Structure Reassignment and Synthesis of Jenamidines A_1/A_2. Synthesis of (+)-NP25302, and Formal Synthesis of SB-311009 Analogues

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Supporting Material

General Procedures. All reactions were performed under nitrogen atmosphere. All commercially available reagents were used without further purification unless otherwise noted. Dichloromethane was distilled from CaH_2 under nitrogen. Ether and tetrahydrofuran were freshly distilled from benzophenone ketyl radical under nitrogen prior to use. Flash chromatography was performed with silica gel (40-63 μm). Optical rotations were measured on a precision automated polarimeter. NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts are reported in δ and coupling constants (*J* values) in Hz. IR spectra were recorded on an FT-IR spectrometer and are reported in cm^{-1}. The Wittig reactions of **76** were carried out in a sealed vessel in a CEM Discover microwave oven with automatic temperature and pressure display.

5a,6,8,9-Tetrahydro-5*H*-pyrido[2,1-b]quinazoline-7,11-dione (6). A solution of 2,3-dihydro-4-pyridinone (**4**)[4] (100 mg, 1.09 mmol), isatoic anhydride (**5**, 178 mg, 1.09 mmol), and triethylamine (0.17 mL, 1.20 mmol) in 10 mL of dry THF was stirred in a sealed tube under N_2 for 8 h in an 80 °C oil bath. The mixture was cooled and concentrated to yield a mixture of recovered **4**, anthranilic acid, the desired product **6**, and the decomposition product **7**. Flash chromatography on silica gel (95:5 CH_2Cl_2/MeOH) yielded 150 mg of a mixture of **6** and **7** followed by 65 mg of **4** (65%). The mixture of **6** and **7** was diluted with $CHCl_3$ and filtered. The filtrate was concentrated and the resulting oil was then taken up in minimal CH_2Cl_2. The solution was filtered and added dropwise to a solution of hexanes. The milky suspension was filtered and the precipitate was collected to give 67 mg of 90% pure **6** (29% yield, 65% based on recovered SM). Quinazoline **6** was unstable at room temperature and decomposed to form **7** over time.

Data for **6**: mp 122-123 °C; ^{1}H NMR (CD_3OD) 7.71 (d, 1, *J* = 8.0), 7.25 (dd, 1, *J* = 8.0, 7.7), 6.73 (dd, 1, *J* = 8.0, 7.7), 6.65 (d, 1, *J* = 8.0), 5.12 (dd, 1, *J* = 3.7, 9.2), 4.51 (ddd, 1, *J* = 4.3, 6.1, 13.4), 3.29 (ddd, 1, *J* = 4.3, 10.4, 13.4), 2.86 (dd, 1, *J* = 9.2, 15.3), 2.64 (dd, 1, *J* = 3.7, 15.3), 2.52 (ddd, 1, *J* = 6.1, 10.4, 15.9), 2.42 (ddd, 1, *J* = 4.3, 4.3,

15.9); ^{1}H NMR ($CDCl_3$) 7.91 (d, 1, *J* = 7.9), 7.31 (dd, 1, *J* = 7.9, 7.3), 6.86 (dd, 1, *J* = 7.9, 7.3), 6.67 (d, 1, 7.9), 5.17 (ddd, 1, *J* = 1.8, 3.8, 9.2), 4.96 (br s, 1, NH), 4.73 (ddd, 1, *J* = 4.0, 6.1, 13.7), 3.24 (ddd, 1, *J* = 4.0, 10.7, 13.7), 2.92 (dd, 1, *J* = 9.2, 14.8), 2.72 (dd, 1, *J* = 3.8, 14.8), 2.62 (ddd, 1, *J* = 6.1, 10.7, 16.2), 2.49 (ddd, 1, *J* = 4.0, 4.0, 16.2); ^{13}C NMR (CD_3OD) 207.8, 165.4, 148.5, 135.2, 129.1, 119.5, 115.7, 115.2, 67.6, 47.8, 40.9, 39.7; ^{13}C NMR ($CDCl_3$) 205.7, 163.2, 145.5, 134.0, 128.5, 119.5, 114.7, 114.6, 66.5, 47.7, 40.2, 38.9; IR (KBr) 3303, 1720, 1640.

3-(3-Oxobutyl)-4(3*H*)-quinazolone (7). Complete conversion to **7** was easily achieved by washing a solution of 10 mg of **6** in CH_2Cl_2 three times with 5% aqueous HCl. The organic fraction was dried over magnesium sulfate and concentrated to give 8 mg of **7**: ^{1}H NMR ($CDCl_3$) 8.28 (d, 1, *J* = 6.7), 8.27 (s, 1), 7.76 (dd, 1, *J* = 7.9, 7.4), 7.71 (d, 1, *J* = 7.9), 7.50 (dd, 1, *J* = 7.4, 6.7), 4.22 (t, 2, *J* = 6.1), 3.07 (t, 2, *J* = 6.1), 2.16 (s, 3); ^{13}C NMR 206.2, 161.2, 148.0, 147.5, 134.2, 127.4, 127.1, 126.3, 121.9, 42.2, 41.4, 30.0; IR (neat) 1714, 1672. The ^{1}H NMR spectral data are identical to those previously reported.[6]

1,3-Bis[[(trifluoromethyl)sulfonyl]oxy]-6,7-dihydro-5*H*-pyrrolizine (16). Keto amide **15**[11] (100 mg, 0.71 mmol) in 1 mL of dry CH_2Cl_2 was added to NaH (63 mg, 1.56 mmol) in 1 mL of dry CH_2Cl_2 at 0 °C under N_2. The mixture was stirred for 10 min and Tf_2O (0.24 mL, 1.42 mmol) was added dropwise. The mixture was stirred for 1 h at 0 °C, quenched with 2 mL of saturated NH_4Cl solution, diluted with CH_2Cl_2, and stirred for 30 min at 25 °C. The organic layer was separated, washed with H_2O and brine, dried over $MgSO_4$, and concentrated to yield 260 mg (91%) of 90% pure bistriflate **16**. Flash chromatography on silica gel (97:2:1 hexanes/EtOAc/pyridine) gave 50 mg (17%) of pure unstable bistriflate **16**: ^{1}H NMR ($CDCl_3$) 5.93 (s, 1), 4.02 (t, 2, *J* = 7.0), 2.95 (t, 2, *J* = 7.3), 2.56 (tt, 2, *J* = 7.0, 7.3).

***N*-Cyano-*N'*-methoxy-*N'*-methylprolinamide (18).** *N*-Methylmorpholine (5.1 mL, 46.5 mmol) in 20 mL of dry CH_2Cl_2 and then ethyl chloroformate (8.6 mL, 90

mmol) in 20 mL of dry CH_2Cl_2 were added to *N*-Boc-proline (10 g, 46.5 mmol) in 60 mL of dry CH_2Cl_2 at -15 °C under N_2 and the mixture was stirred for 15 min. *N*-Methylmorpholine (10.0 mL, 90.3 mmol) and *N,O*-dimethylhydroxylamine were added portionwise and the mixture was stirred for 1 h at -15 °C and at 25 °C for 15h. The mixture was diluted with H_2O and extracted with EtOAc. The combined organic extracts were washed successively with 10% sodium bicarbonate solution, brine, 5% HCl solution, and brine, dried over $MgSO_4$, and concentrated. Flash chromatography on silica gel (1:1 EtOAc/CH_2Cl_2) afforded 9.3 g (78%) of the *N*-Boc Weinreb amide as a 1:1 mixture of rotamers: ^{1}H NMR ($CDCl_3$) 4.68-4.74 (m, 1 × 0.5), 4.57-4.62 (m, 1 × 0.5), 3.79 (s, 3 × 0.5), 3.72 (s, 3 × 0.5), 3.35-3.65 (m, 2), 3.20 (s, 3), 1.80-2.25 (m, 4), 1.46 (s, 9 × 0.5), 1.42 (s, 9 × 0.5).

The *N*-Boc Weinreb amide (316 mg, 1.2 mmol) was stirred in 4 mL of 1:1 TFA/CH_2Cl_2 solution for 18 h and concentrated. A solution of the resulting oil in 4 mL of EtOH was added to a solution of sodium bicarbonate (500 mg, 6.0 mmol) and cyanogen bromide (140 mg, 1.32 mmol) in 9 mL of EtOH. The mixture was stirred for 2 h at 25 °C, treated with 2 mL of H_2O, stirred for 15 min, and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated. Flash chromatography on silica gel (98:2 CH_2Cl_2/MeOH) gave 185 mg (84%) of cyanamide **18**: ^{1}H NMR ($CDCl_3$) 4.57 (dd, 1, J = 3.7, 8.5), 3.74 (s, 3), 3.62-3.70 (m, 1), 3.45-3.55 (m, 1), 3.23 (s, 3), 2.20-2.28 (m, 1), 1.90-2.10 (m, 3).

Addition of *tert*-Butyl Acetate to 18. *tert*-Butyl acetate (0.18 mL, 1.3 mmol) was added to a freshly prepared solution of LDA (1.3 mmol in 4 mL THF) at -78 °C under N_2 and the mixture was stirred for 15 min. Weinreb amide cyanamide **18** (215 mg, 1.17 mmol) was added in 2 mL of dry THF. The mixture was stirred for 2 h at -78 °C, quenched with 5% HCl solution, and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated. Flash chromatography on silica gel (98:2 CH_2Cl_2/MeOH) gave 90 mg (30%) of **24**, followed by 50 mg (21%) of **23**,

and 75 mg (32%) of **22**. A solution of urea **23** in $CDCl_3$ containing several drops of TFA completely isomerized to **22** in 2 h.

Data for *tert*-butyl 1-(2,5,6,7-tetrahydro-3-oxo-3*H*-pyrrolo[1,2-*c*]imidazole)acetate (**22**): ^{1}H NMR ($CDCl_3$) 9.30 (br s, 1, NH), 3.66 (t, 2, *J* = 6.7), 3.27 (s, 2), 2.66 (t, 2, *J* = 7.3), 2.40 (tt, 2, *J* = 6.7, 7.3), 1.45 (s, 9); ^{13}C NMR ($CDCl_3$) 169.0, 151.1, 124.6, 105.4, 81.5, 41.8, 32.2, 28.3, 27.9 (3 C), 22.0.

Data for *tert*-butyl (2*Z*)-(2,5,6,7-tetrahydro-3-oxo-3*H*-pyrrolo[1,2-*c*]imidazol-1-ylidene)acetate (**23**): ^{1}H NMR ($CDCl_3$) 8.70 (br s, 1, NH), 5.19 (s, 1), 4.87 (dd, 1, *J* = 7.3, 7.3), 3.59 (ddd, 1, *J* = 8.0, 8.0, 11.0), 3.24-3.34 (m, 1), 2.58-2.66 (m, 1), 2.00-2.10 (m, 2), 1.40-1.52 (m, 1), 1.46 (s, 9); ^{13}C NMR ($CDCl_3$) 166.5, 161.8, 155.1, 91.8, 79.5, 64.6, 44.8, 30.1, 28.3 (3 C), 26.4; HRMS (DCI/NH_3) calcd for $C_{12}H_{19}N_2O_3$ (MH^+) 239.1396, found 239.1402.

Data for *tert*-butyl 2-(1-carbamoyl-pyrrolidine)-3-hydroxypropenoate (**24**): ^{1}H NMR ($CDCl_3$) 8.95 (br s, 1, OH or NH_2), 4.87 (s, 1), 4.33 (dd, 1, *J* = 7.9, 7.9), 3.59 (ddd, 1, *J* = 7.9, 7.9, 11.0), 3.15-3.22 (m, 1), 1.95-2.20 (m, 3), 1.55-1.65 (m, 1), 1.48 (s, 9).

***tert*-Butyl 3-Amino-5,6,7,7a-tetrahydro-1-oxo-1*H*-pyrrolizine-2-carboxylate (26).** *tert*-Butyl acetate (1.5 mL, 11.1 mmol) was added dropwise over a period of 10 min to a freshly prepared solution of LDA (10 mmol in 27 mL THF) at -45 °C under N_2. The solution was stirred for 15 min and treated with methyl (*S*)-1-cyano-2-pyrrolidinecarboxylate (**25**)[19] (680 mg, 4.4 mmol) in 5 mL of dry THF. The mixture was stirred for 1 h at -45 °C, treated dropwise with LHMDS (5 mL, 1.0 M in THF) and allowed to warm to 25 °C. The mixture was stirred for 2 h at 25 °C, quenched with H_2O, and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated. Flash chromatography on silica gel (95:5 CH_2Cl_2/MeOH) gave 250 mg (24%) of byproduct **28** followed by 280 mg (27%) of pure **26**.

Data for **26**: mp 200-203 °C; $[\alpha]^{22}_D$ -66.9 (*c* 1.2, MeOH); UV (MeOH) λ_{max} nm (log ε) 211(4.17), 241 (4.21), 264 (4.11); ^{1}H NMR ($CDCl_3$) 8.00 (br, 1, NH), 5.42 (br, 1,

NH), 3.87 (dd, 1, *J* = 6.7, 9.8), 3.34-3.42 (m, 1), 3.20-3.28 (m, 1), 2.06-2.26 (m, 3), 1.54-1.60 (m, 1), 1.55 (s, 9); ^{13}C NMR ($CDCl_3$) 193.1, 174.0, 164.9, 90.5, 79.9, 69.7, 46.6, 28.5 (3 C), 27.6, 26.7; IR (KBr) 3475, 3077, 1714, 1638; HRMS (DEI) calcd for $C_{12}H_{18}N_2O_3$ (M^+) 238.1317, found 238.1315.

Data for **28**: ^{1}H NMR ($CDCl_3$) 9.95 (br s, 1, NH), 4.34 (s, 1), 3.98 (dd, 1, *J* = 8.6, 8.6), 3.31-3.38 (m, 1), 3.21 (ddd, 1, *J* = 7.9, 7.9, 10.4), 1.98-2.26 (m, 3), 1.64-1.75 (m, 1), 1.47 (s, 9); ^{13}C NMR ($CDCl_3$) 173.4, 169.4, 160.9, 79.1, 72.6, 63.6, 49.9, 28.4 (3 C), 27.3, 27.1. A 1D NOESY experiment showed an NOE from the alkene hydrogen (δ 4.34) to the *tert*-butyl hydrogens (δ 1.47) and the methylene group adjacent to the ring fusion nitrogen (δ 3.21 and δ 3.31-3.38) establishing that the stereochemistry is *E* as drawn.

3-(2-Methyl-2*E*-butenoylamino)-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-1-one (31). 2-Methyl-2*E*-butenoyl chloride (27 mg, 0.23 mmol) was treated with **26** (25 mg, 0.10 mmol) and NaH (10 mg, 0.25 mmol) and hydrolyzed and decarboxylated with 9:1 CH_2Cl_2/TFA as described below for the preparation of **39d** to give 15 mg (69%) of **31** after flash chromatography on silica gel (98:2 CH_2Cl_2/MeOH): $[\alpha]^{22}_D$ 1.3 (*c* 0.7, MeOH); ^{1}H NMR (CD_3OD) 6.60 (q, 1, *J* = 6.7), 5.65 (s, 1), 3.95 (dd, 1, *J* = 8.2, 8.2), 3.42-3.50 (m, 1), 3.22 (ddd, 1, *J* = 7.3, 7.3, 11.0), 2.06-2.22 (m, 3), 1.88 (s, 3), 1.87 (d, 3, *J* = 6.7), 1.50-1.60 (m, 1); ^{13}C NMR (CD_3OD) 204.5, 173.7, 169.9, 136.3, 133.2, (93.6, 93.5), 70.7, 28.8, (27.5, 27.4), 14.4, 12.3 (one C is obscured by the CD_3OD peak between 49-50).

Jenamidines A_1/A_2 4'-Acetate (39a). (*S*)-4-Acetoxy-2-methylpent-2*E*-enoyl chloride (**38a**, 80 mg, 0.44 mmol) (prepared as described for **39d** using AcCl instead of methoxyacetyl chloride) was treated with **26** (36 mg, 0.15 mmol) and NaH (14 mg, 0.33 mmol) and hydrolyzed and decarboxylated with 9:1 CH_2Cl_2/TFA as described below for the preparation of **39d** to give 37 mg (84%) of **39a** as a 1:1 mixture of diastereomers upon flash chromatography (95:5 CH_2Cl_2/MeOH): $[\alpha]^{22}_D$ -27.5 (*c* 0.8, MeOH); ^{1}H NMR

(CD_3OD) 6.28-6.38 (m, 1), 5.59-5.68 (m, 1), 5.62 (s, 1), 3.94 (dd, 1, J = 8.5, 7.9), 3.39-3.46 (m, 1), 3.16-3.24 (m, 1), 2.06-2.20 (m, 3), 2.03 (s, 3 × 0.5), 2.02 (s, 3 × 0.5), 1.95 (s, 3 × 0.5), 1.94 (s, 3 × 0.5), 1.48-1.57 (m, 1), 1.35 (d, 3 × 0.5, J = 6.7), 1.34 (d, 3 × 0.5, J = 6.7); ^{13}C NMR (CD_3OD) 204.6, 173.5, 172.0, (169.5, 169.4), (138.74, 139.69), 133.7, 93.9, 70.8, (68.9, 68.8), 28.8, 27.5, 21.0, 19.7, 13.2, one C is obscured by the CD_3OD peak between 49-50; HRMS (MeOH/NBA) calcd for $C_{15}H_{21}N_2O_4$ (MH^+) 293.1501, found 293.1504.

Triisopropylsilylation of Hydrocupreine. Triisopropylsilyl chloride (4.28 g, 22.2 mmoL) was added to a solution of hydrocupreine[36] (3.45 g, 11.1 mmol) and imidazole (1.51 g, 22.2 mmol) in 21 mL of DMF and the resulting solution was stirred overnight at room temperature and then poured into ethyl acetate (115 mL). The organic solution was washed with water (3 × 100 mL), dried over Na_2SO_4, and concentrated to give the crude TIPS silyl ether as a yellow oil. Flash chromatography on silica gel ($CHCl_3$ 200 mL, then 9:1:0.1 $CHCl_3$/MeOH/ NH_4OH) afforded 4.94 g (95%) of TIPS-DHQ: $[\alpha]^{22}_D$ -8.1 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 8.63 (d, 1, J = 4.3), 7.64 (d, 1, J = 9.1), 7.63 (d, 1, J = 4.3), 7.35 (d, 1, J = 2.4), 6.97 (dd, 1, J = 2.4, 9.1), 6.41 (br s, 1, OH), 6.23 (br s, 1), 4.42-4.52 (m, 1), 3.37 (dd, 1, J = 12.0, 12.0), 3.24 (dd, 1, J = 9.7, 13.4), 2.98-3.08 (m, 1), 2.63 (br d, 1, J = 13.4), 2.09-2.15 (m, 1), 2.01-2.06 (m, 1), 1.94 (br s, 1), 1.68-1.78 (m, 2), 1.27-1.34 (m, 3), 1.08-1.14 (m, 21), 0.77 (t, 3, J = 7.3); ^{13}C NMR ($CDCl_3$) 153.9, 147.4, 144.6, 143.1, 130.6, 125.2, 124.1, 118.9, 110.3, 66.6, 59.9, 56.6, 43.8, 35.4, 27.0, 24.9, 24.4, 17.91 (3 C), 17.87 (3 C), 12.6 (3 C), 11.4; IR (neat) 3226, 2936, 2861, 1619, 1502, 1456, 1237, 1259.

DHQ-PYR-OH (60). Potassium hydroxide (600 mg, 10.6 mmol) was added to a solution of the TIPS ether (611 mg, 1.33 mmol) and 4,6-dichloro-2,5-diphenylpyrimidine (400 mg, 1.33 mmol) in 27 mL of dry toluene. The mixture was heated in a 90 °C oil bath. The temperature of the oil bath was slowly raised to 115 °C and the mixture was stirred for 1 h at this temperature. The mixture was cooled, diluted with H_2O, and

extracted with EtOAc. The combined organic fractions were dried over $MgSO_4$ and concentrated to give 990 mg of 80% pure TIPS-DHQ-PYR that was used without further purification.

HF (48-51% aqueous solution, 3 mL) was added dropwise to a solution of the above TIPS-DHQ-PYR in 33 mL of CH_3CN. The mixture was stirred for 30 min, carefully quenched with a saturated sodium bicarbonate solution and extracted with EtOAc. The combined organic fractions were dried over $MgSO_4$ and concentrated. Flash chromatography on silica gel (95:5 CH_2Cl_2/MeOH) gave 400 mg (52% from the TIPS ether) of **60**: $[\alpha]^{22}_D$ +259.4 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 8.68 (br s, 1), 8.61 (d, 1, *J* = 4.6), 7.97 (d, 1, *J* = 9.1), 7.87 (br d, 2, *J* = 7.3), 7.60 (dd, 2, *J* = 7.3, 7.3) 7.48-7.56 (m, 3), 7.27 (dd, 1, *J* = 2.1, 9.1), 7.24-7.27 (m, 1), 7.18 (d, 1, *J* = 4.6), 6.95-7.01 (m, 3), 3.05-3.16 (m, 3), 2.67-2.74 (m, 1), 2.31 (d, 1, *J* = 12.8), 1.76-1.81 (m, 1), 1.63 (br s, 1), 1.43-1.52 (m, 2), 1.08-1.21 (m, 3), 0.83 (br s, 1), 0.71 (t, 3, *J* = 7.0) (the OH was not observed); ^{13}C NMR ($CDCl_3$) 165.9, 162.7, 159.7, 157.0, 146.3, 143.8, 143.6, 135.1, 132.2, 131.2, 130.9, 129.9 (2 C), 128.63 (2 C), 128.60, 128.3 (2 C), 128.1 (2 C), 127.2, 123.0, 118.5, 117.1, 107.5, 76.2, 58.4, 58.2, 43.4, 36.7, 27.2, 26.5, 24.8, 20.3, 11.8; IR (neat) 3580, 3055, 2955, 2868, 1619, 1571, 1517, 1408, 1376, 1241, 999, 851, 756, 700; HRMS (CI) Calcd for $C_{35}H_{34}ClN_4O_2$ (MH^+) 577.2370, found 577.2357.

Ethyl 2-Methyl-2-nitro-5-oxohexanoate (52). DABCO (48 mg, 0.41 mmol) was added to a solution of ethyl 2-nitropropionate (**51**, 600 mg, 4.08 mmol) in 6 mL of dry CH_2Cl_2 and the mixture was stirred for 10 min. Methyl vinyl ketone (**50**, 0.85 mL, 10.2 mmol) was then added dropwise and the resulting solution was stirred for 5 h at 25 °C, passed through a short pad of silica gel with Et_2O to remove the catalyst and concentrated to give 866 mg (98%) of pure (±)-**52**, whose data matched those previously reported.[31,34]

A solution of catalyst **60** (240 mg, 0.40 mmol) and ethyl 2-nitropropionate (600 mg, 4.08 mmol) in 8 mL of dry CH_2Cl_2 was kept at -20 °C for 2 h and methyl vinyl ketone (0.85 mL, 10.2 mmol) was then added dropwise. The resulting solution was kept

at -20 °C for 3 d, passed through a short pad of silica gel with Et_2O to remove the catalyst and concentrated to give 890 mg (100%) of pure (+)-**52**: $[\alpha]^{22}_D$ +3.3 (*c* 1.0, MeOH).

