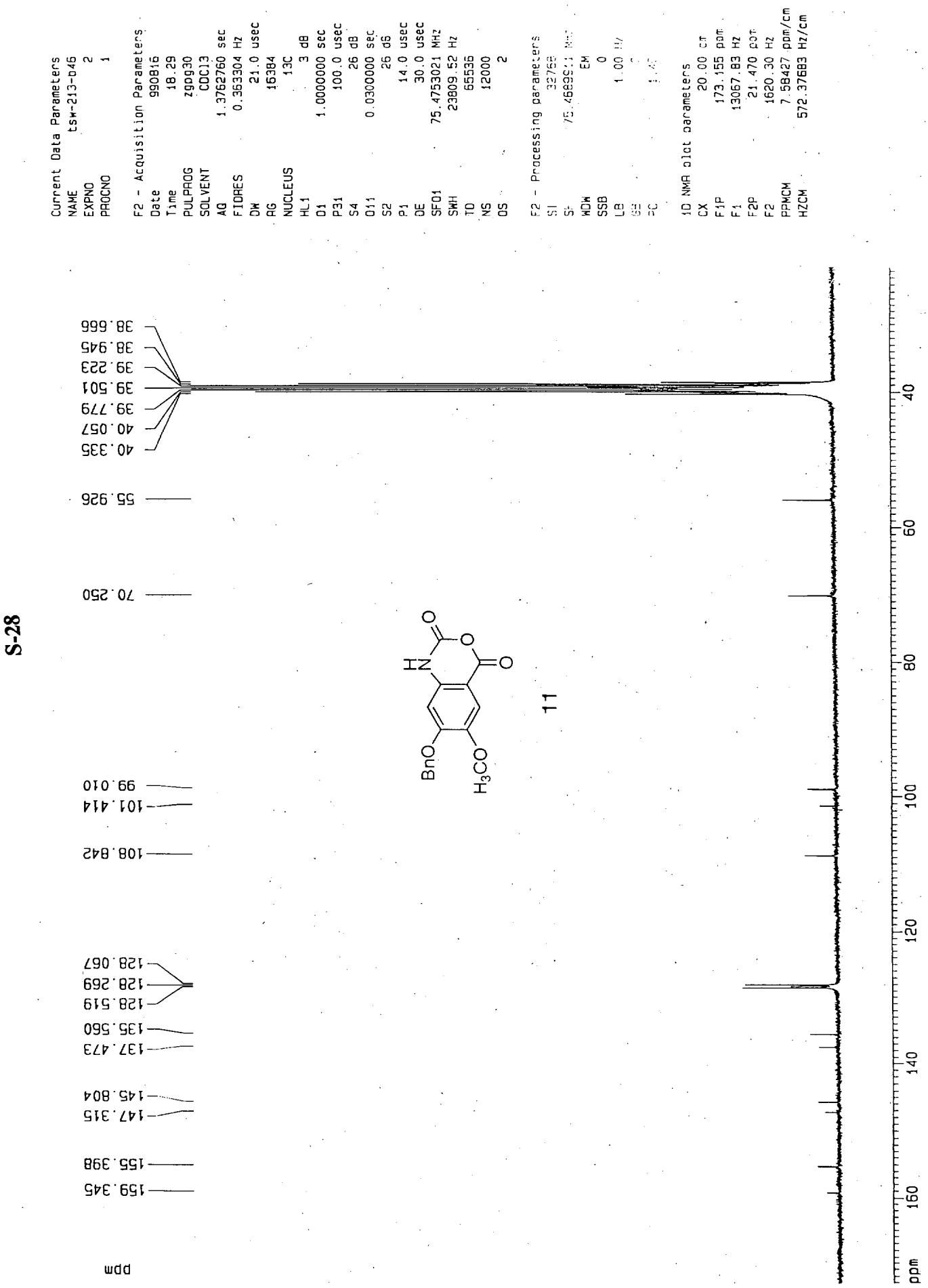
10

© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 26

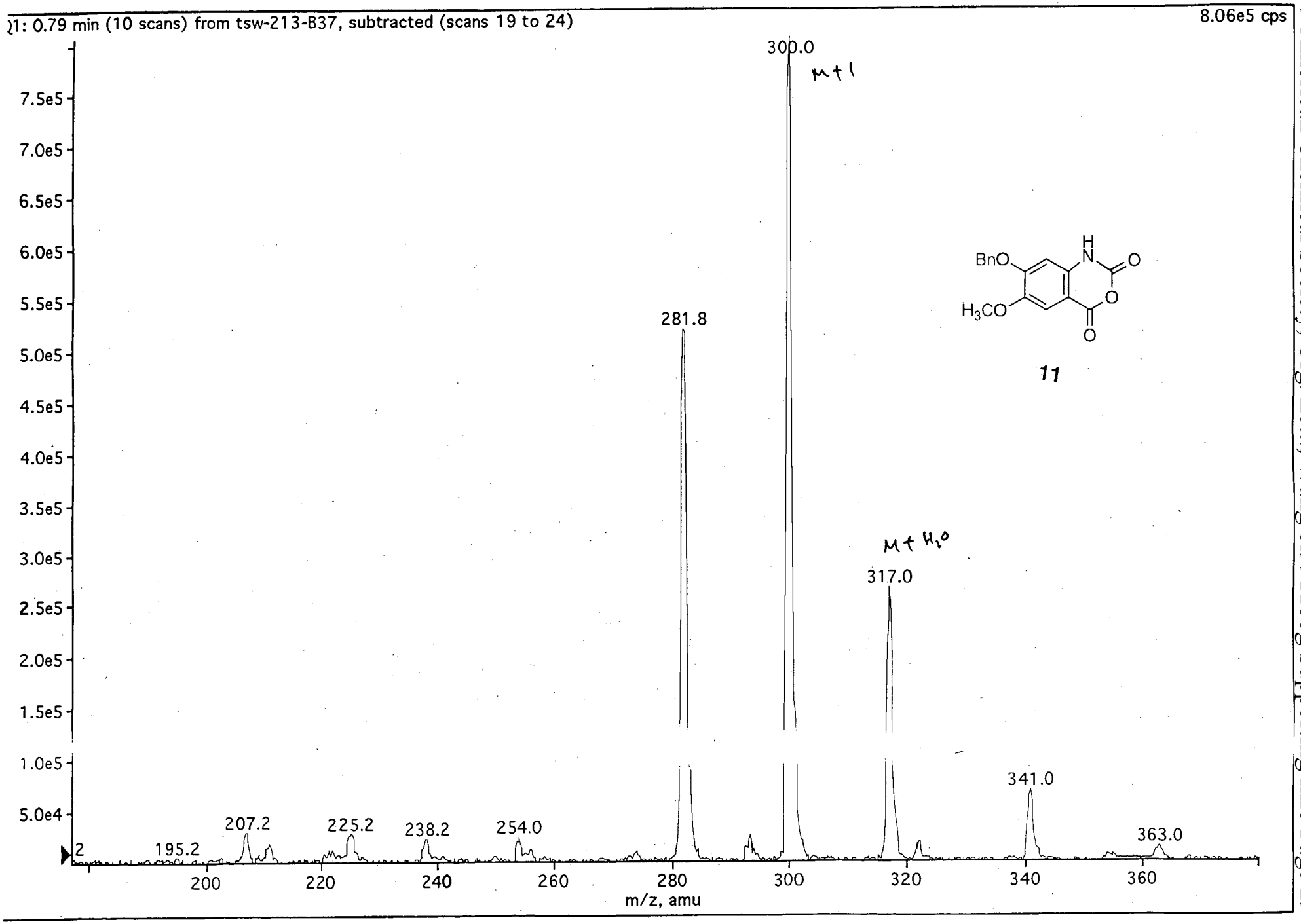
© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 27



© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 28

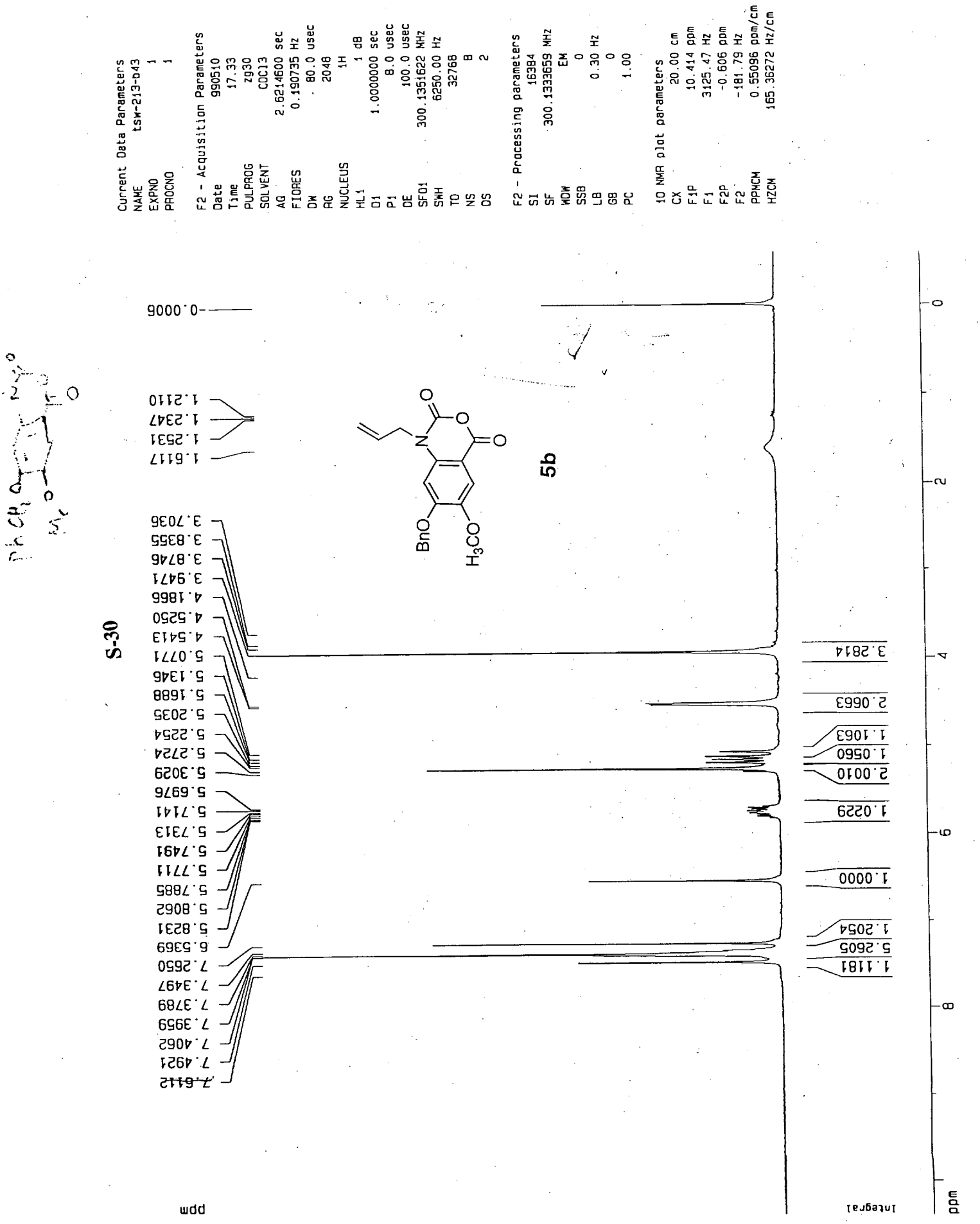


S-28

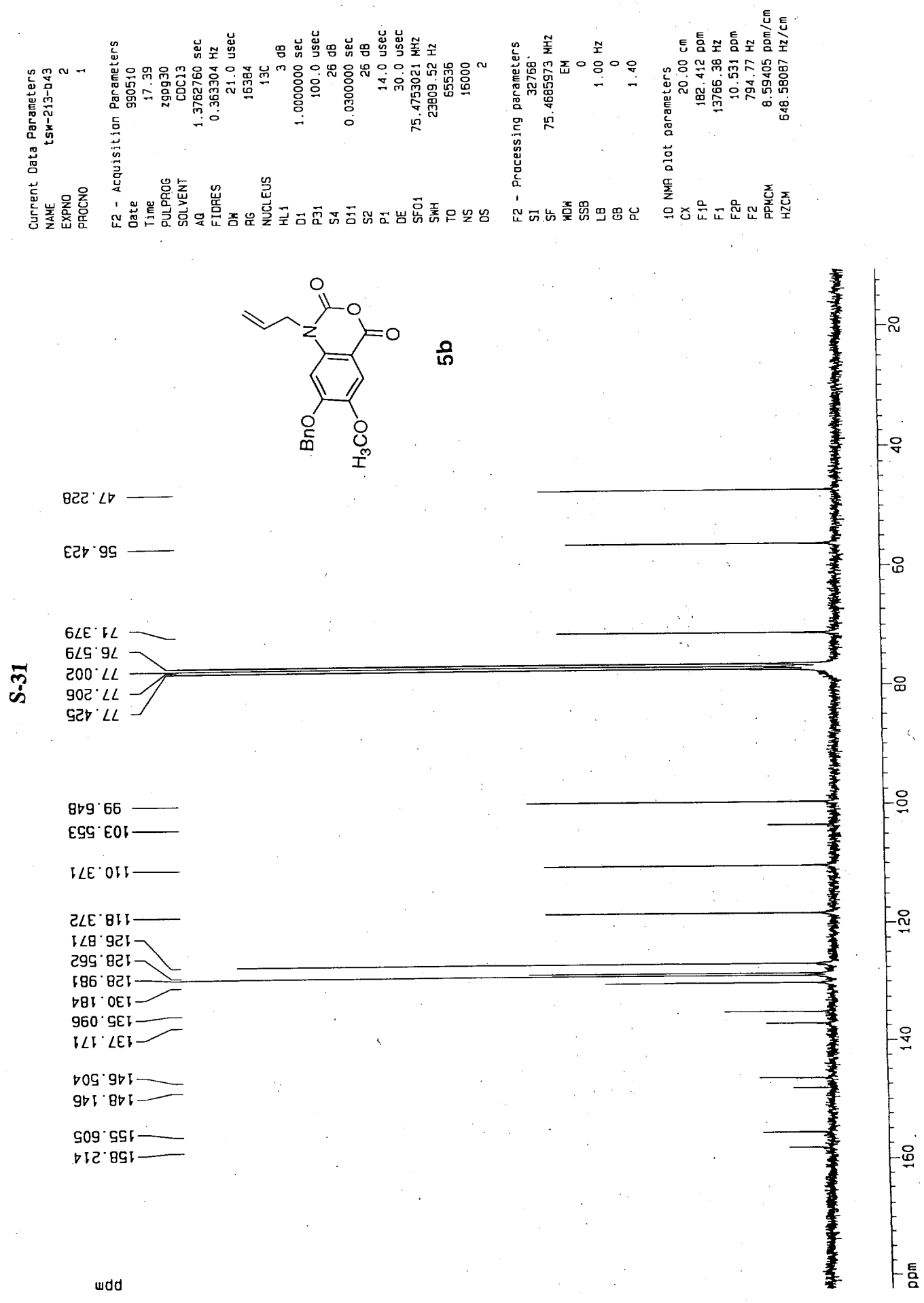


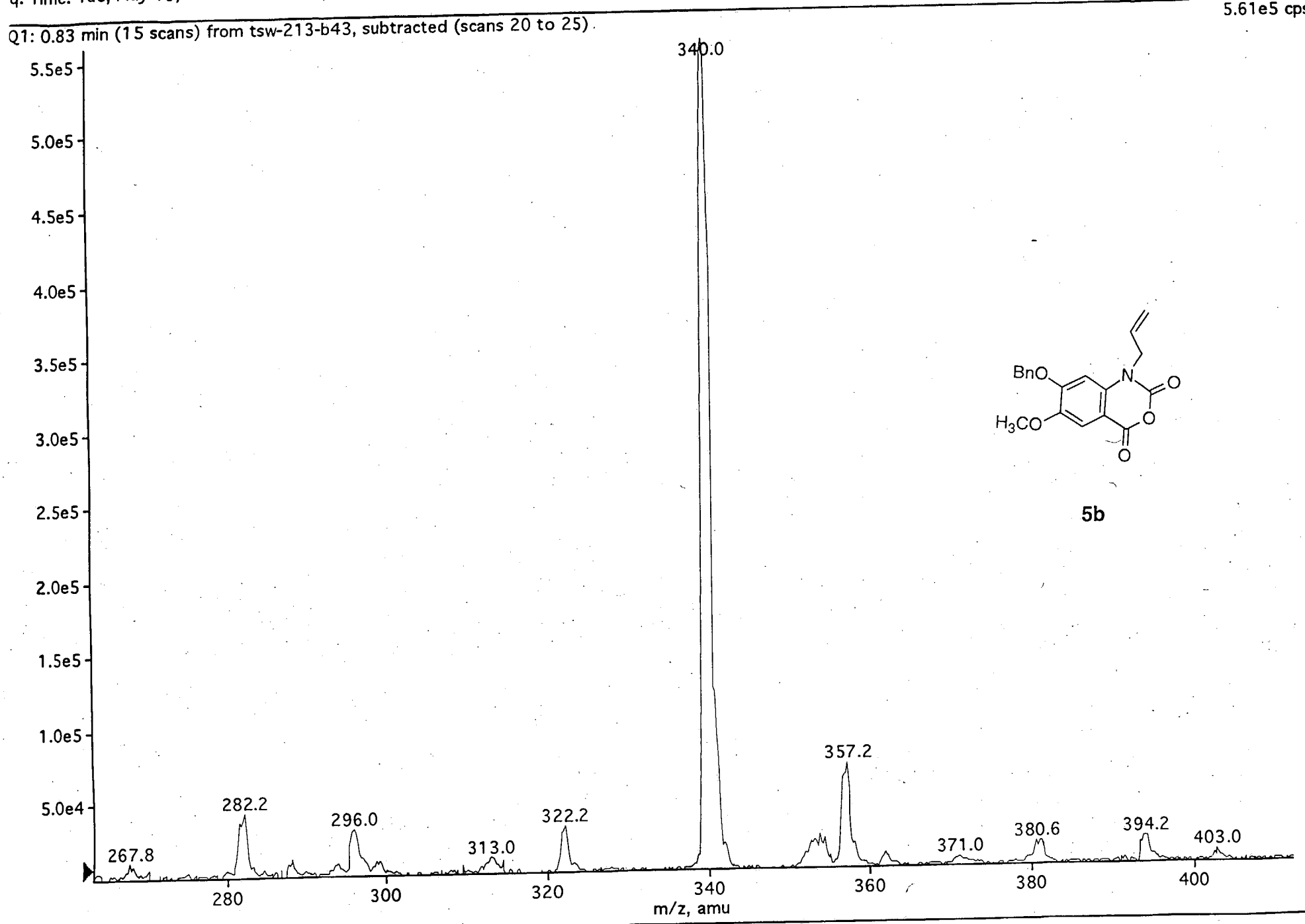
© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 29

© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 30



© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 31

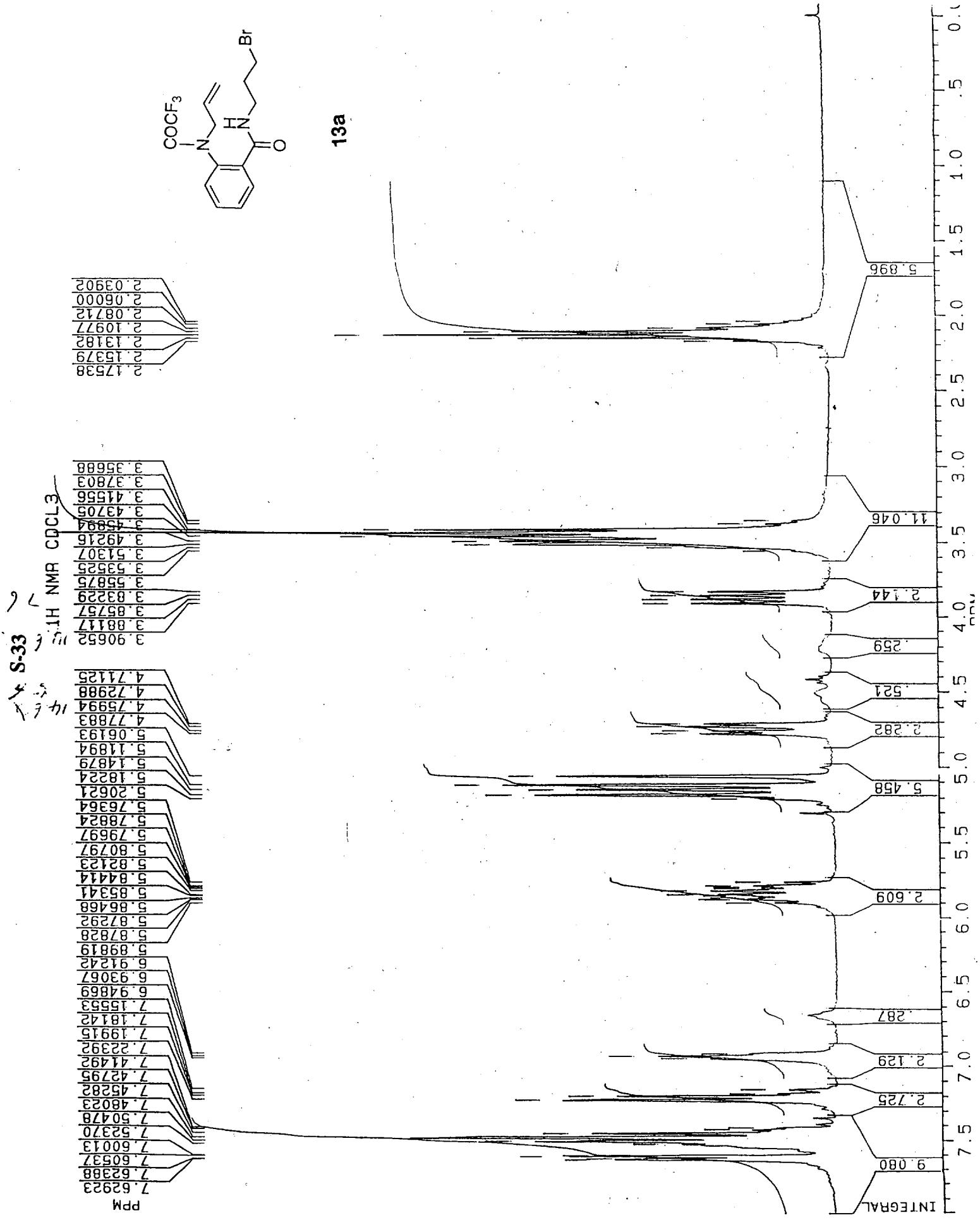




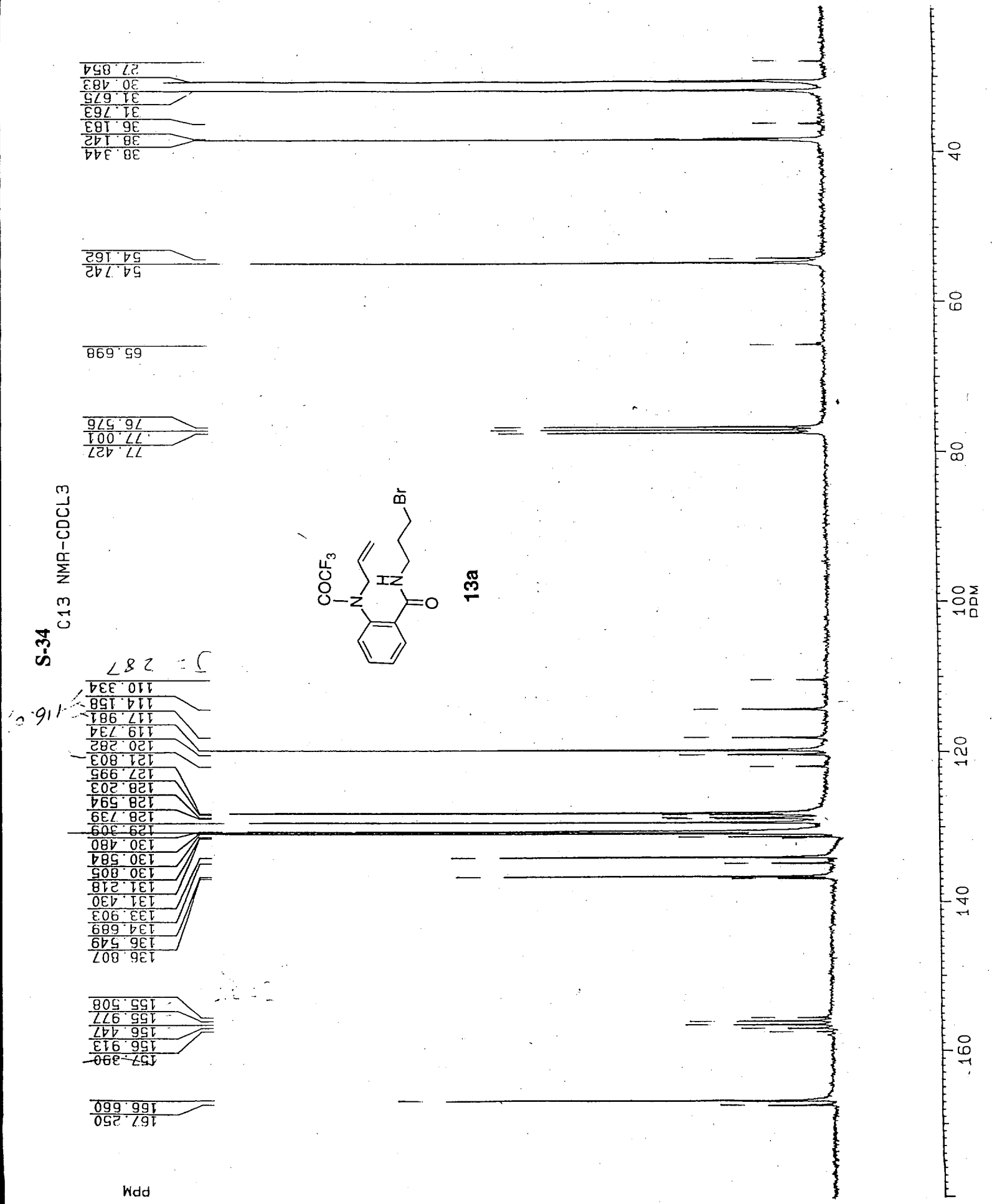
5b

© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 32

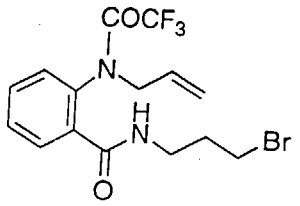
© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 33



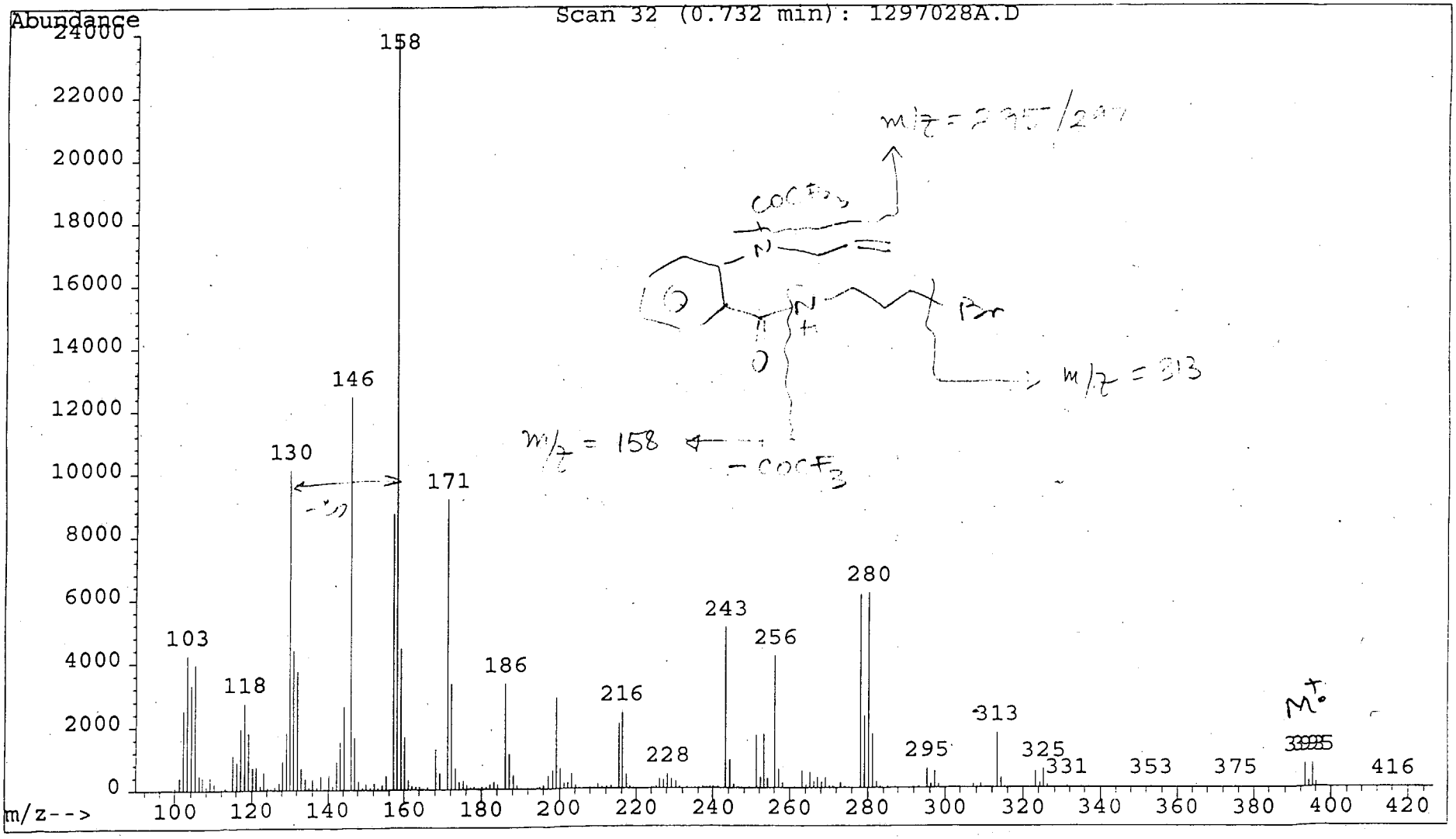
© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 34