Removal of catalyst **60** was critical for the success of the one-pot reduction using H_2 and Pd at neutral and then acidic pH.

Ethyl α,2-Dimethyl-α-nitro-1,3-dioxolane-2-butanoate. A solution of (+)-**52** (20 mg, 0.09 mmol), ethylene glycol (0.1 ml) and TsOH (5 mg) in 2 mL of benzene was stirred at reflux for 4 h as described by Feringa.[34] The mixture was cooled, diluted with saturated sodium bicarbonate solution and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated to give 22 mg (94%) of pure dioxolane: $[\alpha]^{22}_D$ -4.7 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) 4.27 (q, 2, *J* = 7.3), 3.90-4.00 (m, 4), 2.36 (ddd, 1, *J* = 13.1, 13.1, 4.2), 2.25 (ddd, 1, *J* = 13.1, 13.1, 4.2), 1.77 (s, 3), 1.69 (ddd, 1, *J* = 13.1, 13.1, 4.2), 1.60 (ddd, 1, *J* = 13.1, 13.1, 4.2), 1.33 (s, 3), 1.29 (t, 3, *J* = 7.3); ^{13}C NMR ($CDCl_3$) 167.3, 108.9, 92.3, 64.7 (2 C), 62.8, 33.0, 30.9, 23.9, 21.4, 13.8.

The enantiomer excess was determined to be 90% (95:5) by HPLC analysis [Daicel chiralcel OJ, hexanes/IPA, 90:10, 1.00 ml/min, λ 220 nm, t (major) = 11.3 min, t (minor) = 12.6 min].[34] A similar analysis performed with Michael adduct (-)-**52**, formed using catalyst **59**,[35] showed a 90:10 mixture of enantiomers (80% ee): t (major) = 12.6 min, t (minor) = 11.3 min].

Reduction of 52 over Pd at 1 atm of H_2. A solution of **52** (866 mg, 3.99 mmol) in 20 mL of EtOH containing 10% Pd on activated carbon (430 mg, 0.41 mmol) and Na_2SO_4 (600 mg, 4.22 mmol) was stirred under 1 atm of H_2 at 25 °C for 12 h. The mixture was filtered through Celite and concentrated to give 735 mg (99%) of ethyl 2,5-dimethyl-1-pyrroline-5-carboxylate 1-oxide (**55**): ^{1}H NMR ($CDCl_3$) 4.15-4.31 (m, 2), 2.75-2.86 (m, 1), 2.64-2.73 (m, 1), 2.41-2.49 (m, 1), 2.10 (s, 3), 1.98-2.08 (m, 1), 1.71 (s, 3), 1.29 (t, 3, *J* = 7.0); ^{13}C NMR ($CDCl_3$) 170.4, 145.2, 78.6, 62.0, 30.4, 30.3, 20.9, 13.9, 13.0.

Ethyl 2,5-Dimethyl-1-hydroxy-2-pyrrolidinecarboxylate (53). Nitrone **55** (735 mg, 3.97 mmol) was stirred with PtO_2 (92 mg, 0.40 mmol) in 20 mL of EtOH under 1 atm of H_2 at 25 °C for 8 h. The mixture was filtered through Celite and concentrated to give 750 mg (100%) of hydroxylamine **53** containing 5% of the diastereomer **54** that was used without purification. An analytical sample of **53** was prepared by flash chromatography on silica gel (75:25 hexanes/EtOAc): ^{1}H NMR ($CDCl_3$) 5.08 (br s, 1, OH), 4.15-4.23 (m, 2), 3.04-3.12 (m, 1), 2.08-2.16 (m, 1), 1.85-1.95 (m, 1), 1.72-1.80 (m, 1), 1.30-1.40 (m, 1) 1.35 (s, 3), 1.28 (t, 3, J = 7.0), 1.22 (d, 3, J = 6.1); ^{13}C NMR ($CDCl_3$) 175.5, 69.6, 60.8, 58.2, 31.2, 26.0, 19.0, 16.6, 14.2; IR (neat) 3446, 1731; HRMS (NH_3/CI) Calcd for $C_9H_{18}NO_3$ (MH^+) 188.1287, found 188.1283.

Ethyl *trans*-2,5-Dimethyl-2-pyrrolidinecarboxylate (49). Zn dust (1.28 g, 19.5 mmol) and $Cu(OAc)_2$ (71 mg, 0.39 mmol) were stirred for 15 min at 25 °C in 4 mL of HOAc and then treated with a solution of hydroxylamine **53** (730 mg, 3.9 mmol) in 2 mL of EtOH and 4 mL of HOAc. The mixture was stirred for 2.5 h at 70 °C and then cooled to rt. EDTA (4 g) was added and the solution was adjusted to pH 10 with 2 M NaOH and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated to give 422 mg (63%) of pure **49**: ^{1}H NMR ($CDCl_3$) 4.18 (q, 2, J = 7.0), 3.27 (ddd, 1, J = 6.1, 6.1, 9.2), 2.32 (br s, 1, NH), 2.22-2.31 (m, 1), 1.88-1.96 (m, 1), 1.66-1.75 (m, 1), 1.38 (s, 3), 1.28 (t, 3, J = 7.0), 1.18-1.28 (m, 1), 1.19 (d, 3, J = 6.1); ^{13}C NMR ($CDCl_3$) 177.6, 65.8, 61.1, 54.5, 38.5, 34.6, 26.6, 20.9, 14.1; IR (neat) 3345, 1727; HRMS (EI) Calcd for $C_9H_{16}NO_2$ ($M\text{-}H^+$) 170.1181, found 170.1181.

(*S*)-Mosher Amide of (-)-49 (63). The Mosher acid chloride was prepared analogously (see preparation of **64**) from (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (32 mg, 0.14 mmol), DMF (10 μL, 0.14 mmol) and oxalyl chloride (60 μL, 0.66 mmol). The acid chloride was stirred with (-)-**49**•HCl (20 mg, 0.12 mmol, prepared with catalyst **60**) and diisopropylethylamine (42 μL, 0.24 mmol) in 1 mL of dry CH_2Cl_2 for 1 h at 25 °C. The mixture was concentrated, taken up in a saturated ammonium chloride

solution, and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated. Flash chromatography on silica gel (80:20 hexanes/EtOAc) gave 35 mg (76%) of Mosher amide **63**: $[\alpha]^{22}_D$ -98 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) 7.50-7.54 (m, 2), 7.37-7.41 (m, 3), 4.16-4.27 (m, 2), 3.73 (s, 3), 3.25-3.31 (m, 1), 2.16 (ddd, 1, *J* = 12.8, 12.8, 6.1), 1.70-1.76 (m, 1), 1.67 (s, 3), 1.56-1.64 (m, 1), 1.26-1.35 (m, 1), 1.28 (t, 3, *J* = 7.0), 1.24 (d, 3, *J* = 6.7); ^{13}C NMR ($CDCl_3$) 173.6, 165.0, 134.5, 129.2, 128.1 (2 C), 126.5 (2 C), 123.7 (q, *J* = 291), 84.4 (q, *J* = 23), 68.4, 61.3, 56.2, 55.1, 34.9, 32.1, 20.3, 19.8, 14.1; IR (neat) 1749, 1643; HRMS (ES) Calcd for $C_{19}H_{25}NO_4F_3$ (MH^+) 388.1736, found 388.1731.

(*R*)-Mosher Amide of (-)-49 (64). Oxalyl chloride (60 μL, 0.66 mmol) was added to a solution of (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (32 mg, 0.14 mmol) and DMF (10 μL, 0.14 mmol) in 1 mL of hexane and the mixture was stirred for 1 h at 25 °C, filtered, and concentrated. The resulting acid chloride was stirred with (-)-**49**•HCl (20 mg, 0.12 mmol, prepared with catalyst **60**) and diisopropylethylamine (42 μL, 0.24 mmol) in 1 mL of dry CH_2Cl_2 for 1 h at 25 °C. The mixture was concentrated, taken up in a saturated ammonium chloride solution, and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated. Flash chromatography on silica gel (80:20 hexanes/EtOAc) gave 34 mg (74%) of Mosher amide **64**: $[\alpha]^{22}_D$ +70 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) 7.59-7.62 (m, 2), 7.36-7.40 (m, 3), 4.53-4.60 (m, 1), 4.17-4.27 (m, 2), 3.67 (s, 3), 2.04-2.20 (m, 2), 1.78-1.82 (m, 1), 1.63 (s, 3), 1.57-1.63 (m, 1), 1.31 (t, 3, *J* = 7.0), 0.21 (d, 3, *J* = 6.1); ^{13}C NMR ($CDCl_3$) 173.5, 163.8, 133.5, 129.4, 128.1 (2 C), 127.2 (2 C), 123.7 (q, *J* = 290), 84.5 (q, *J* = 24), 68.1, 61.2, 54.8, 54.7, 34.5, 32.8, 20.7, 19.0, 14.1; IR (neat) 1731, 1641; HRMS (ES) Calcd for $C_{19}H_{25}NO_4F_3$ (MH^+) 388.1736, found 388.1732.

Oxidation of 26 with Two Equivalents of Lead Tetraacetate at Reflux to Give *tert*-Butyl (4β,7aβ)-4,7a-Diacetoxy-3-amino-5,6,7,7a-tetrahydro-1-oxo-1*H*-pyrrolizine-2-carboxylate (65). Lead tetraacetate (257 mg, 0.58 mmol) was added to a

solution of **26** (70 mg, 0.29 mmol) in 9 mL of dry benzene. The mixture was stirred under N_2 at reflux for 20 h, filtered, and washed with saturated sodium bicarbonate solution. The organic layer was dried over $MgSO_4$ and concentrated to give 45 mg of crude diacetate **65**. Flash chromatography on silica gel (97:3 CH_2Cl_2/MeOH) gave 40 mg (39%) of pure **65**: UV (MeOH) λ_{max} nm (log ε) 207 (3.98), 239 (4.16), 268 (4.08); ^{1}H NMR ($CDCl_3$) 8.28 (br s, 1, NH), 7.95 (br s, 1, NH), 6.04 (dd, 1, *J* = 6.1, 6.7, H-4), 2.55-2.65 (m, 2, H-5), 2.34 (dd, 1, *J* = 6.1, 13.5, H-6α), 2.14 (s, 3), 2.08 (s, 3), 1.74 (ddd, 1, *J* = 12.8, 12.8, 9.2, H-6β), 1.54 (s, 9); ^{13}C NMR ($CDCl_3$) 185.0, 173.2, 171.3, 168.2, 165.2, 97.6, 88.2, 84.2, 80.4, 32.2, 31.9, 28.4 (3 C), 21.3, 21.0; IR (neat) 1759, 1730, 1656, 1625; HRMS (ES) Calcd for $C_{16}H_{23}N_2O_7$ (MH^+) 355.1505, found 355.1517.

An NOE was observed between H_4 at δ 6.04 and one or both H_5's at δ 2.55-2.65, H_6 at δ 1.74 and the acetate at δ 2.14.

Oxidation of (7a*S*)-*tert*-Butyl 3-Amino-5,6,7,7a-tetrahydro-1-oxo-1*H*-pyrrolizine-2-carboxylate (26) with One Equivalent of Lead Tetraacetate at 25 °C. Lead tetraacetate (110 mg, 0.25 mmol) was added to a solution of **26** (50 mg, 0.20 mmol) in 6 mL of dry benzene. The mixture was stirred under N_2 at 25 °C for 20 h, filtered, and washed with saturated sodium bicarbonate solution. The organic layer was dried over $MgSO_4$ and concentrated to give 30 mg of a mixture of **26**, **66**, and **67.** Flash chromatography on silica gel (39:1 CH_2Cl_2/MeOH) gave 12 mg of 90% pure **66**, followed by 4 mg of pure **66**, 1 mg of a 2:1 mixture of **66** and **68**, 3 mg of pure **68** and 6 mg of recovered **26**.

Data for *tert*-butyl 3-amino-5,6,7,7a-tetrahydro-7a-methoxy-1-oxo-1*H*-pyrrolizine-2-carboxylate (**68**): UV (MeOH) λ_{max} nm (log ε) 211 (3.73), 239 (3.83), 270 (3.60); ^{1}H NMR ($CDCl_3$) 8.35 (br s, 1, NH), 5.48 (br s, 1, NH), 3.42-3.50 (m, 1), 3.27-3.35 (m, 1) , 3.21 (s, 3), 2.30-2.42 (m, 1), 2.06-2.16 (m, 2), 1.60-1.70 (m, 1), 1.55 (s, 9); ^{13}C NMR ($CDCl_3$) 80.5, 51.4, 46.2, 32.2, 28.5 (3 C), 26.1, five quaternary carbons were

not observed; IR (neat) 1712, 1650, 1616; HRMS (ES) Calcd for $C_{13}H_{21}N_2O_4$ (MH^+) 269.1501, found 269.1508.

Data for *tert*-butyl (4β,7aβ)-4-acetoxy-3-amino-5,6,7,7a-tetrahydro-1-oxo-1*H*-pyrrolizine-2-carboxylate (**66**): UV (MeOH) λ_{max} nm (log ε) 204 (3.51), 239 (3.63), 260 (3.57); ^{1}H NMR ($CDCl_3$) 8.05 (br s, 1, NH), 7.72 (br s, 1, NH), 5.95 (dd, 1, *J* = 5.5, 5.5, H-4), 4.05 (dd, 1, *J* = 8.0, 9.1, H-7a), 2.50-2.58 (m, 1, H-5), 2.25-2.40 (m, 2, H-5, H-6), 2.16 (s, 3), 1.65-1.75 (m, 1, H-6), 1.55 (s, 9); ^{13}C NMR ($CDCl_3$) 83.6, 68.4, 33.6, 28.5 (3 C), 26.0, 21.4, six quaternary carbons were not observed; IR (neat) 1726, 1652, 1620; HRMS (ES) Calcd for $C_{14}H_{21}N_2O_5$ (MH^+) 297.1450, found 297.1454.

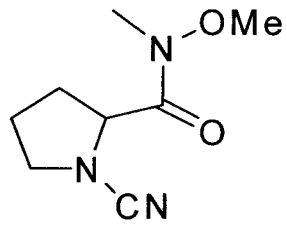
An NOE was observed between H_4 at δ 5.95 and H_5 at δ 2.55. Another NOE was observed between H_{7a} at δ 4.05 and H_6 and/or H_5 at δ 2.3, and lastly, an NOE was observed between H_6 at δ 1.7 and H_6 and/or H_5 at 2.3 and H_5 at 2.55.

Oxidation of 26 with One Equivalent of Lead Tetraacetate at Reflux. Lead tetraacetate (180 mg, 0.40 mmol) was added to a solution of **26** (100 mg, 0.40 mmol) in 12 mL of dry benzene. The mixture was stirred under N_2 at reflux for 1.5 h, filtered, and washed with saturated sodium bicarbonate solution. The organic layer was dried over $MgSO_4$ and concentrated to give 50 mg of a 3:3:2 mixture of **26**, **67**, and **66**, and a trace of diacetate **65**.

(*S*)-Proline-*N*-carboxyanhydride (76) was prepared as previously described.[49] Triphosgene (62 mg, 0.21) in 2 mL of dry THF was added over a 5-10 min period to a solution of proline (**75**, 60 mg, 0.52 mmol) in 2 mL of dry THF at 15 °C. The mixture was submerged in a 40-45 °C oil bath and stirred until the solution was homogenous (60-90 min). The solution was then concentrated to an oil with careful exclusion of air to eliminate any excess HCl present. The oil was dissolved in 2 mL of dry THF and cooled to 0 °C. Triethylamine (72 μL, 0.52 mmol) was added dropwise over a period of 10 min and the mixture was stirred for 30 min. The mixture was filtered with careful exclusion of air to give proline-NCA in a solution of THF that was used immediately.

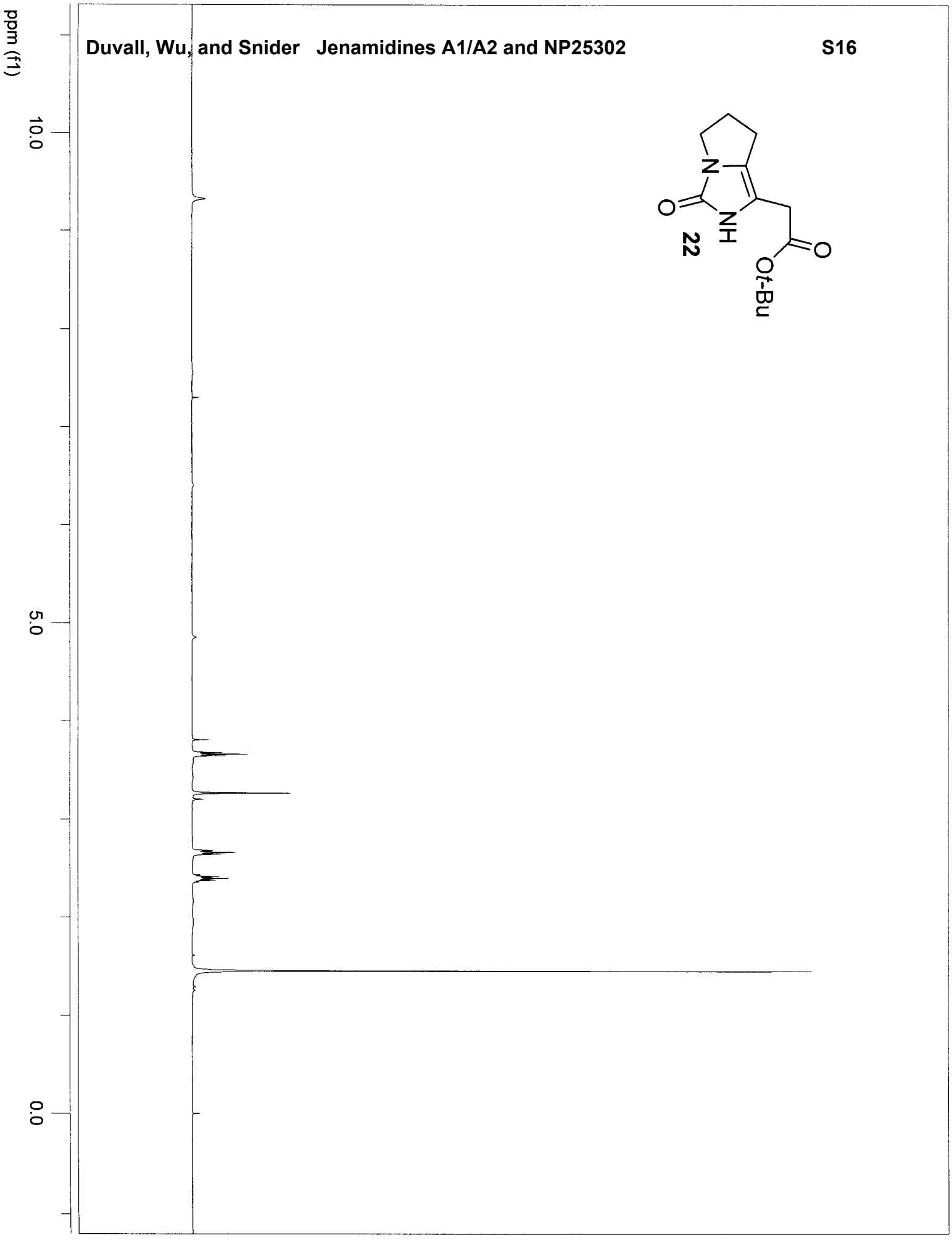
Methyl (2*E*)-[(7a*S*)-Tetrahydro-3-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-1-ylidene]-acetate (78). A solution of **76** in 2 mL of THF (prepared from 0.52 mmol of proline) was added to methyl (triphenylphosphoranylidene)acetate (**77**, 87 mg, 0.26 mmol) in 1 mL of dry toluene under N_2 in a microwave tube. The mixture was heated at 150 °C at 75 psi for 15 min in a microwave. After cooling, the mixture was concentrated to give crude **78** as a 9:1 mixture of the *E* and *Z* products. Flash chromatography on silica gel (98:2 CH_2Cl_2/MeOH) gave 18 mg (35%) of pure **78**: $[\alpha]^{22}_D$ -207 (*c* 1.0, MeOH); UV (MeOH) λ_{max} nm (log ε) 212 (4.01), 238 (4.13); ^{1}H NMR ($CDCl_3$) 5.66 (d, 1, *J* = 1.8), 4.92 (ddd, 1, *J* = 7.3, 7.3, 1.8), 3.73 (s, 3), 3.69 (ddd, 1, *J* = 8.0, 8.0, 11.6), 3.27-3.34 (m, 1), 2.58-2.67 (m, 1), 2.02-2.18 (m, 2), 1.55-1.68 (m, 1); ^{13}C NMR 166.6, 165.6, 156.6, 95.3, 64.2, 51.4, 45.9, 30.2, 26.2; IR (neat) 1804, 1716, 1667; HRMS (ES) Calcd for $C_9H_{12}NO_4$ (MH^+) 198.0766, found 198.0767.

S15



18

Duvall, Wu, and Snider Jenamidines A1/A2 and NP25302



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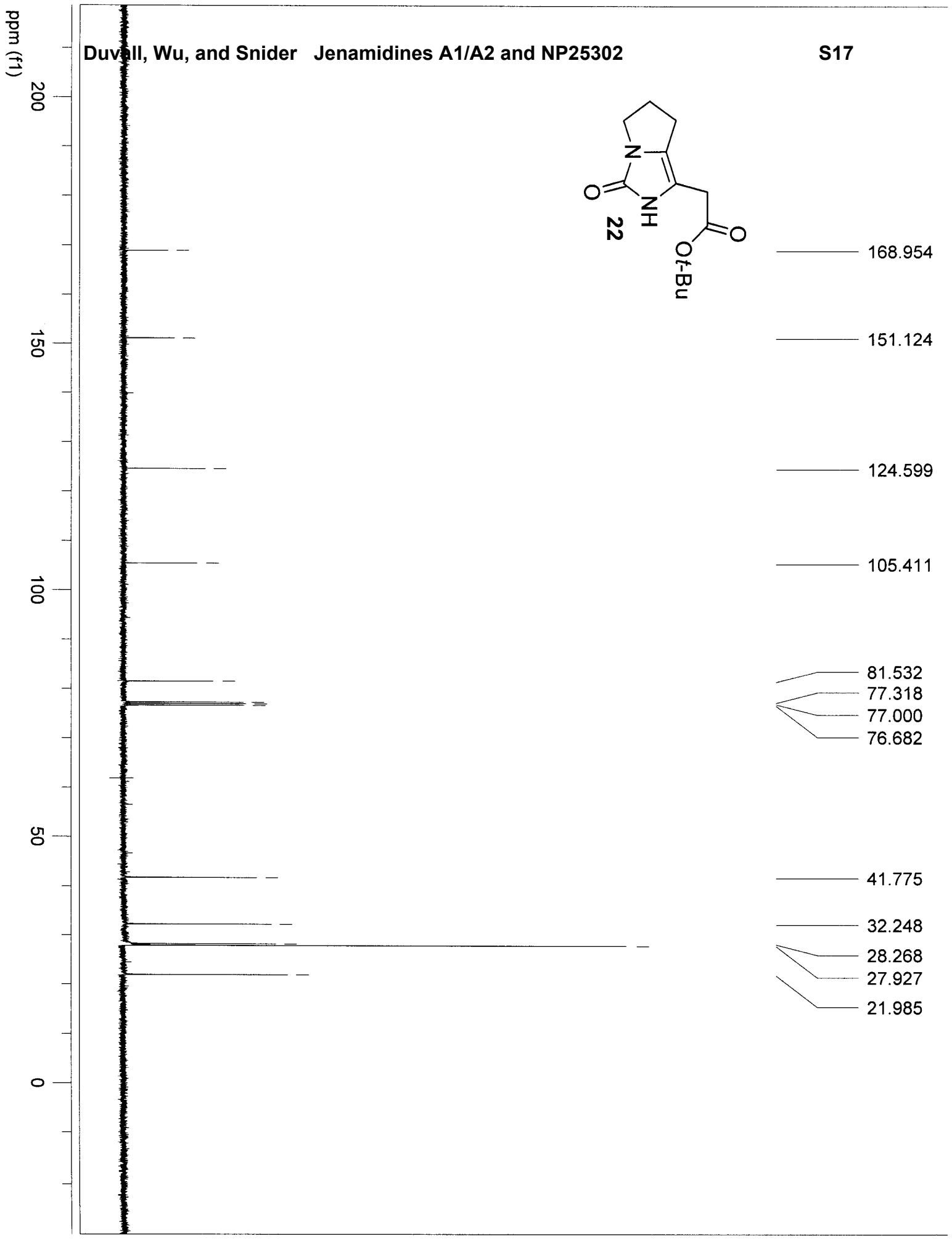
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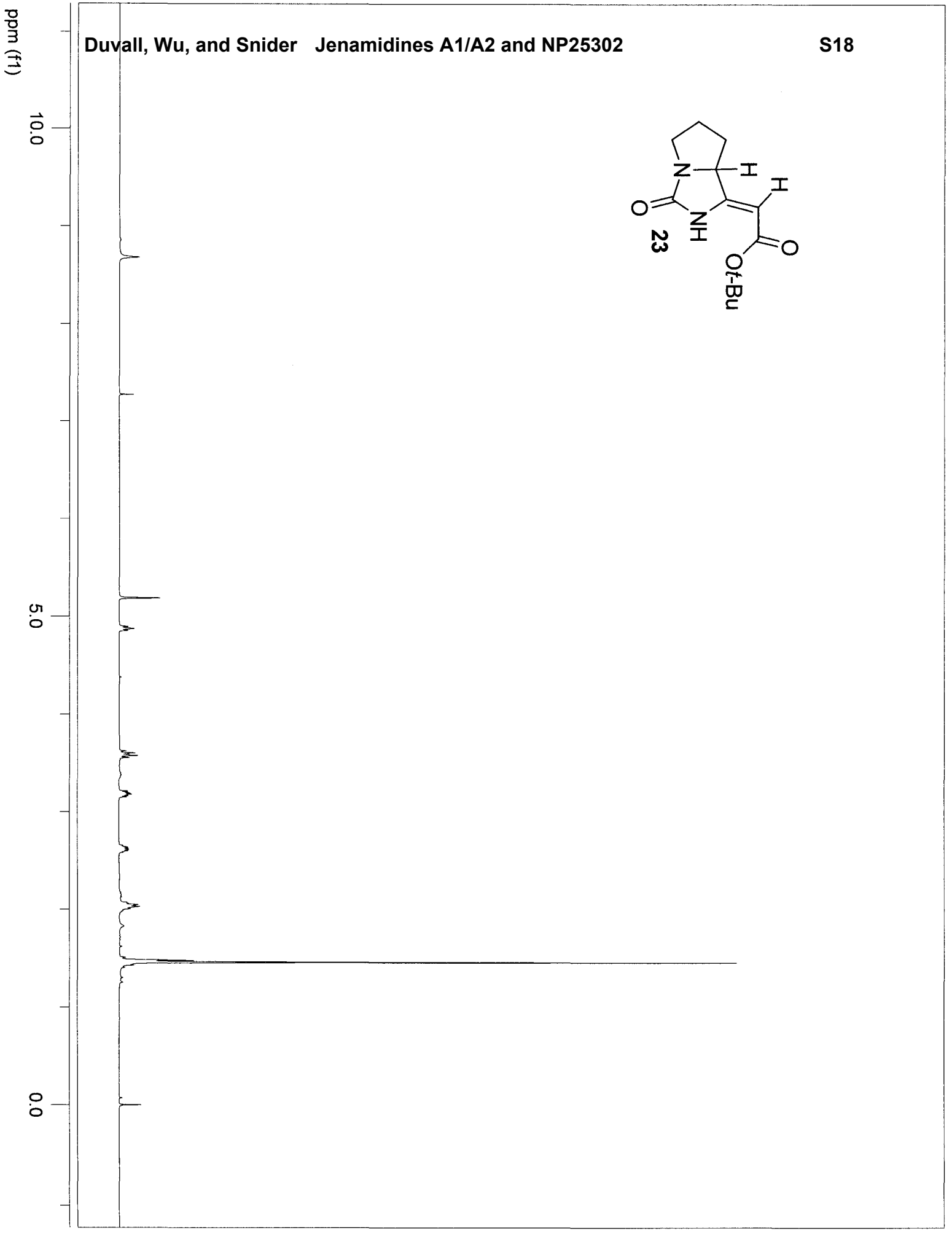
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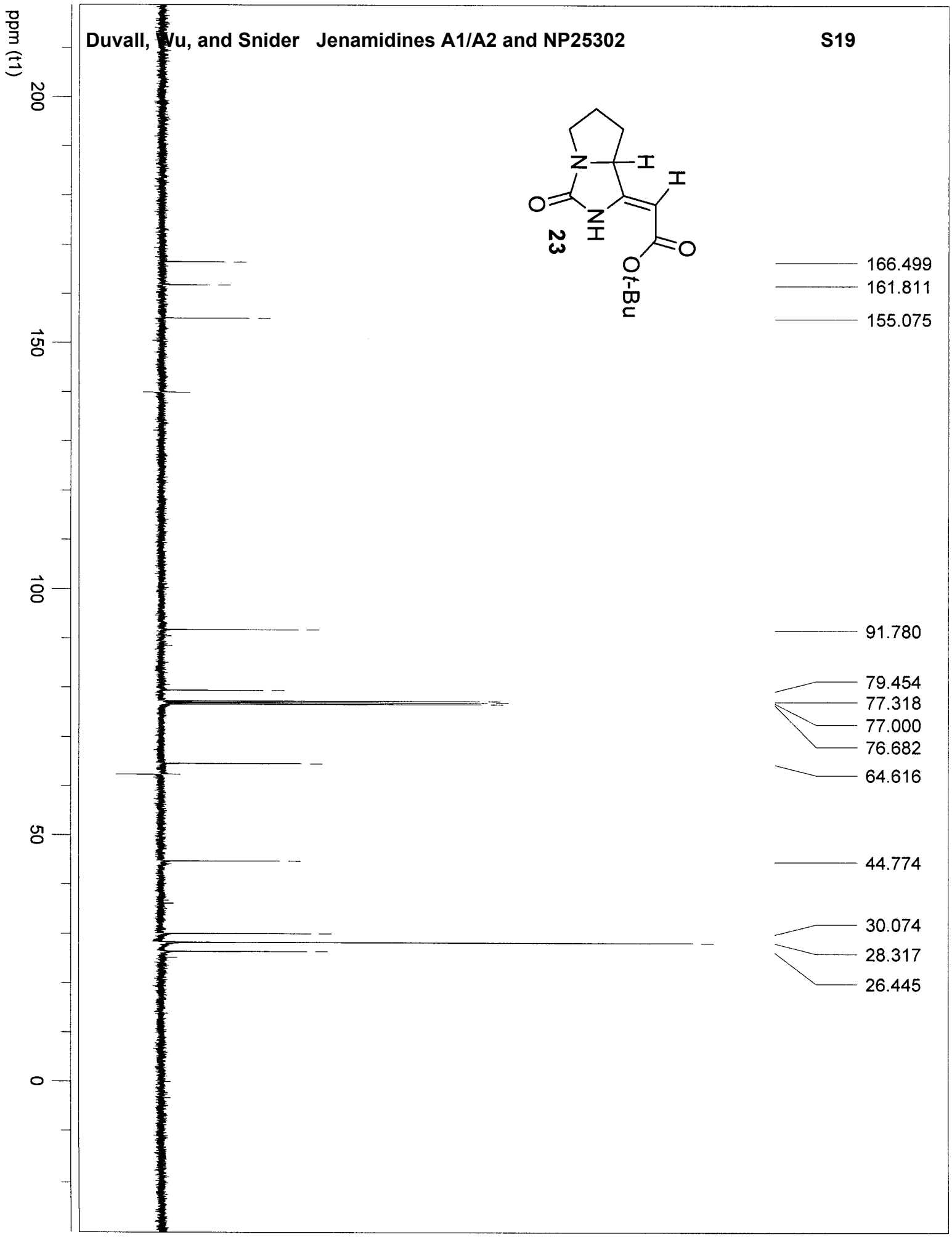
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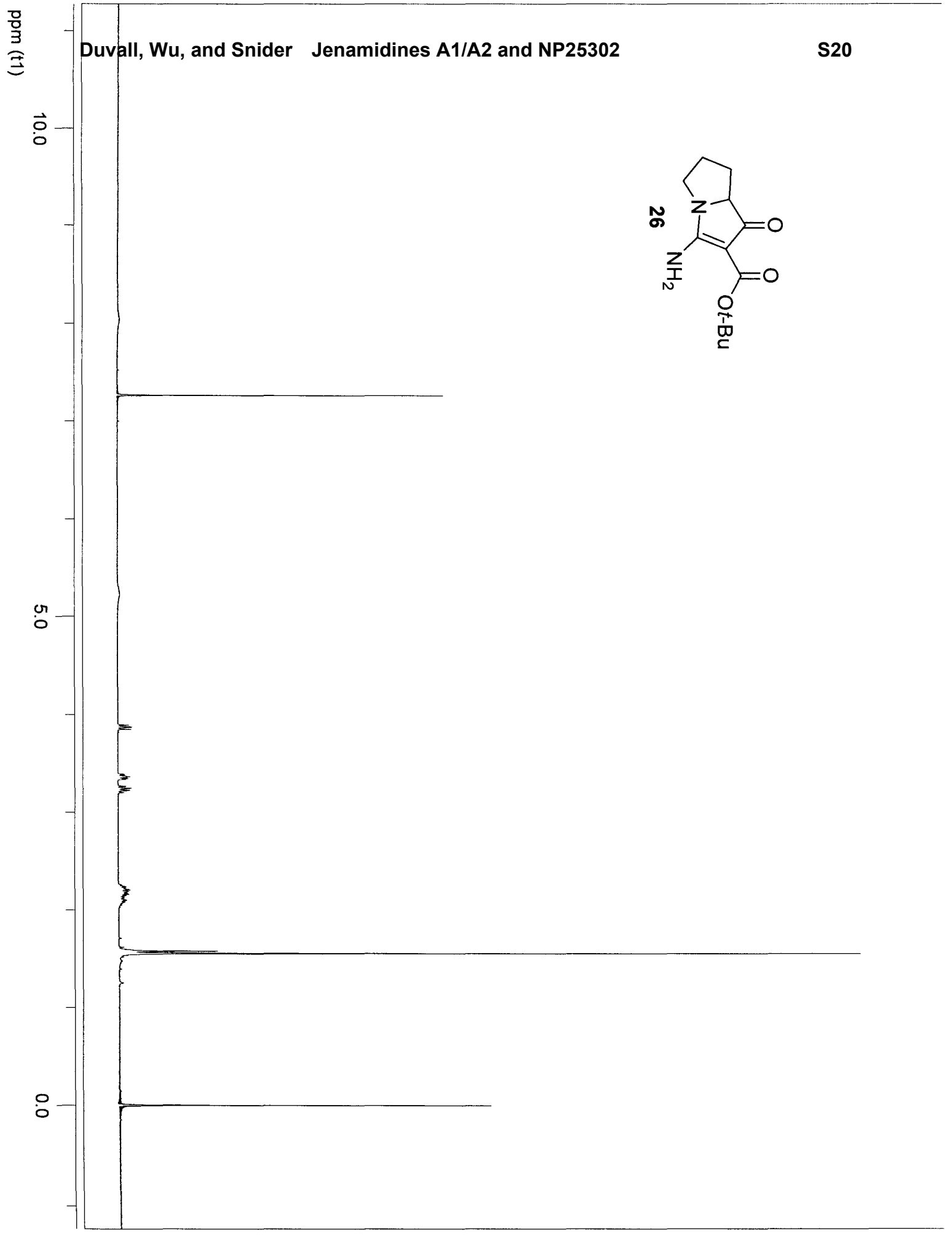
23



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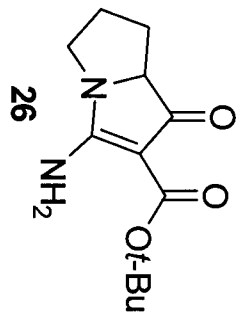
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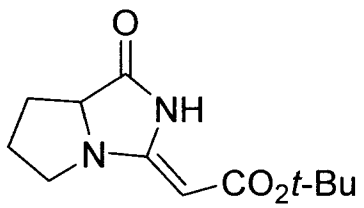

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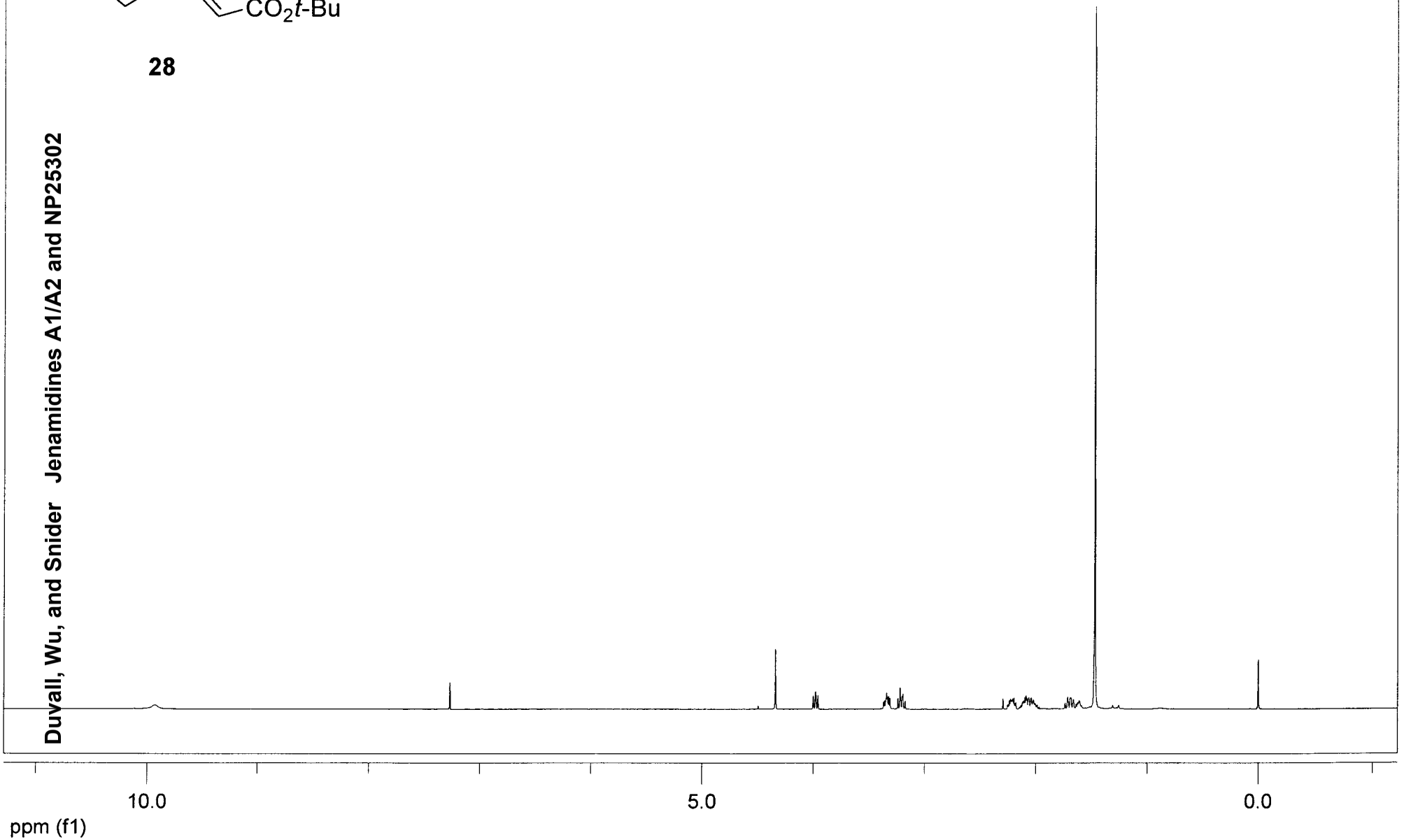

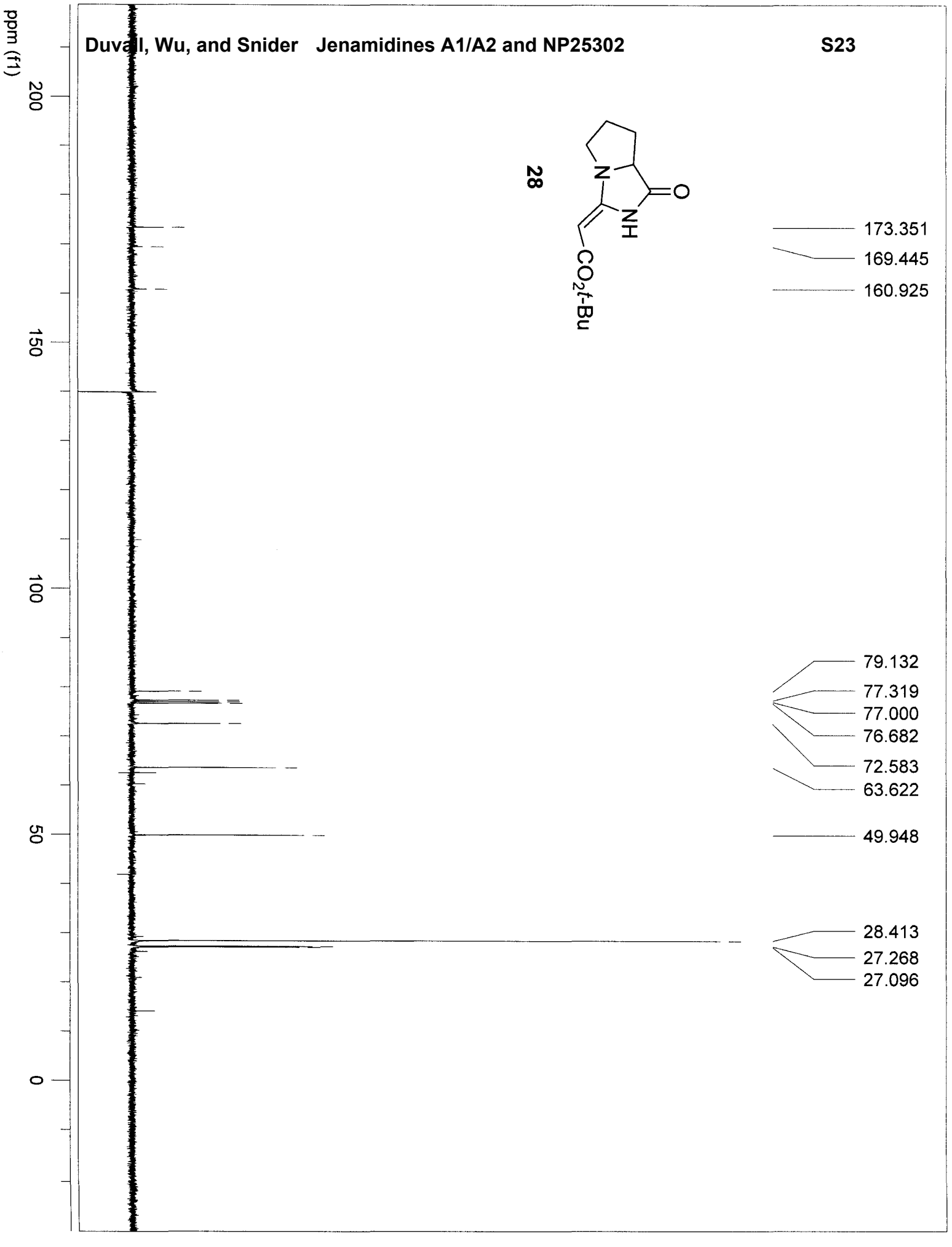
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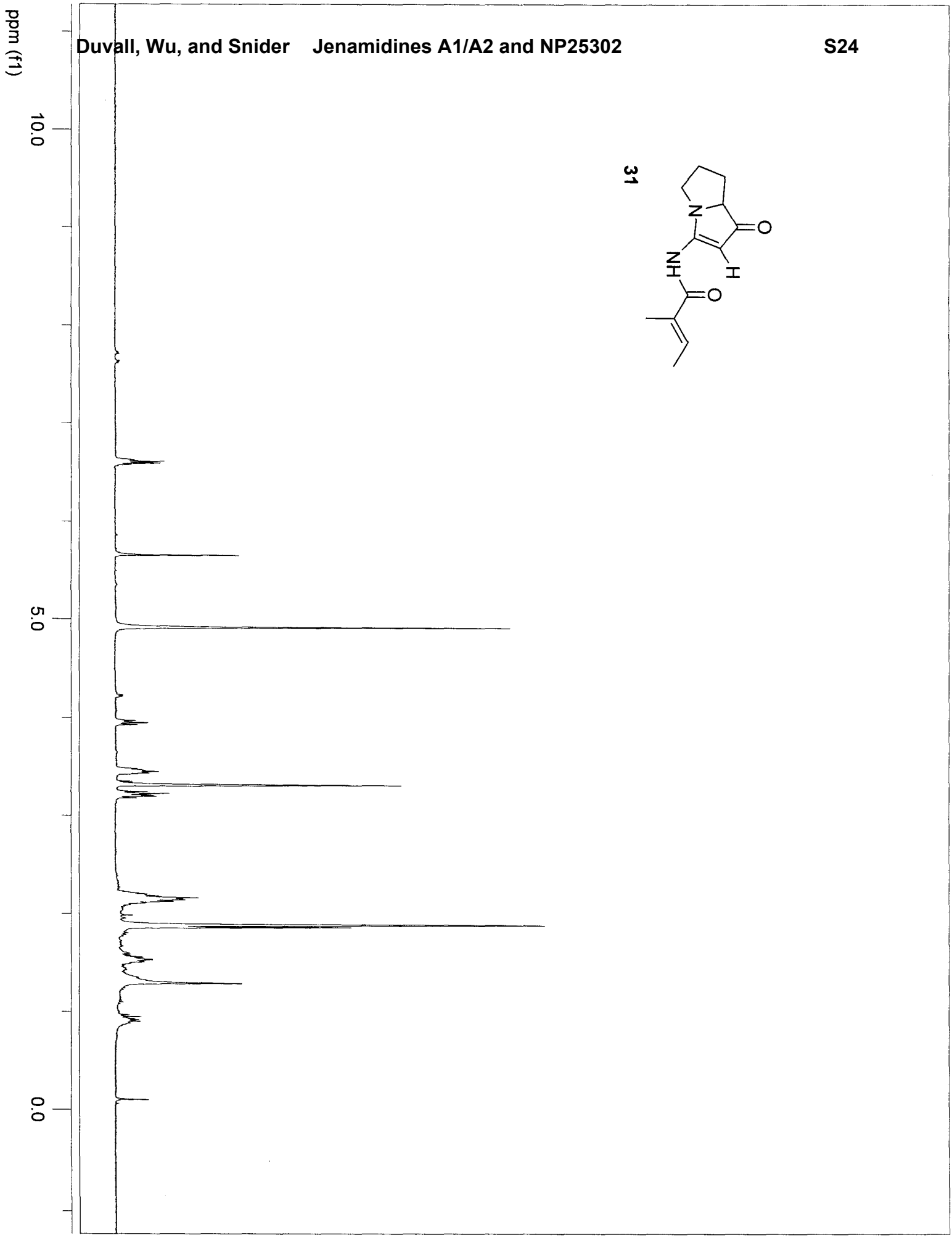