File : C:\HPCHEM\1\DATA\1297028A.D
Operator : rsl
Acquired : 17 Dec 97 3:40 pm using AcqMethod LPEI
Instrument : 5989x - I
Sample Name: ar1297028
Misc Info : pb/ei/loop
Vial Number: 1

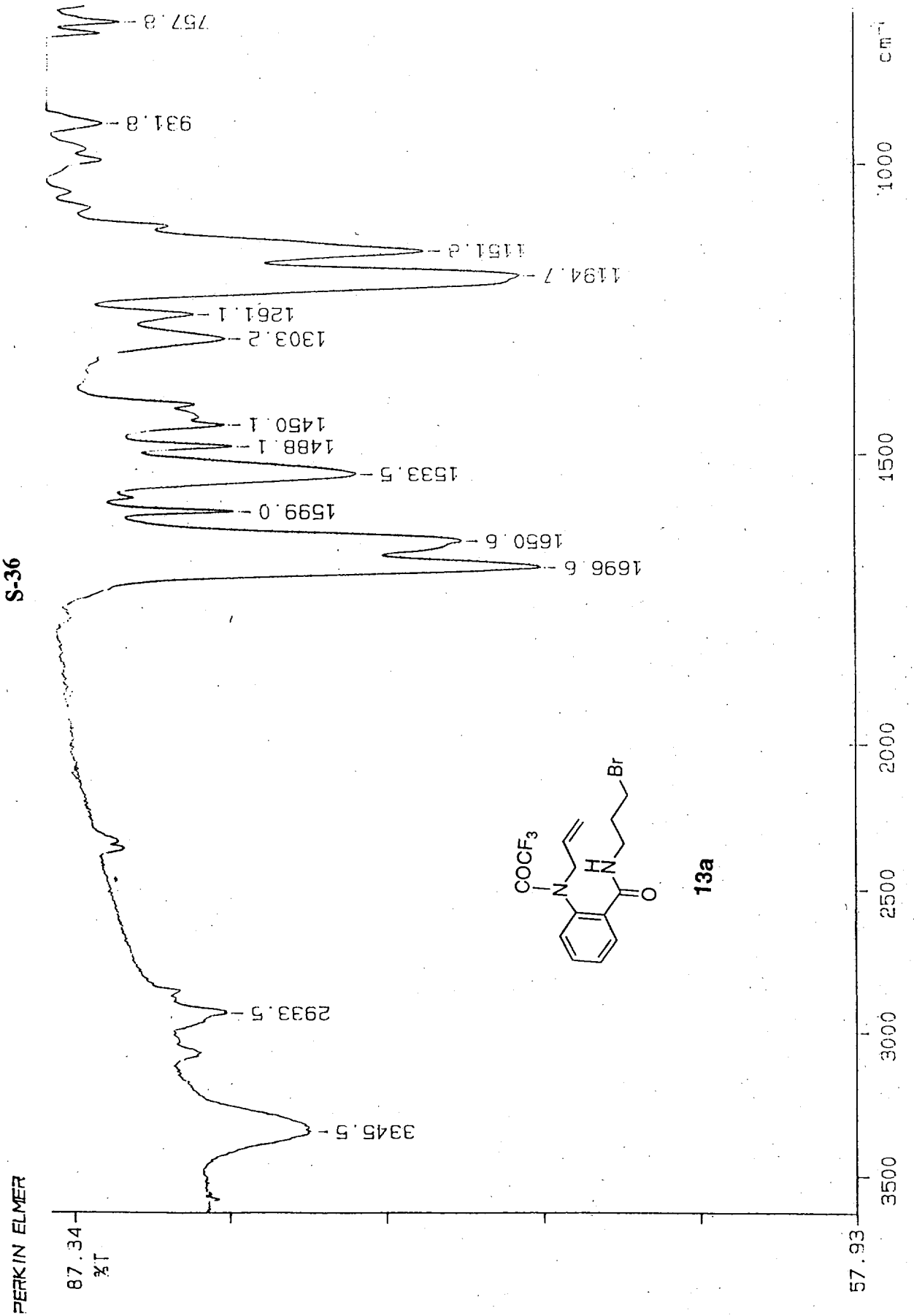