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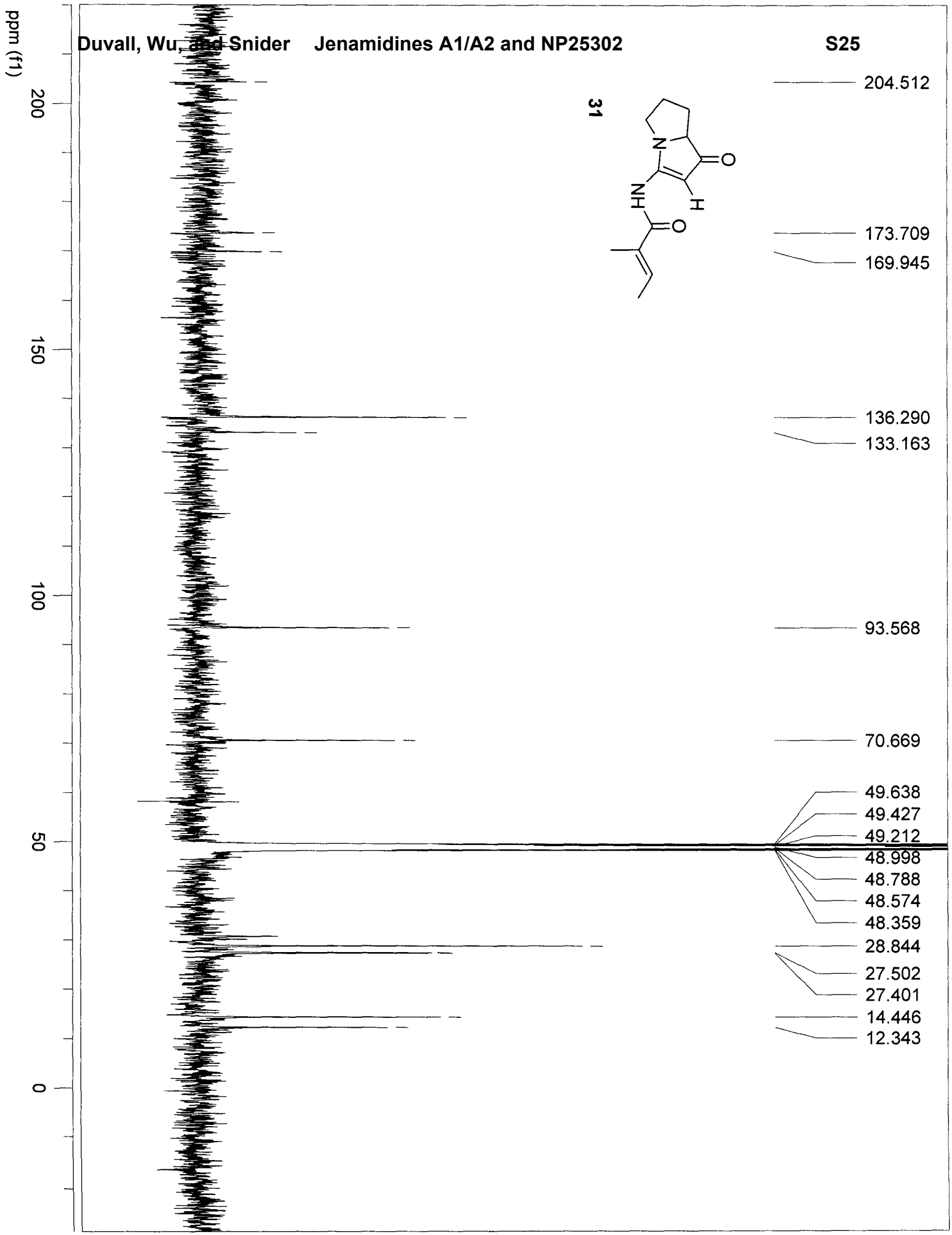
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31

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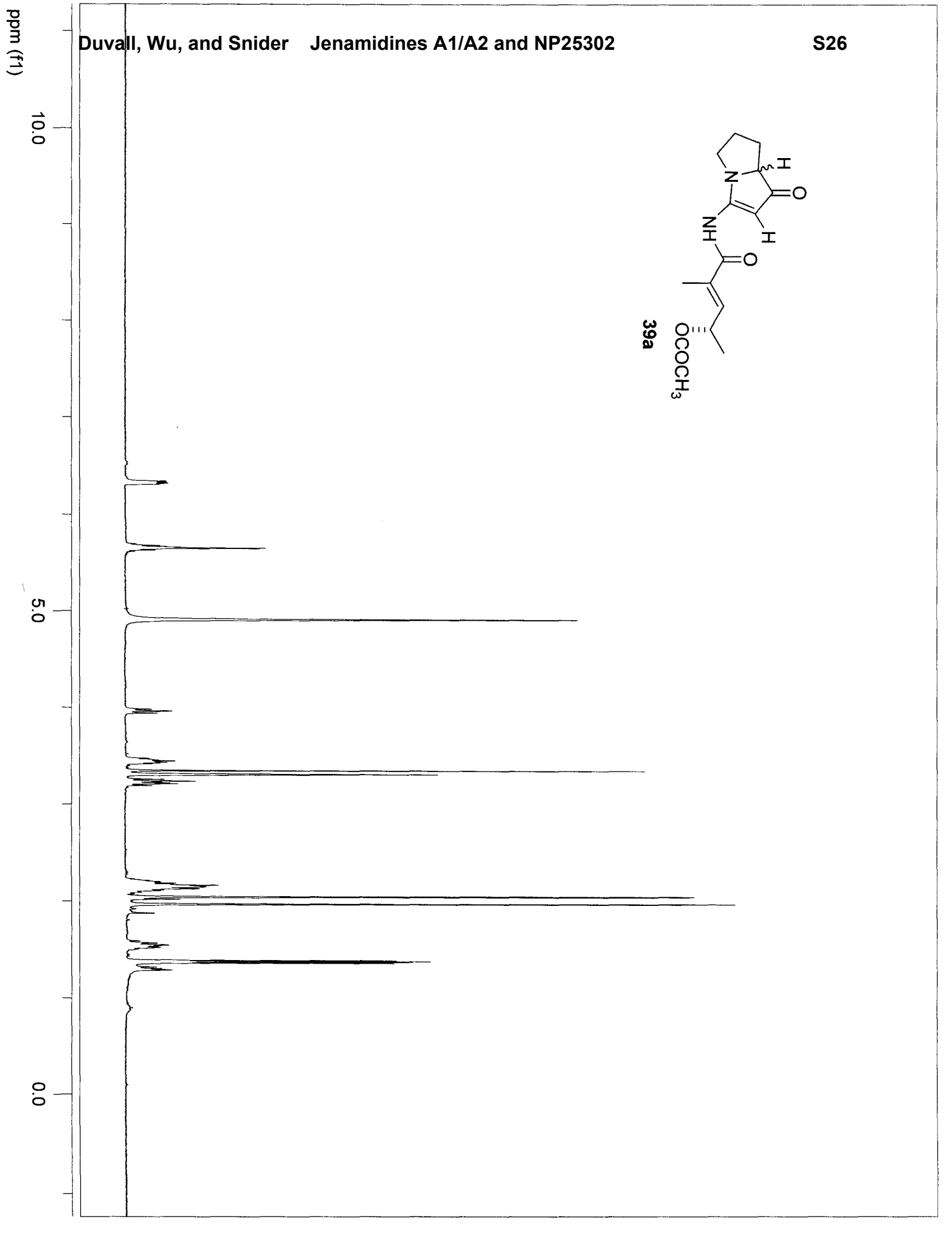

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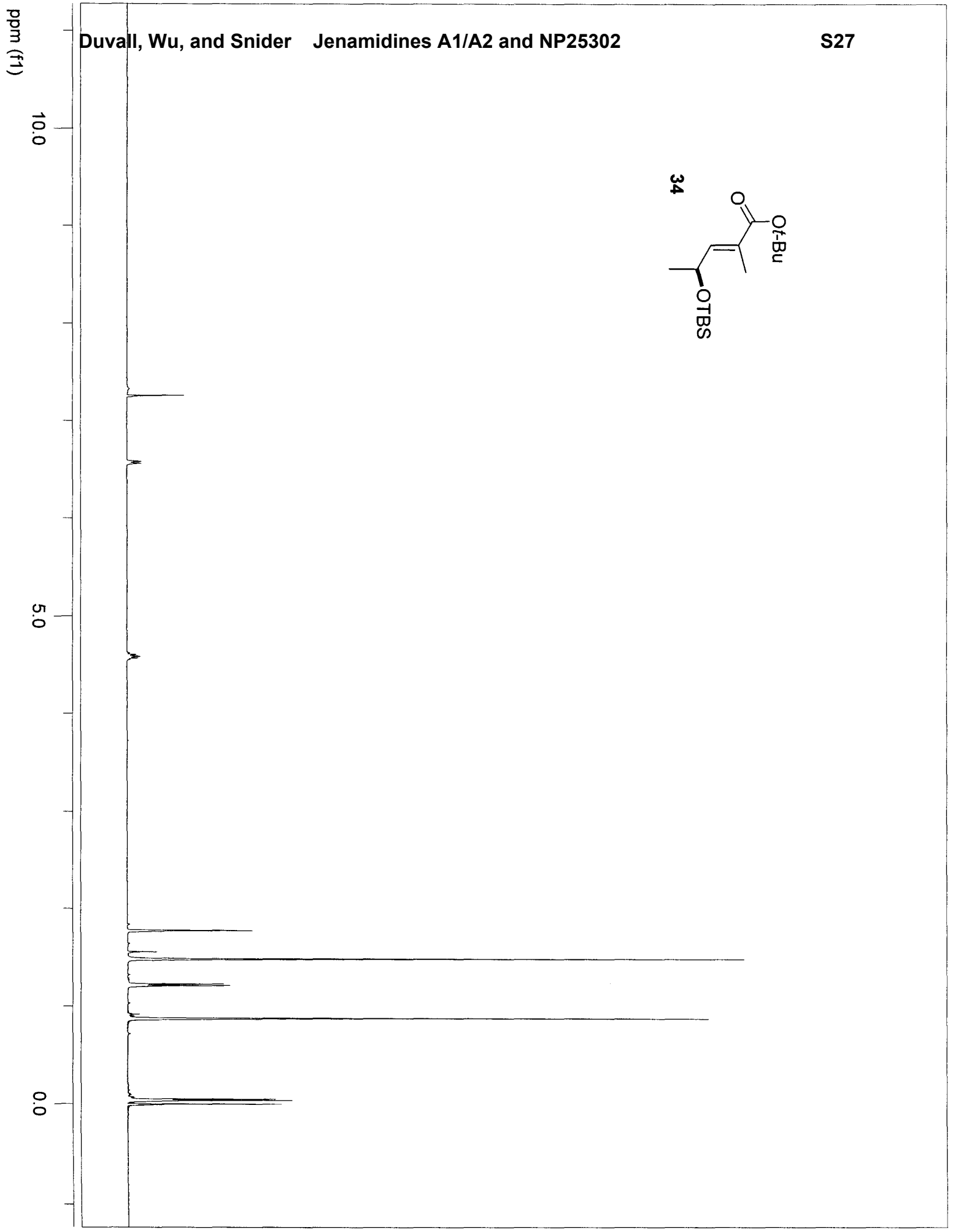

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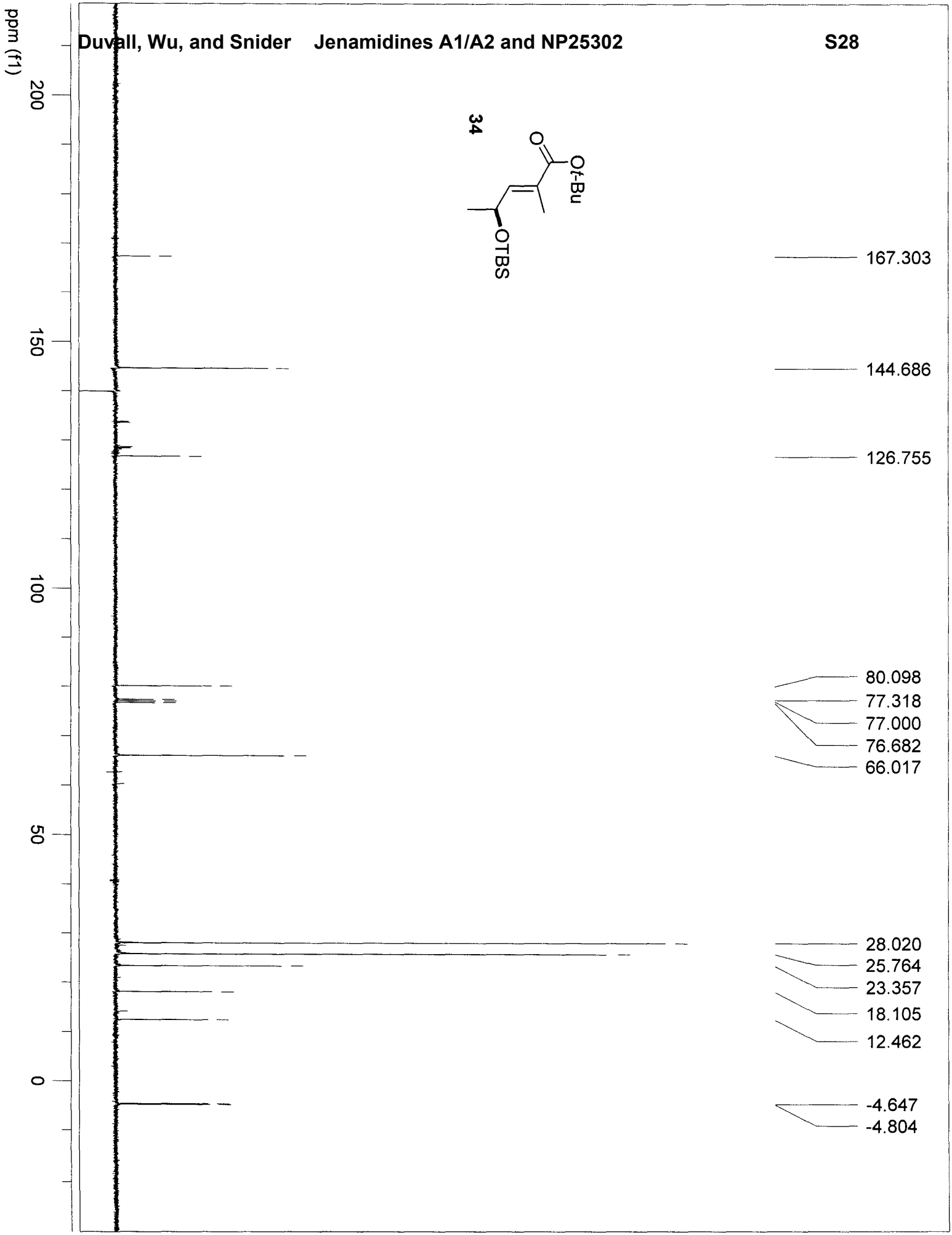
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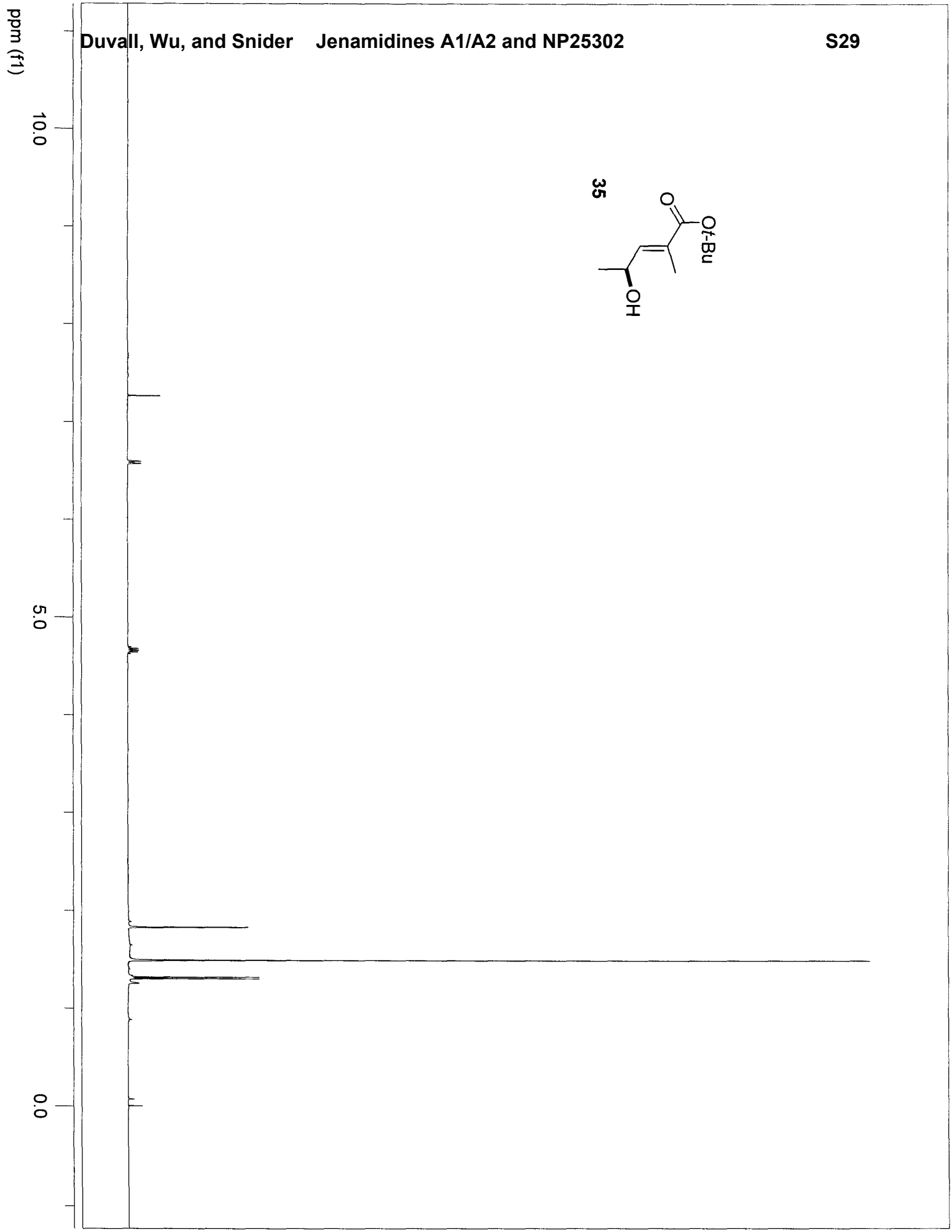

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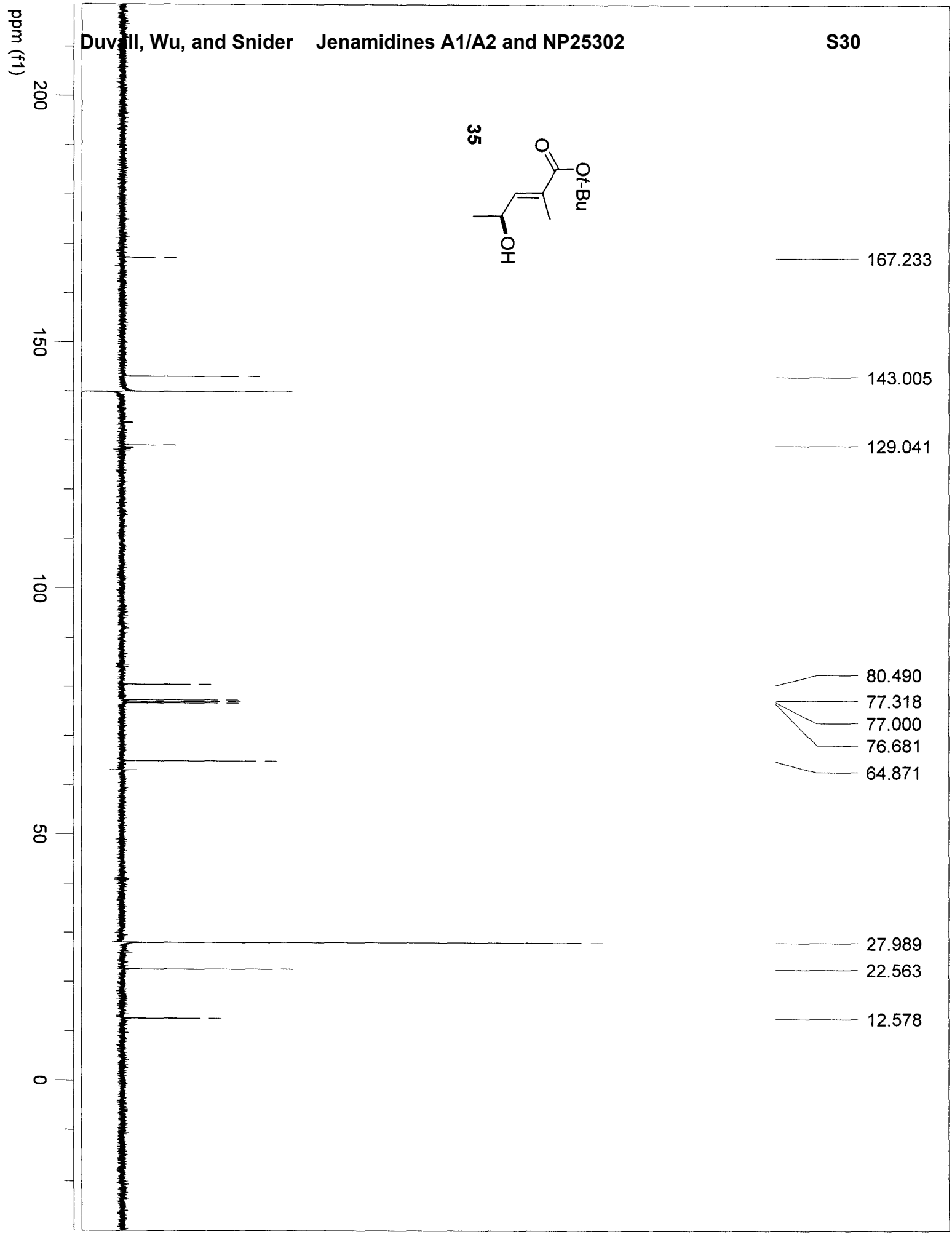
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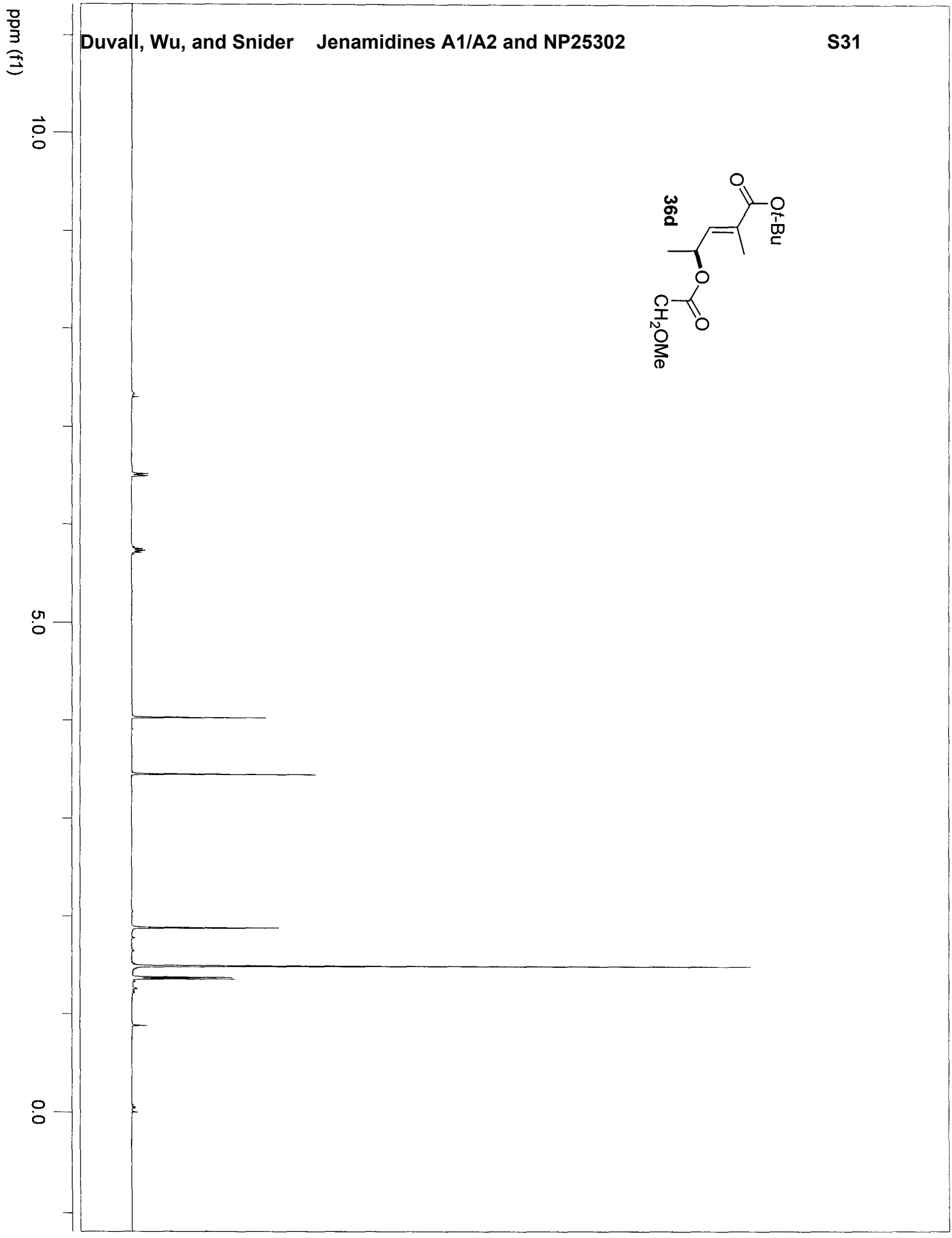
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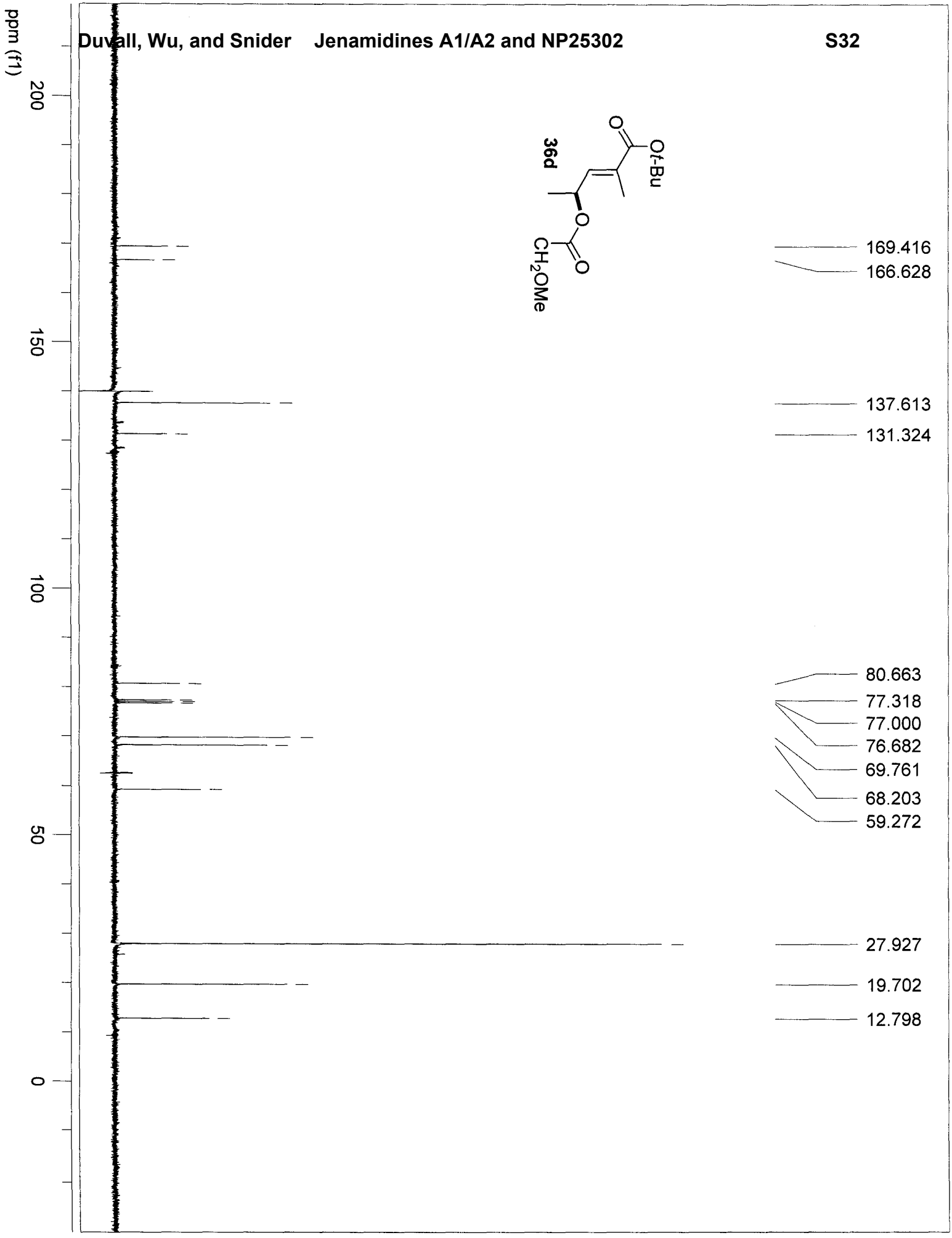
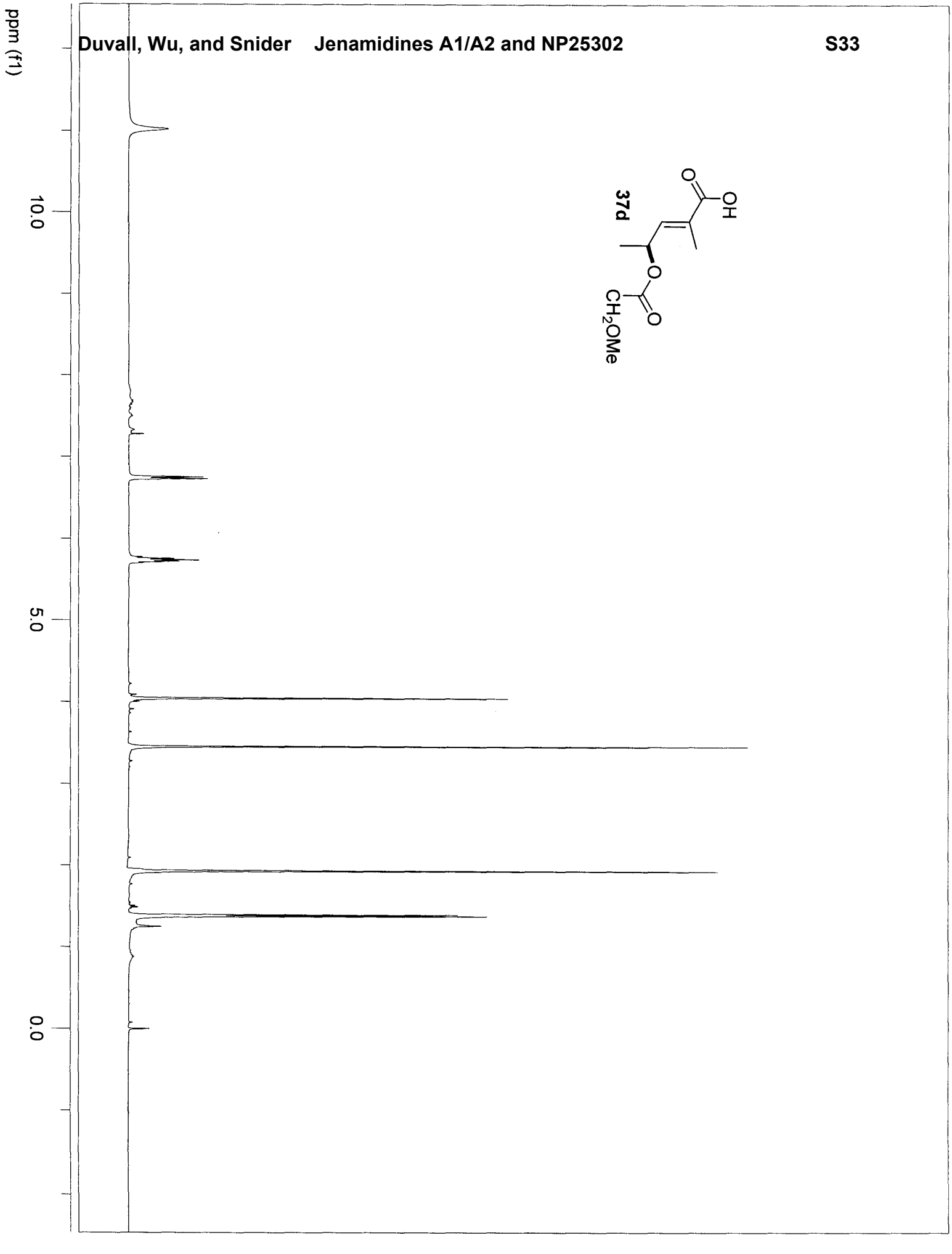
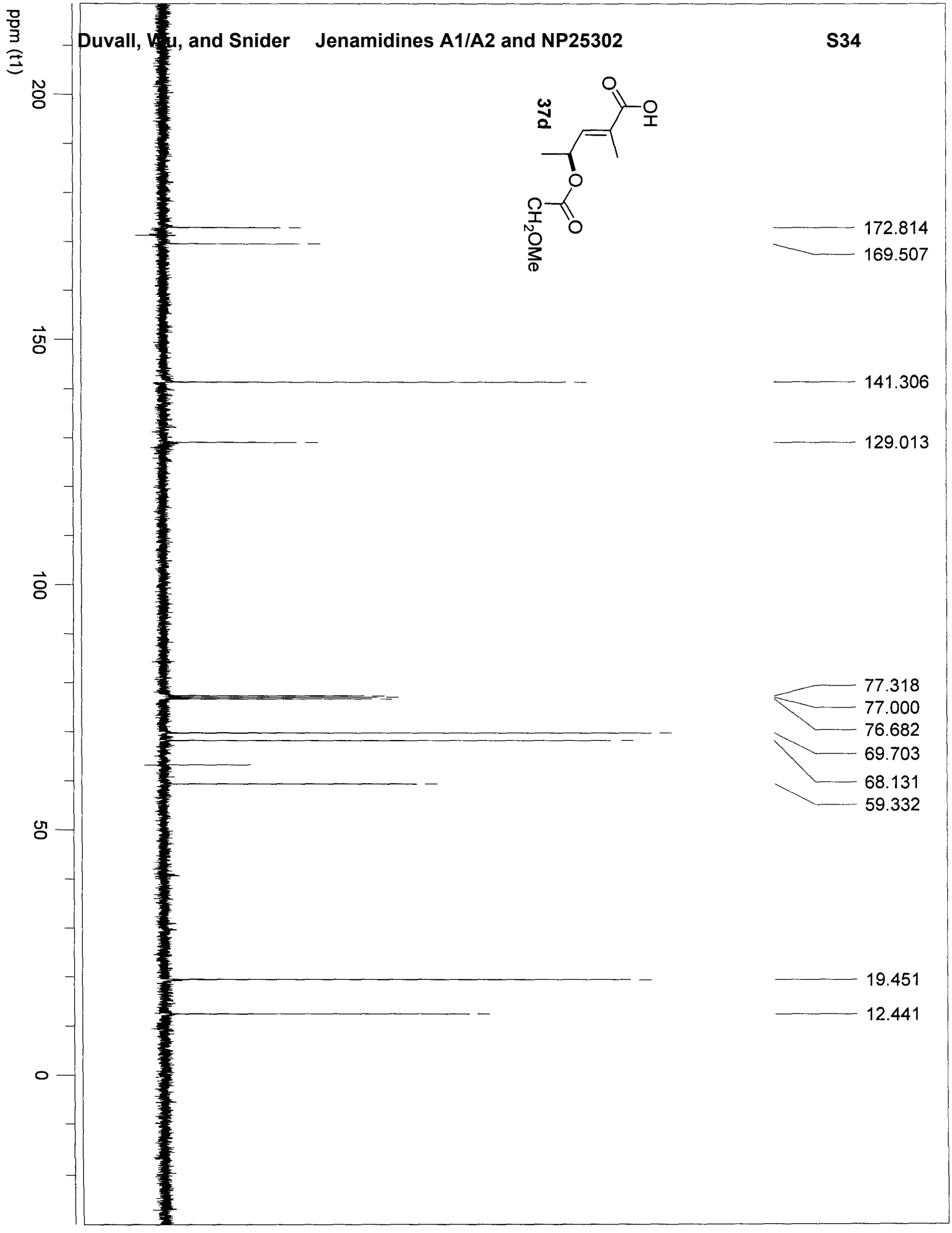
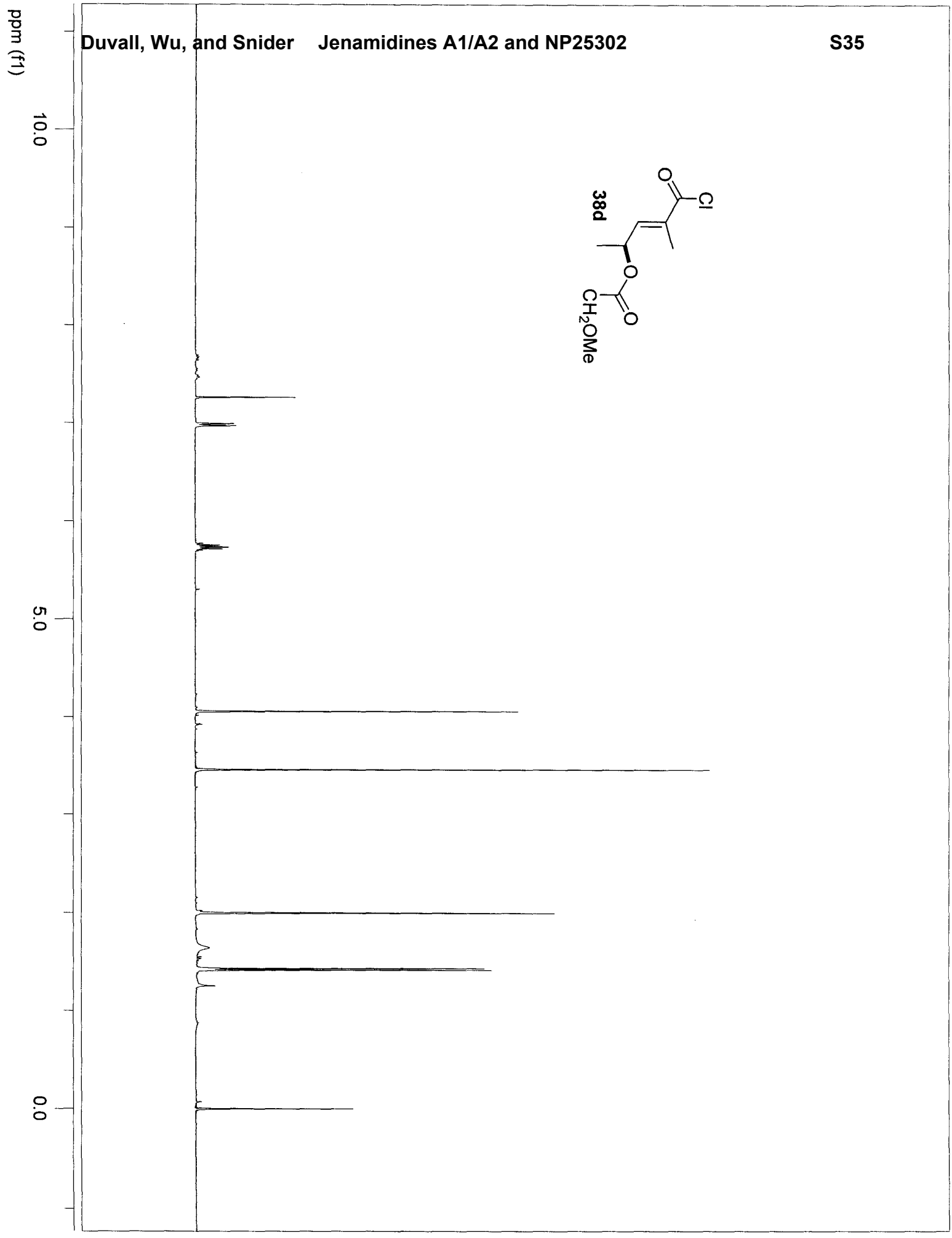
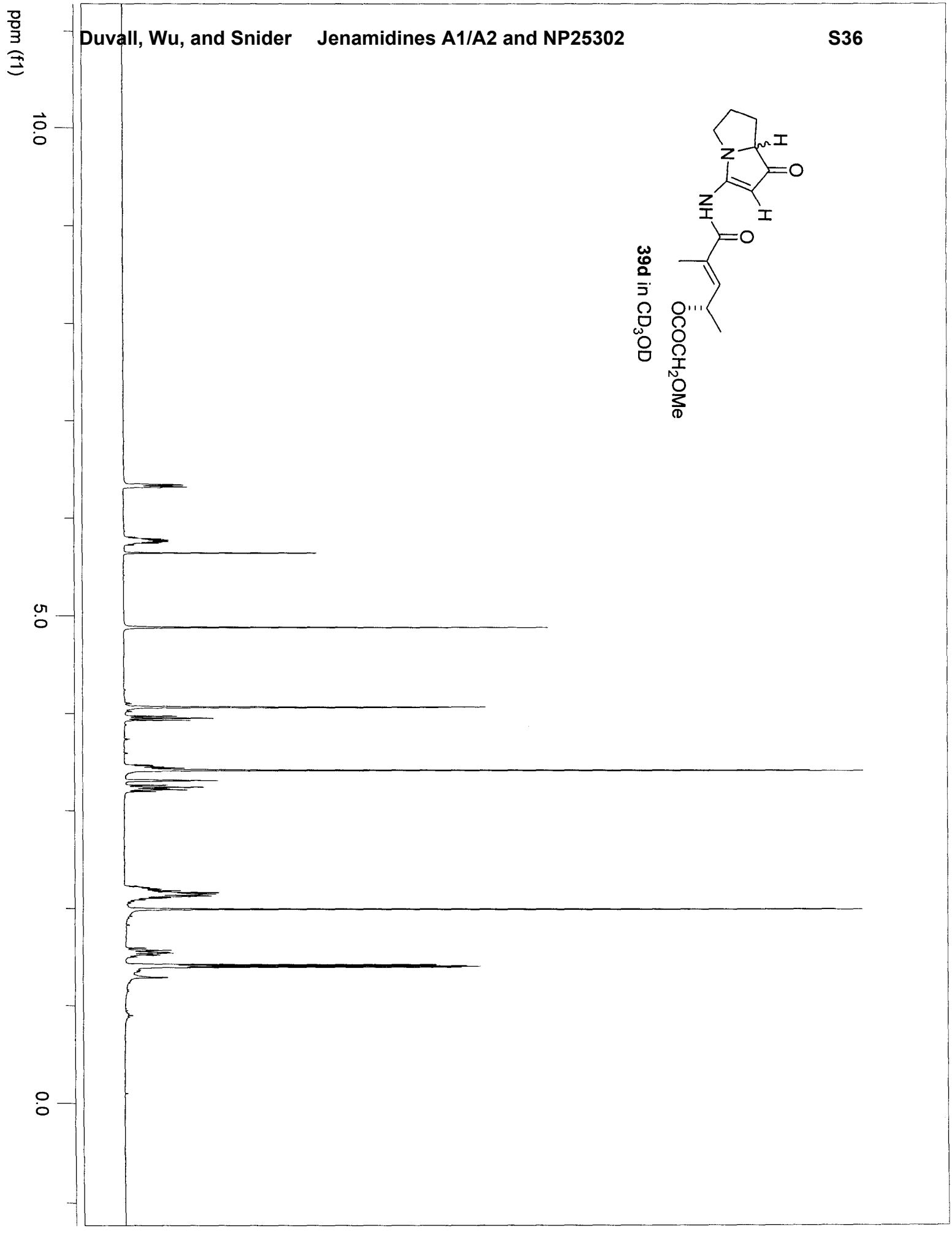
O
CH2OMe