13a

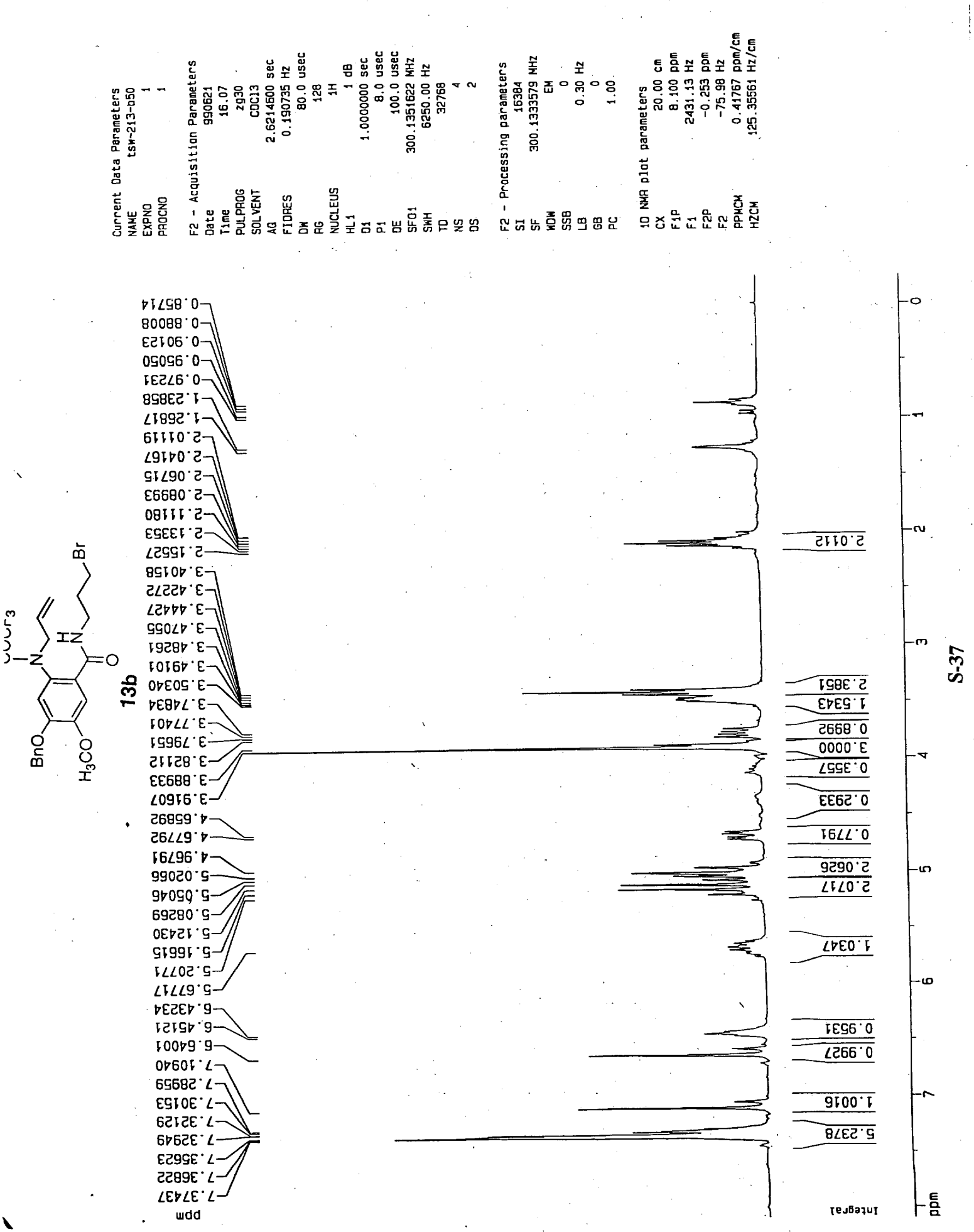


© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 35

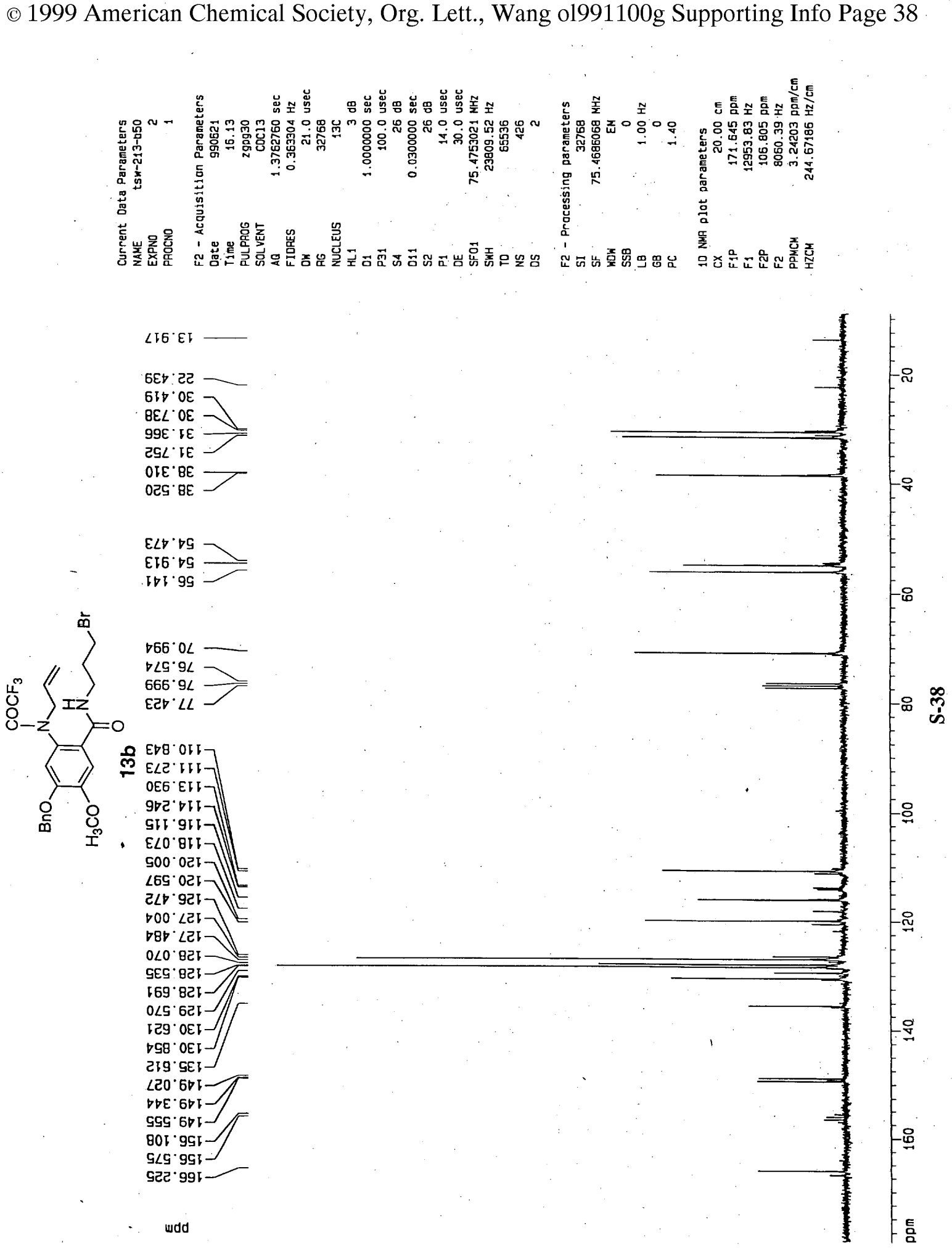
© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 36