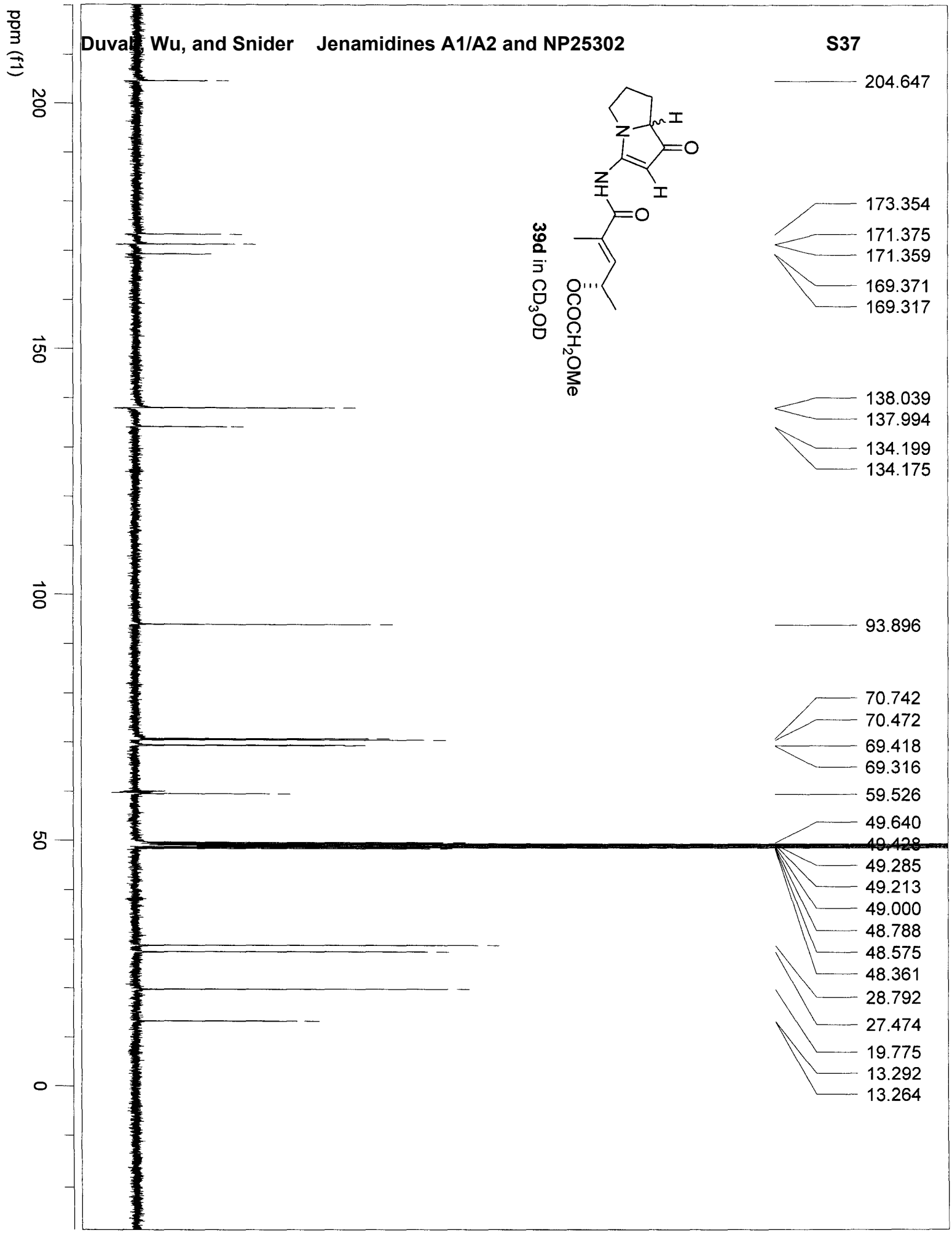

ppm (f1)
200
150
100
50
0
36d
Ot-Bu
O
O
O
CH2OMe
169.416
166.628
137.613
131.324
80.663
77.318
77.000
76.682
69.761
68.203
59.272
27.927
19.702
12.798

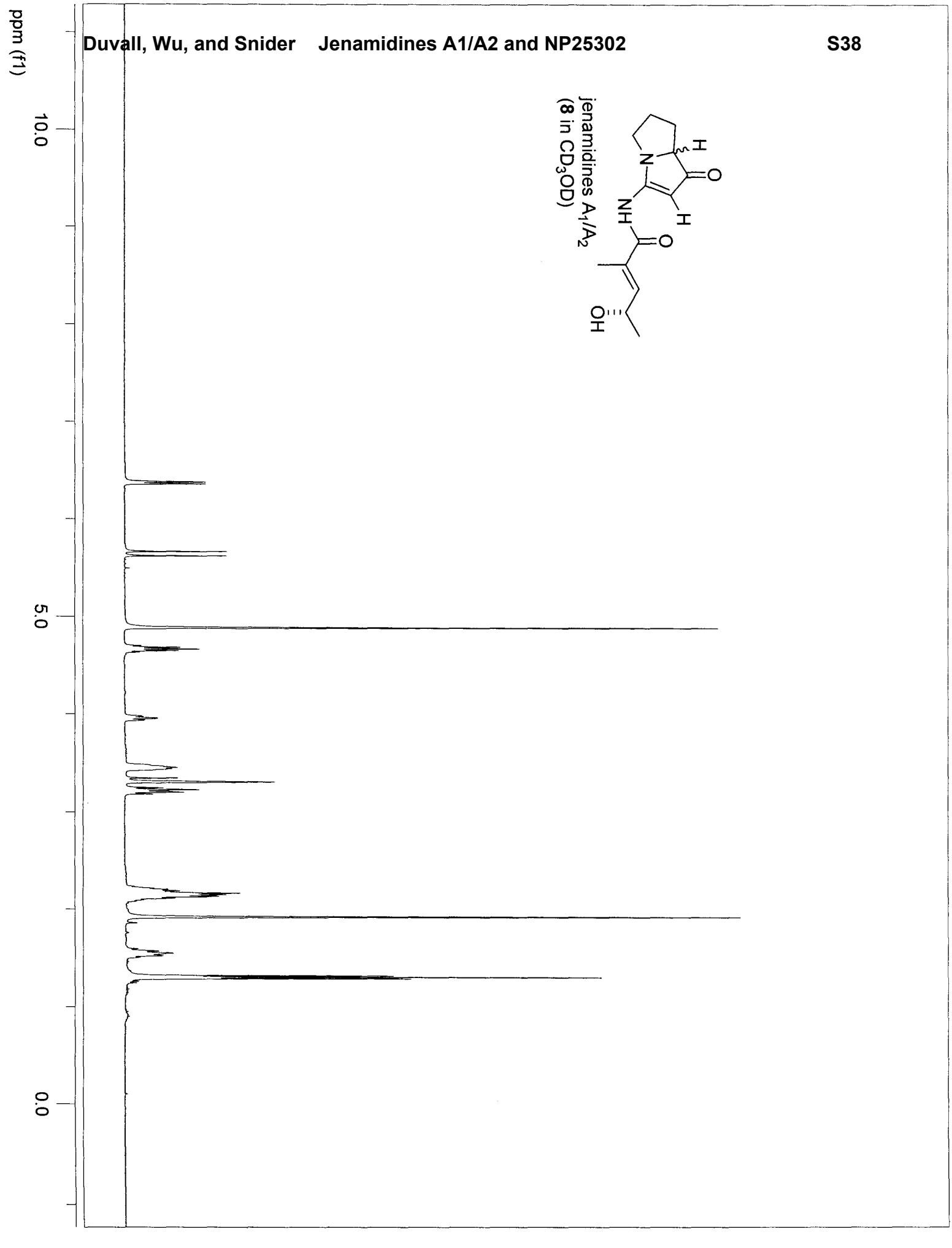

ppm (f1)
10.0
5.0
0.0
37d
OH
O
O
O
CH2OMe

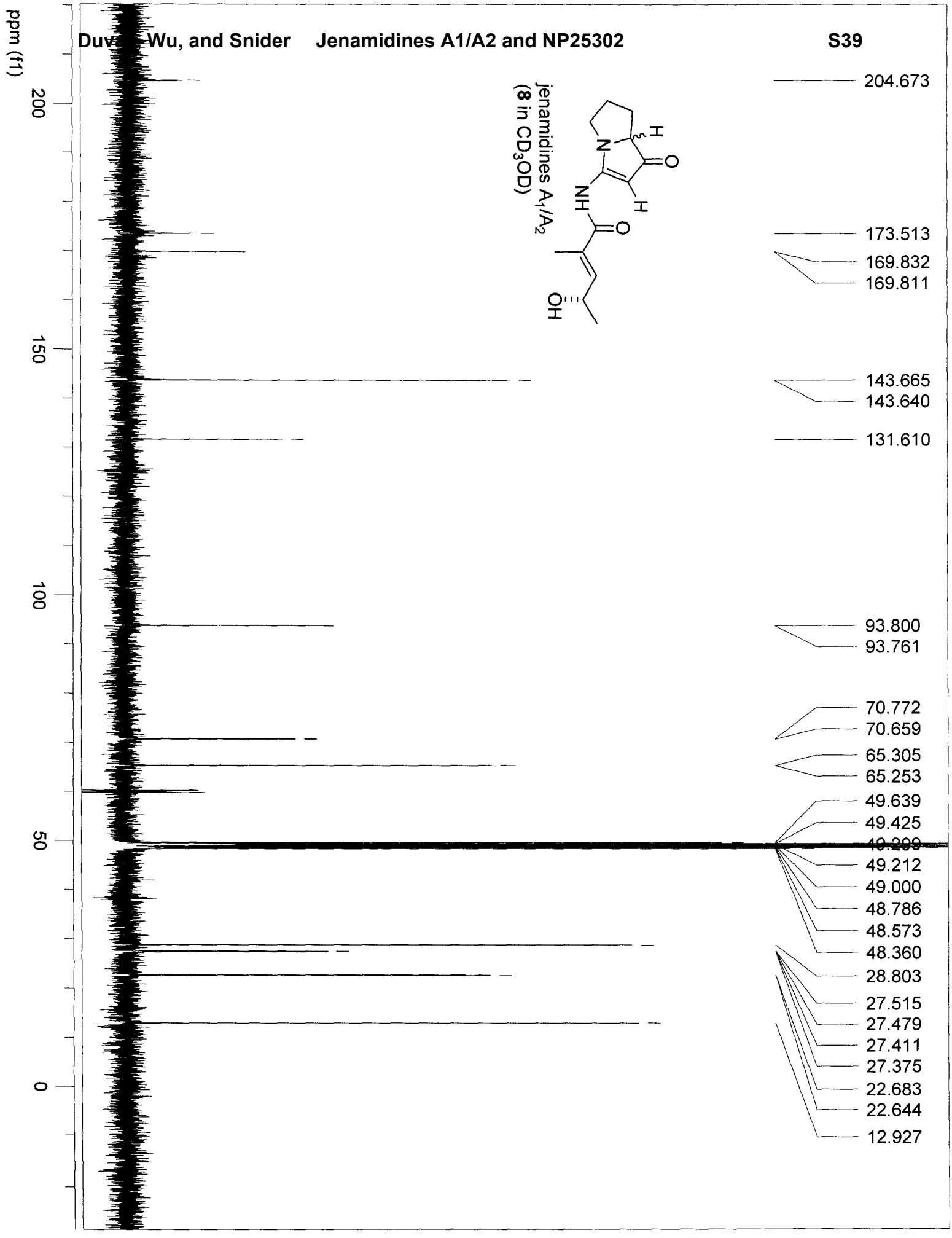

ppm (t1)
200
150
100
50
0
37d
OH
O
O
O
CH2OMe
172.814
169.507
141.306
129.013
77.318
77.000
76.682
69.703
68.131
59.332
19.451
12.441

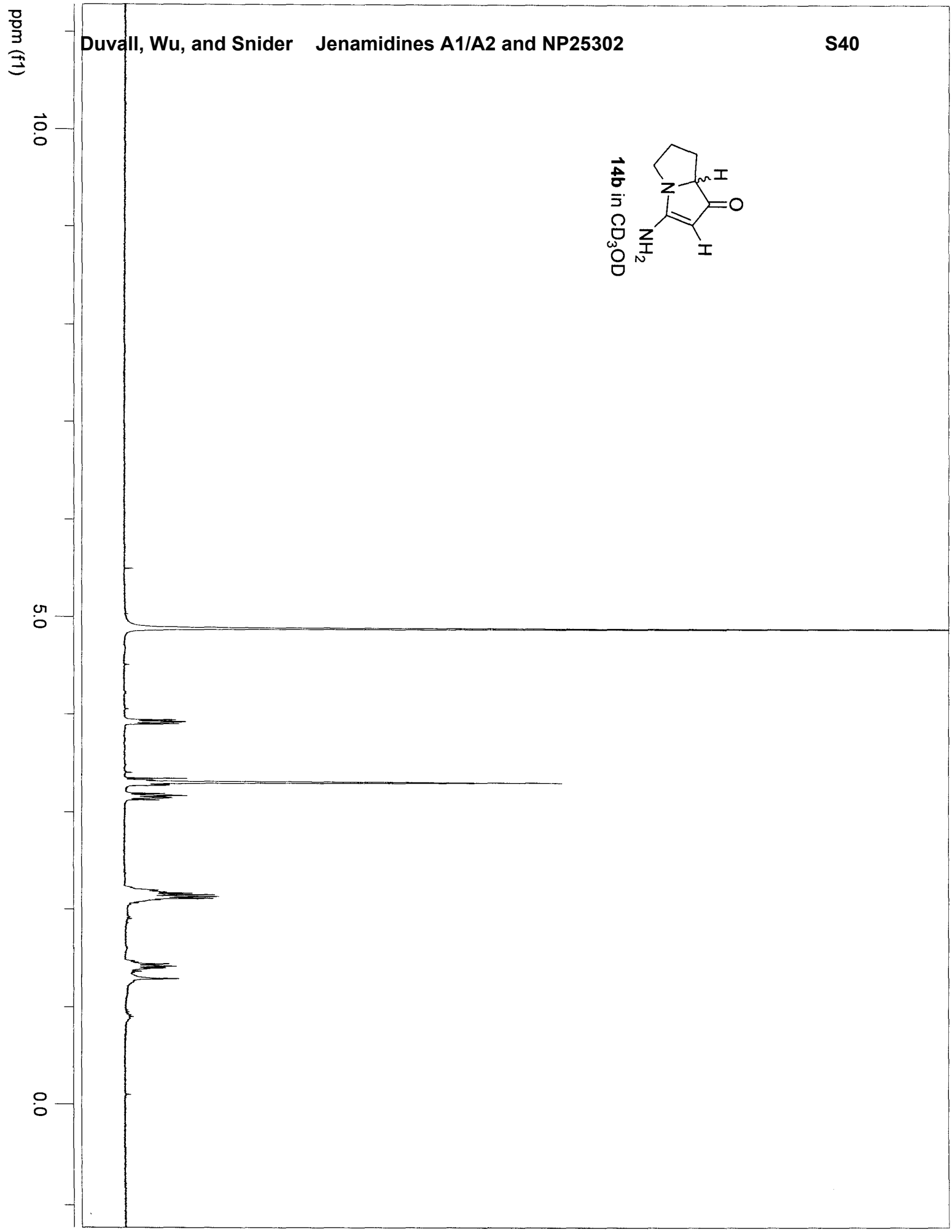

ppm (f1)
10.0
5.0
0.0
38d
Cl
O
O
O
CH2OMe

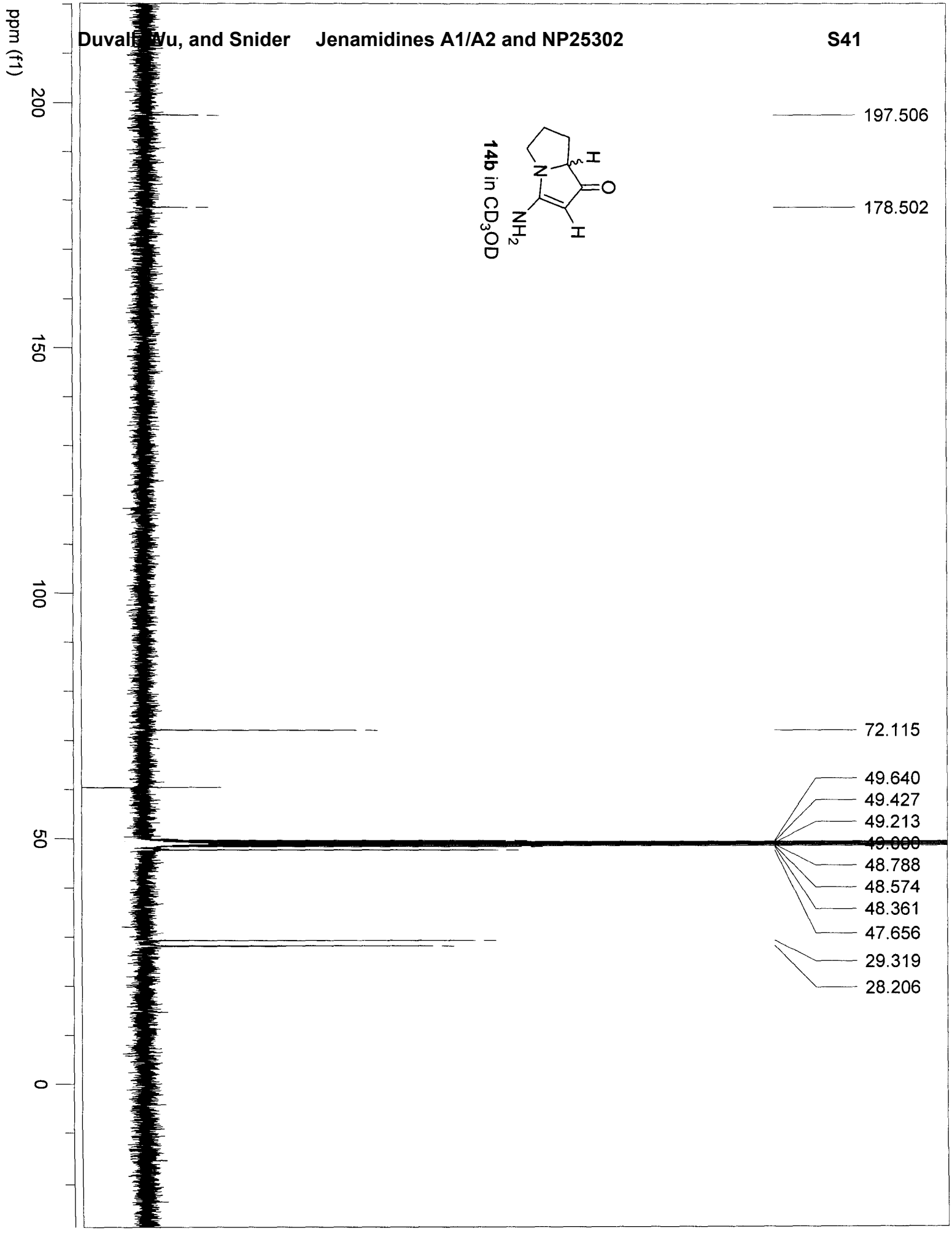

ppm (f1)
10.0
5.0
0.0
39d in CD3OD
OCOCH2OMe

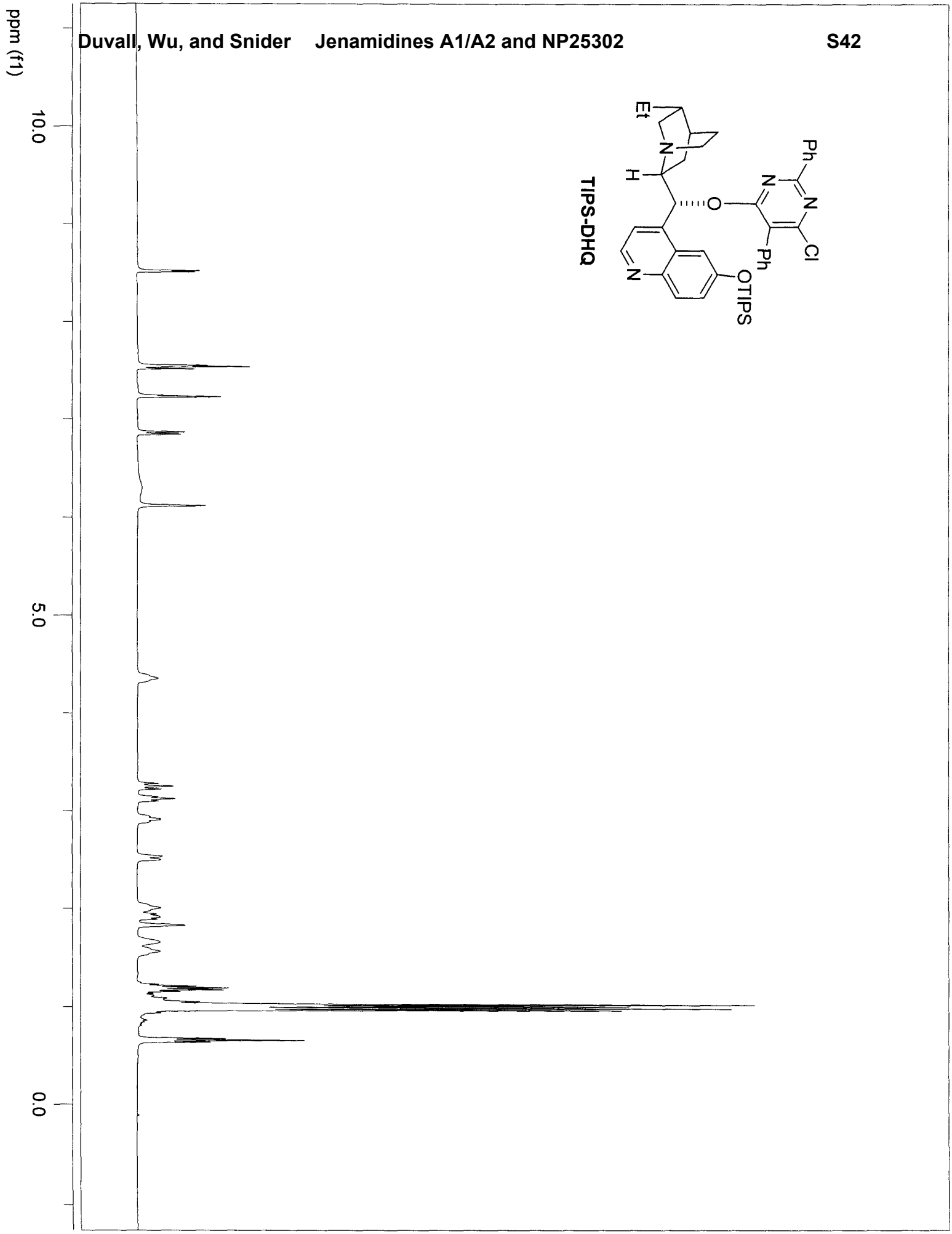

ppm (f1)
200
150
100
50
0
204.647
173.354
171.375
171.359
169.371
169.317
138.039
137.994
134.199
134.175
93.896
70.742
70.472
69.418
69.316
59.526
49.640
49.428
49.285
49.213
49.000
48.788
48.575
48.361
28.792
27.474
19.775
13.292
13.264
39d in CD3OD
OCOCH2OMe


ppm (f1)
10.0
5.0
0.0
jenamidines A_1/A_2
(**8** in CD_3OD)
H
O
N
NH
H
O
OH

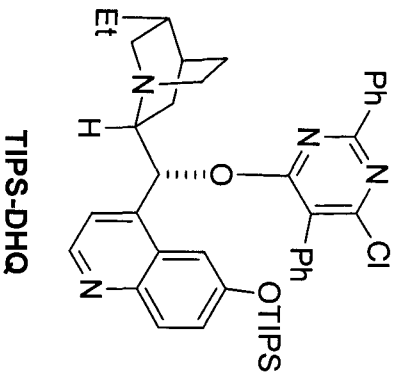

ppm (f1)
200
150
100
50
0
jenamidines A_1/A_2
(**8** in CD_3OD)
204.673
173.513
169.832
169.811
143.665
143.640
131.610
93.800
93.761
70.772
70.659
65.305
65.253
49.639
49.425
49.212
49.000
48.786
48.573
48.360
28.803
27.515
27.479
27.411
27.375
22.683
22.644
12.927


ppm (f1)
10.0
5.0
0.0
14b in CD3OD
NH2
N
O
H
H


ppm (f1)
200
150
100
50
0
14b in CD3OD
NH2
N
O
H
H
197.506
178.502
72.115
49.640
49.427
49.213
49.000
48.788
48.574
48.361
47.656
29.319
28.206

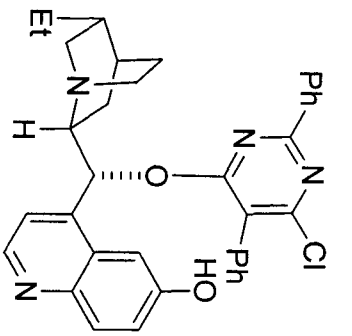


TIPS-DHQ

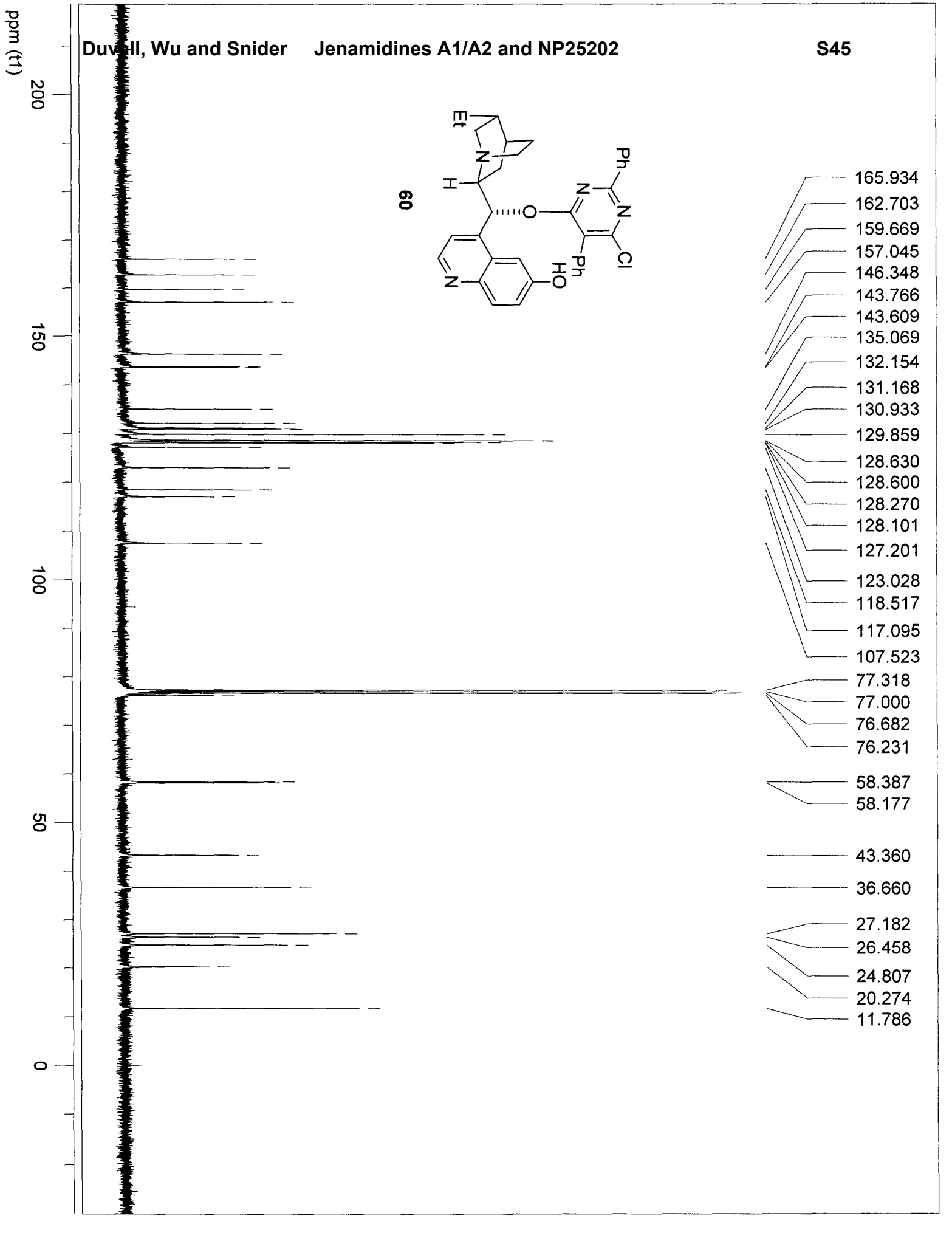

Et
N
H
O
N
N
Ph
N
Cl
Ph
N
OTIPS

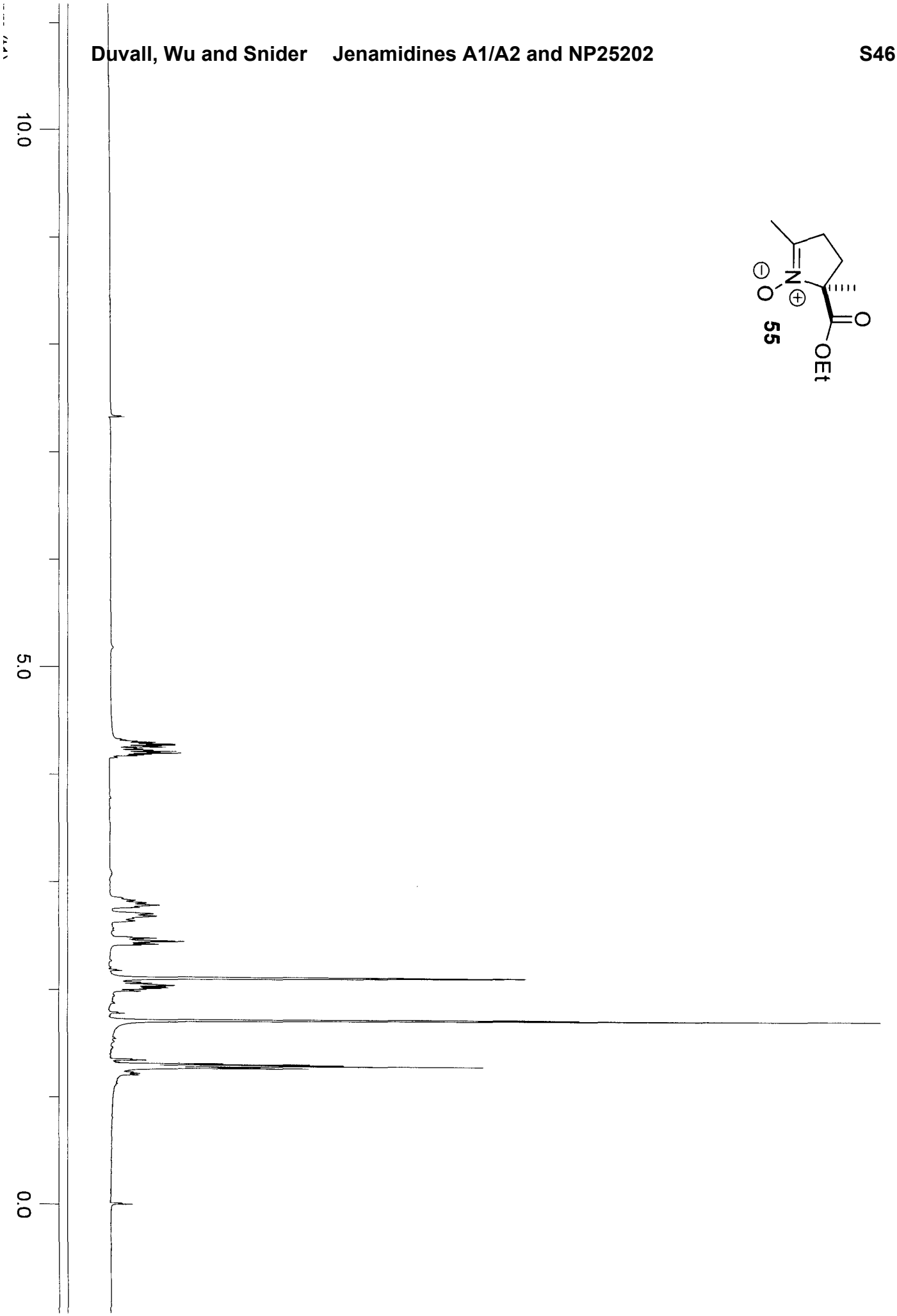
TIPS-DHQ

ppm (t1)
200
150
100
50
0
153.908
147.392
144.593
143.122
130.643
125.240
124.071
118.854
110.250
77.319
77.000
76.681
66.618
59.877
56.647
43.759
35.443
26.981
24.868
24.421
17.917
17.870
12.592
11.366

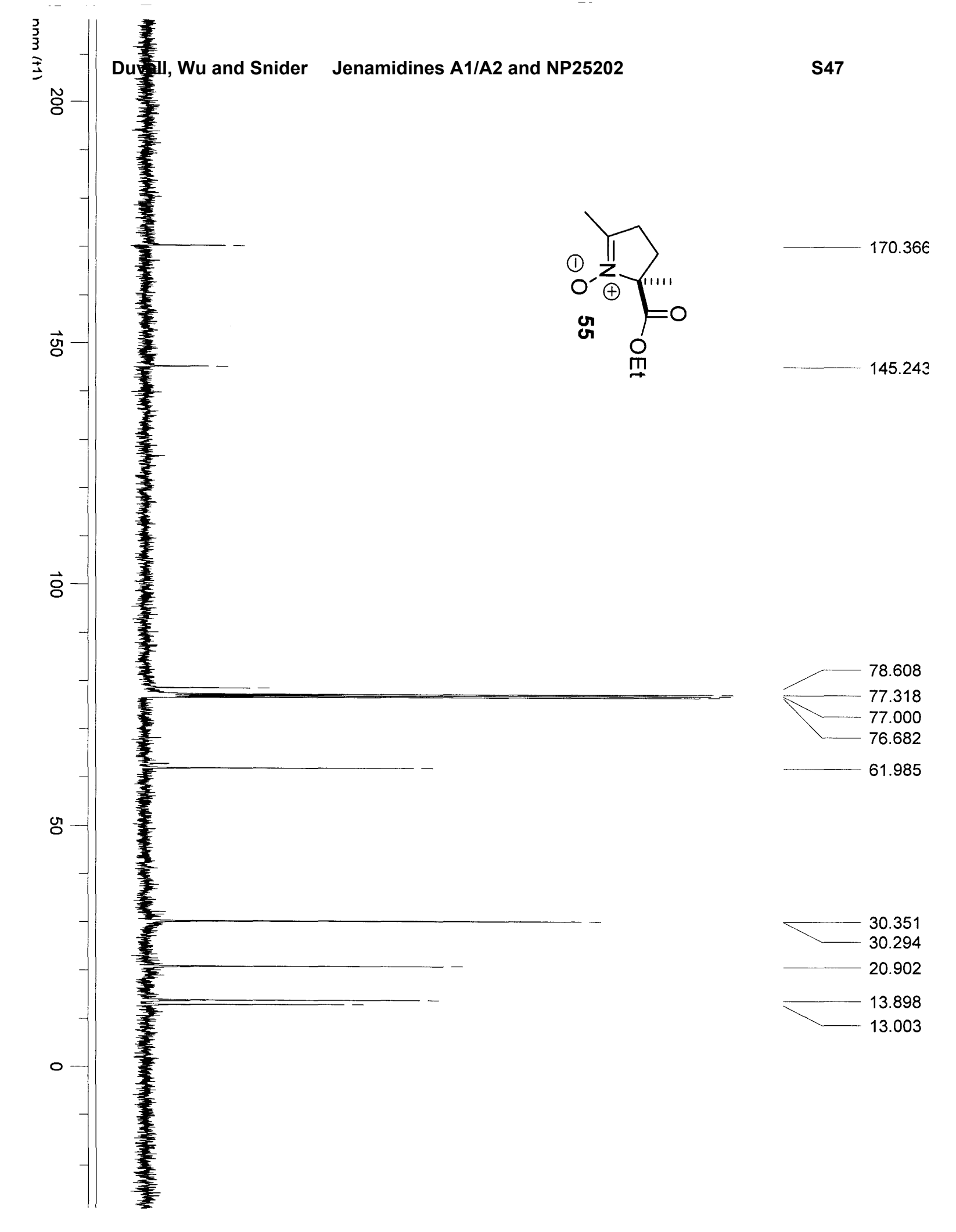


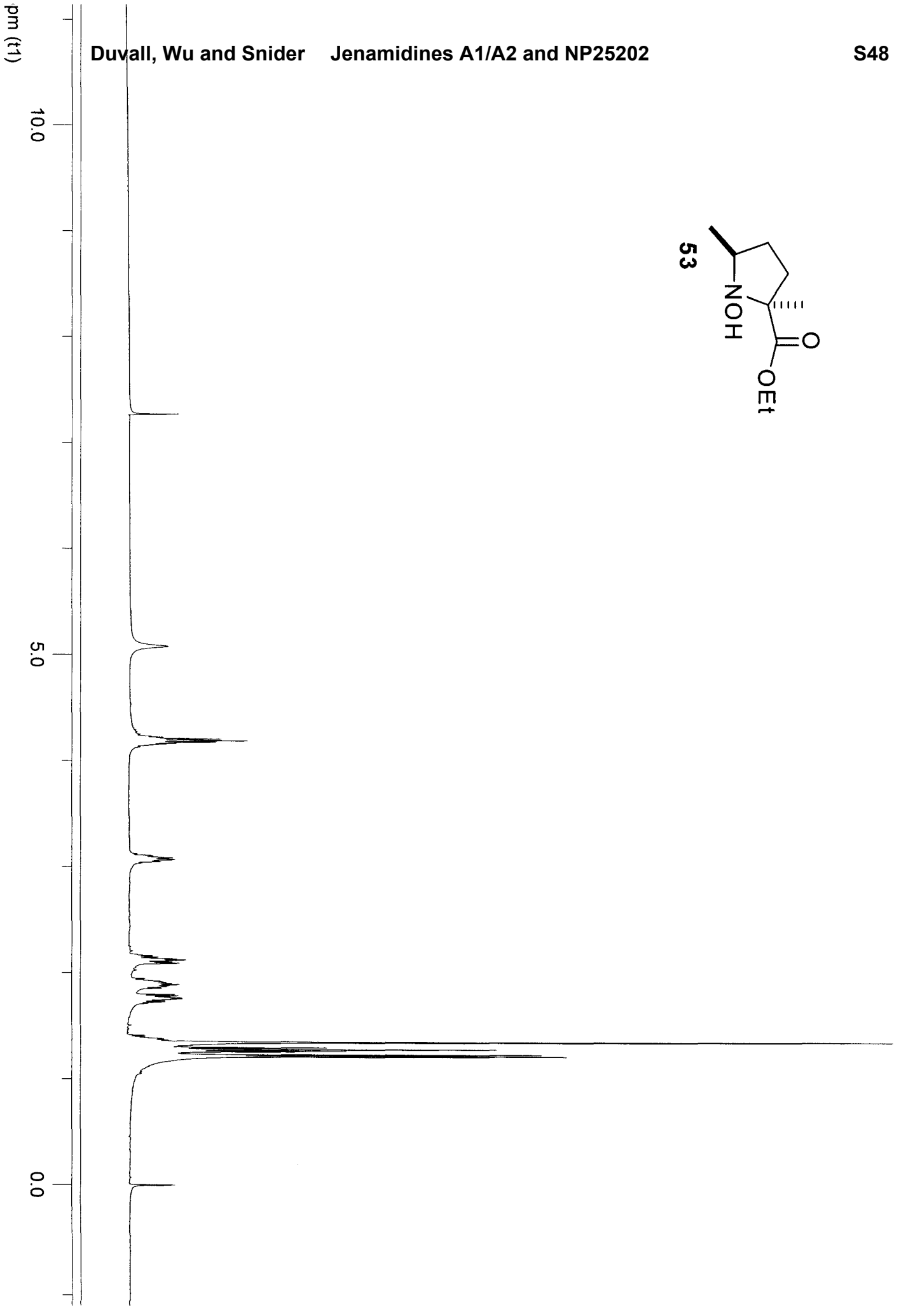
60


ppm (t1)
200
150
100
50
0
60
Et
N
H
O
N
N
Ph
N
Cl
Ph
HO
165.934
162.703
159.669
157.045
146.348
143.766
143.609
135.069
132.154
131.168
130.933
129.859
128.630
128.600
128.270
128.101
127.201
123.028
118.517
117.095
107.523
77.318
77.000
76.682
76.231
58.387
58.177
43.360
36.660
27.182
26.458
24.807
20.274
11.786

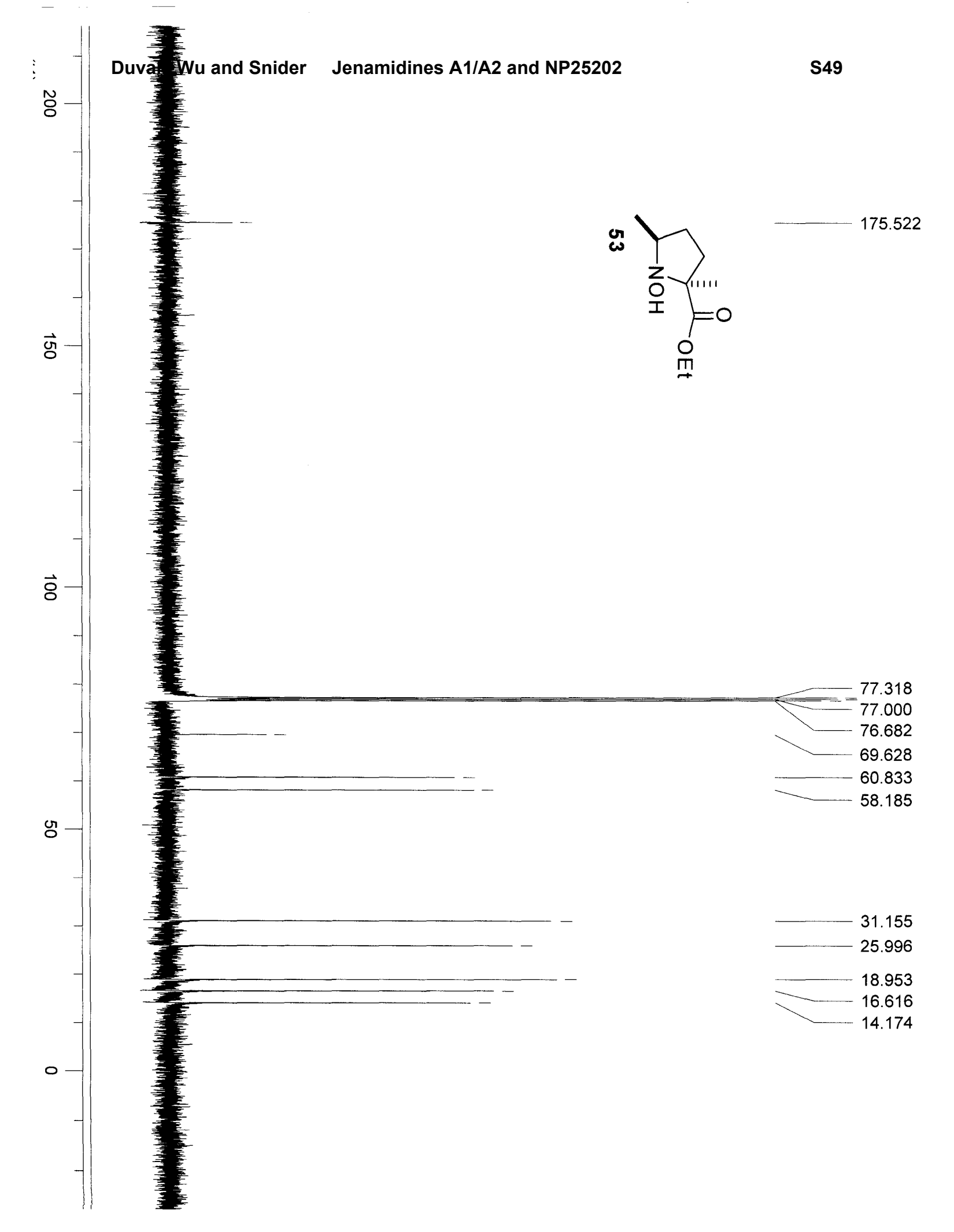

10.0
5.0
0.0

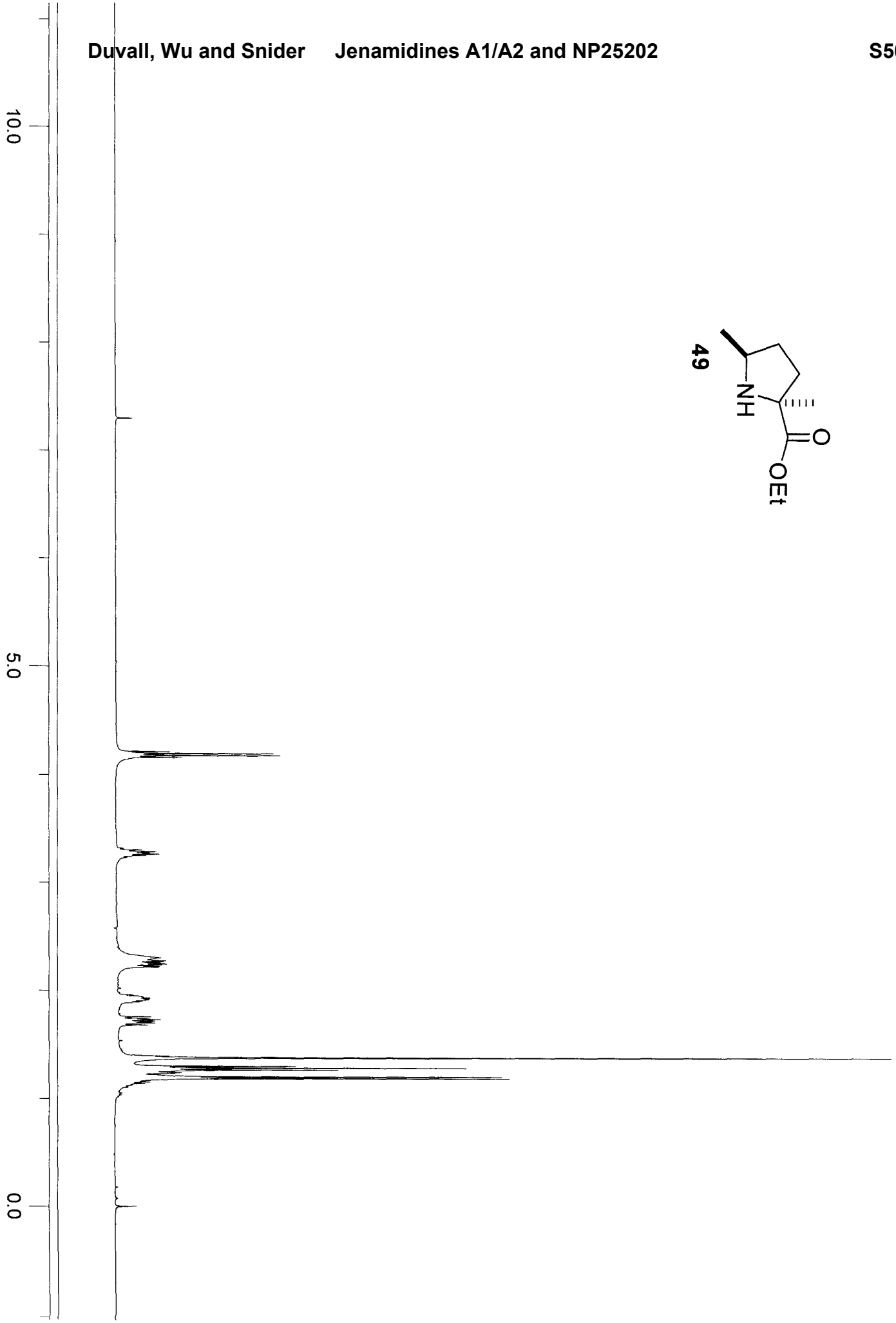
55
OEt


ppm (t1)
200
150
100
50
0
55
OEt
170.366
145.243
78.608
77.318
77.000
76.682
61.985
30.351
30.294
20.902
13.898
13.003