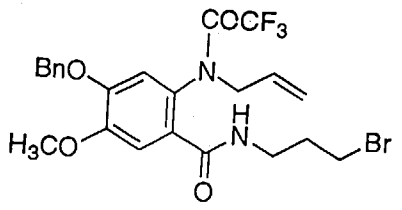
© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 37



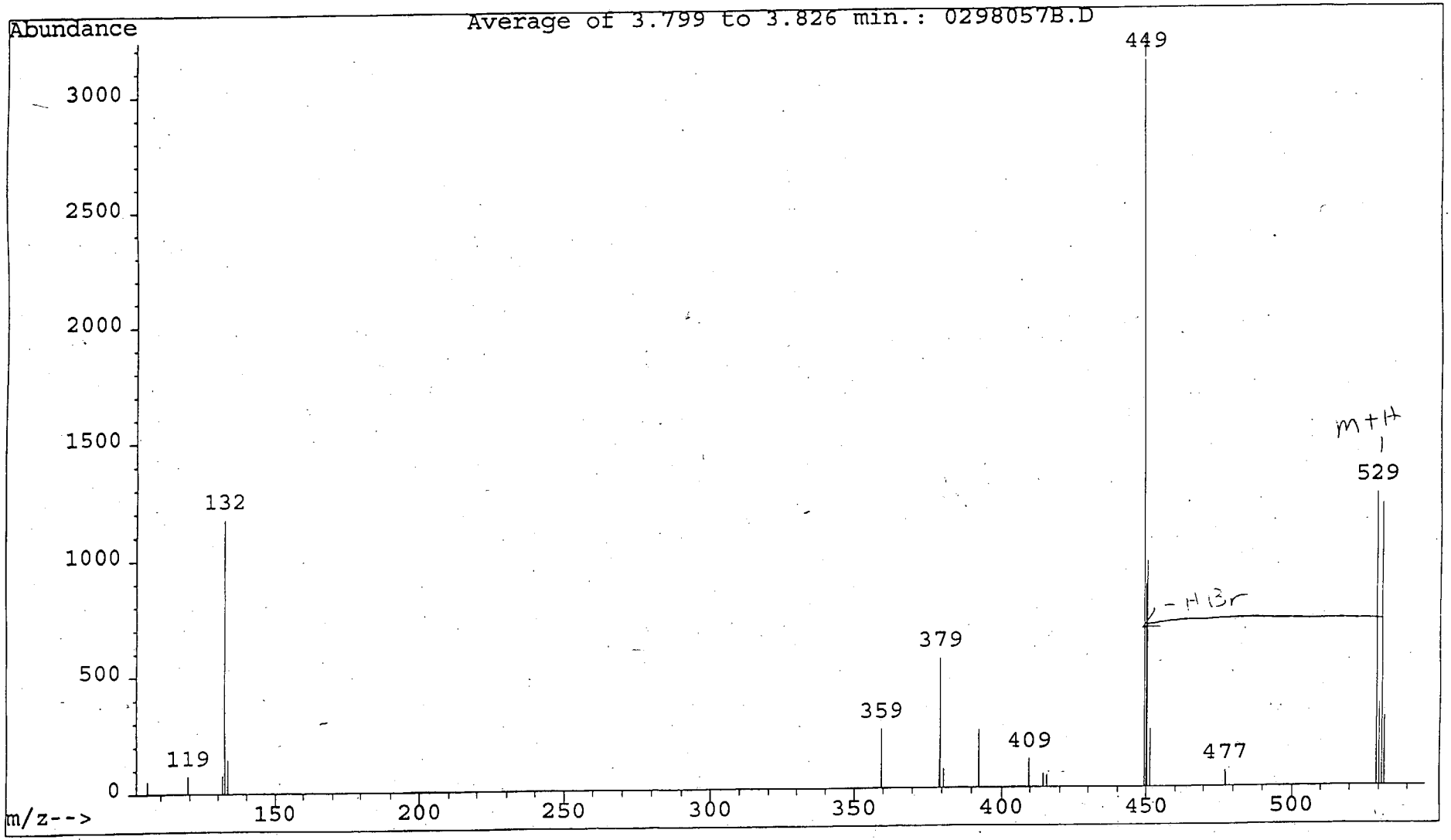
© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 38



File : C:\HPCHEM\1\DATA\0298057B.D
Operator : acs
Acquired : 27 Feb 98 10:23 am using AcqMethod PBGCI1
Instrument : 5989x - I
Sample Name: ar0298057 scan 100-600
Misc Info : pb/ci/ch4/loop
Vial Number: 1



13b



© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 39

© 1999 American Chemical Society, Org. Lett., Wang ol991100g Supporting Info Page 40