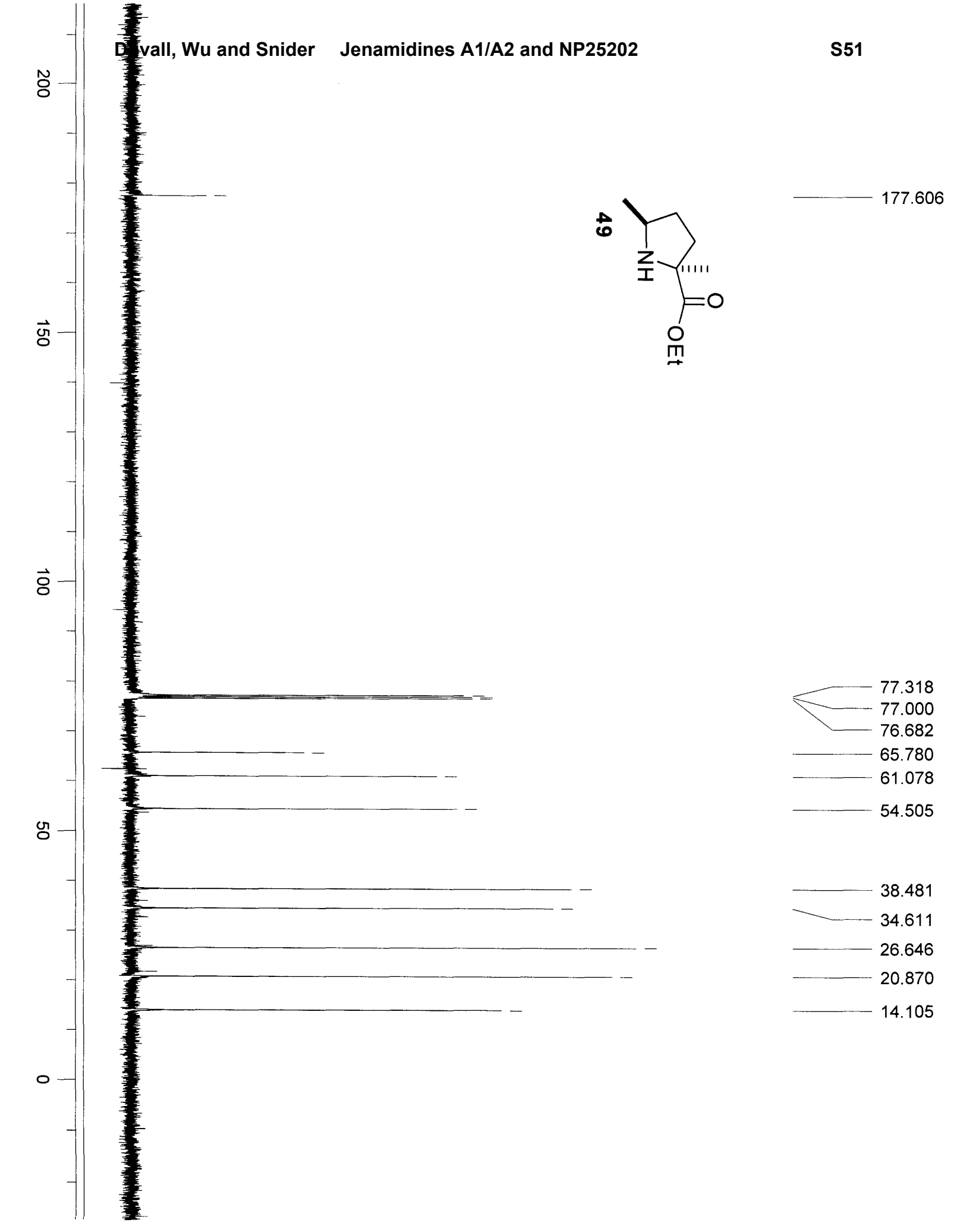


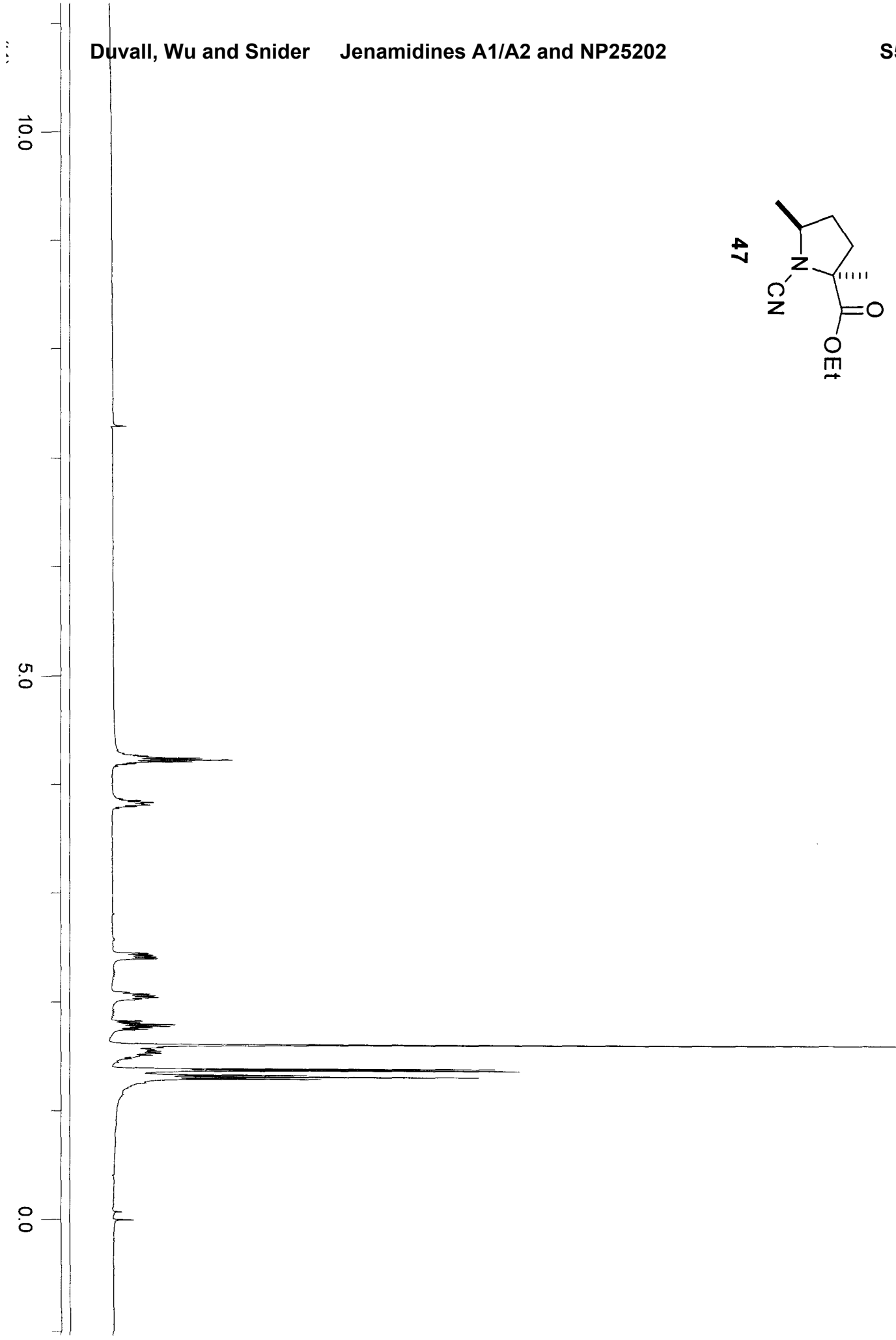
53


200
150
100
50
0
53
NOH
O
OEt
175.522
77.318
77.000
76.682
69.628
60.833
58.185
31.155
25.996
18.953
16.616
14.174

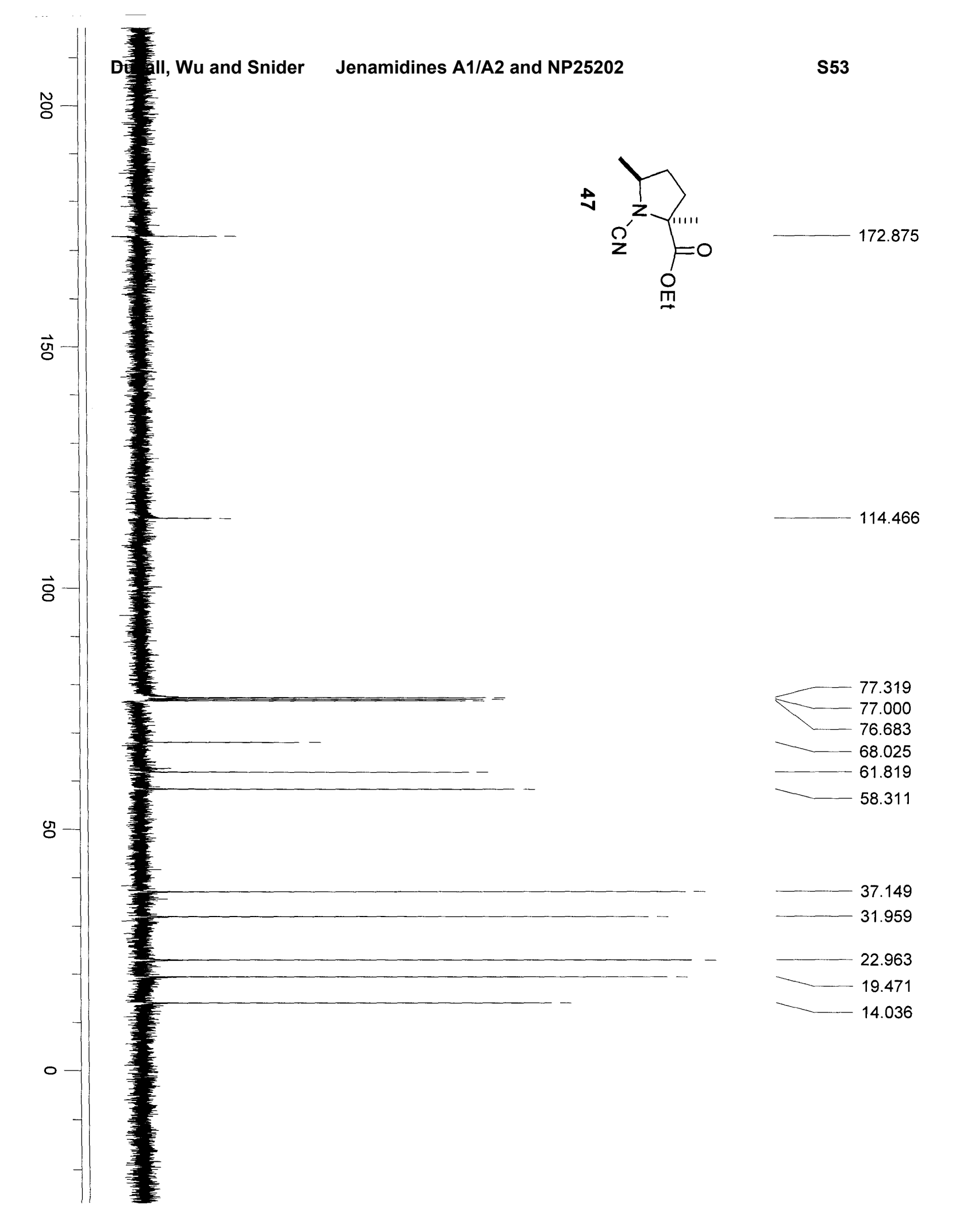

10.0
5.0
0.0

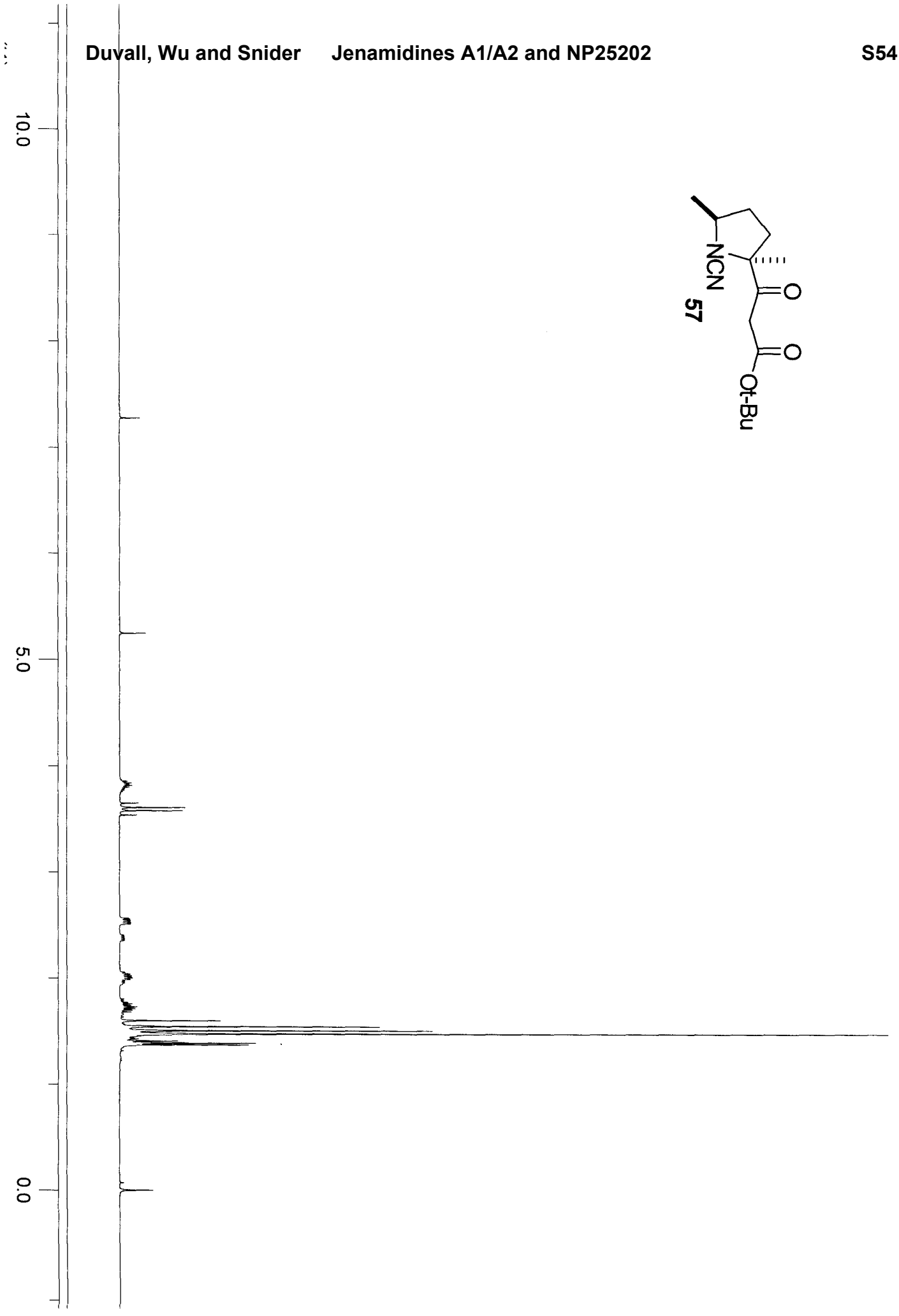
49
NH
O
OEt

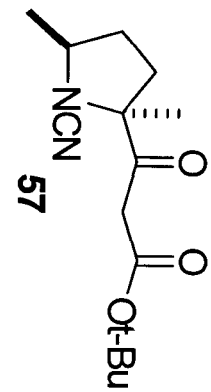

200
150
100
50
0
49
NH
O
OEt
177.606
77.318
77.000
76.682
65.780
61.078
54.505
38.481
34.611
26.646
20.870
14.105



47

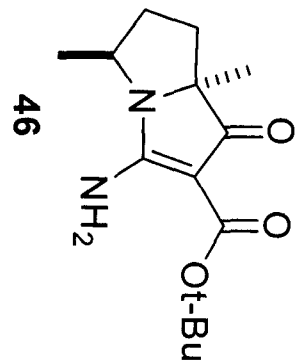

47
N
CN
O
OEt
172.875
114.466
77.319
77.000
76.683
68.025
61.819
58.311
37.149
31.959
22.963
19.471
14.036
200
150
100
50
0


10.0
5.0
0.0
NCN
57
O
O
Ot-Bu

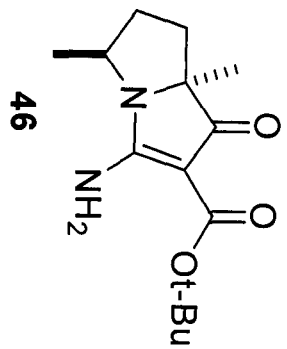


57

203.118
177.067
172.592
165.975
114.671
114.587
89.653
82.153
81.522
77.318
77.000
76.682
73.368
67.400
59.804
58.880
45.300
37.224
35.768
31.798
31.592
28.143
27.856
23.669
21.896
19.452
19.413



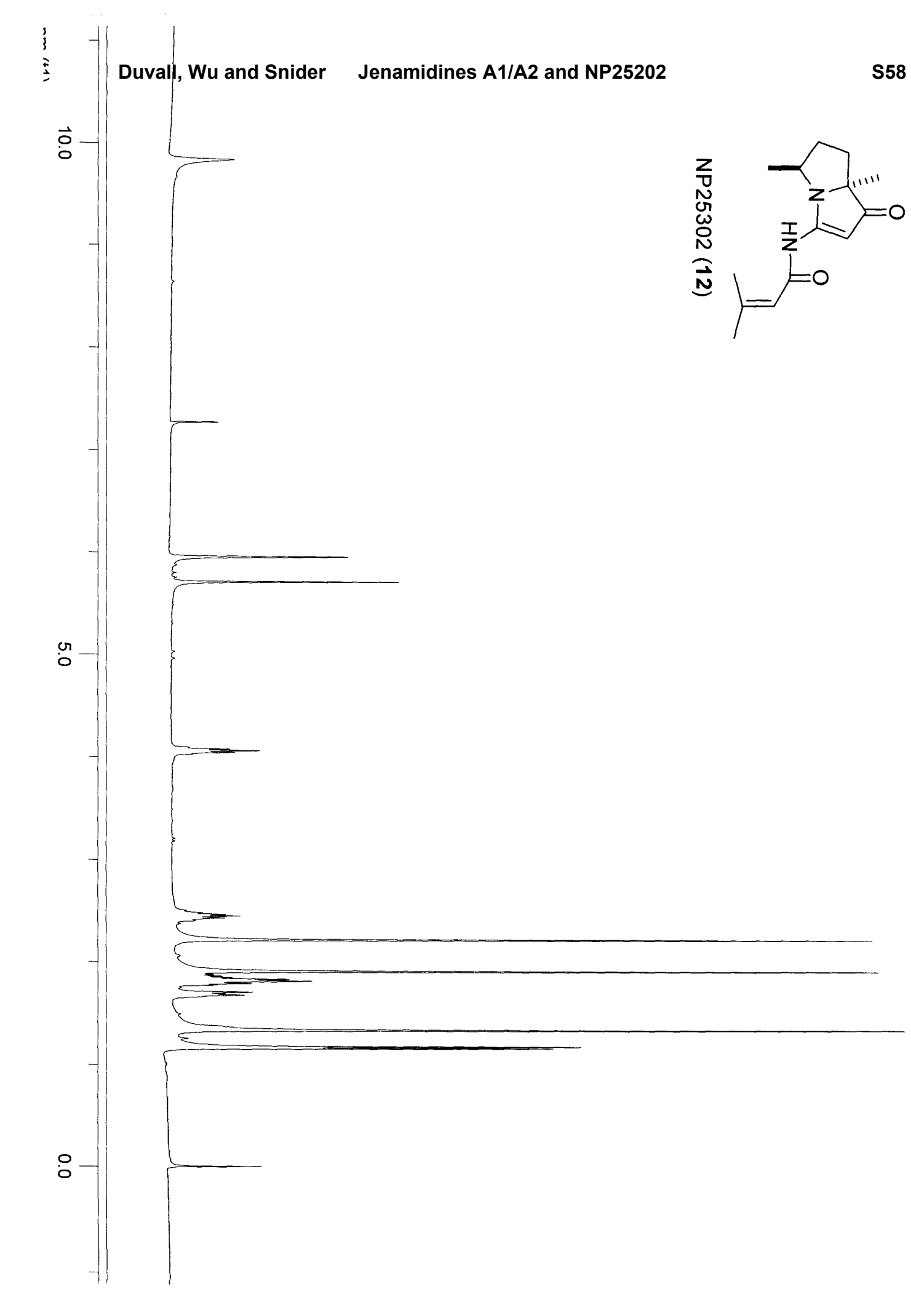
46

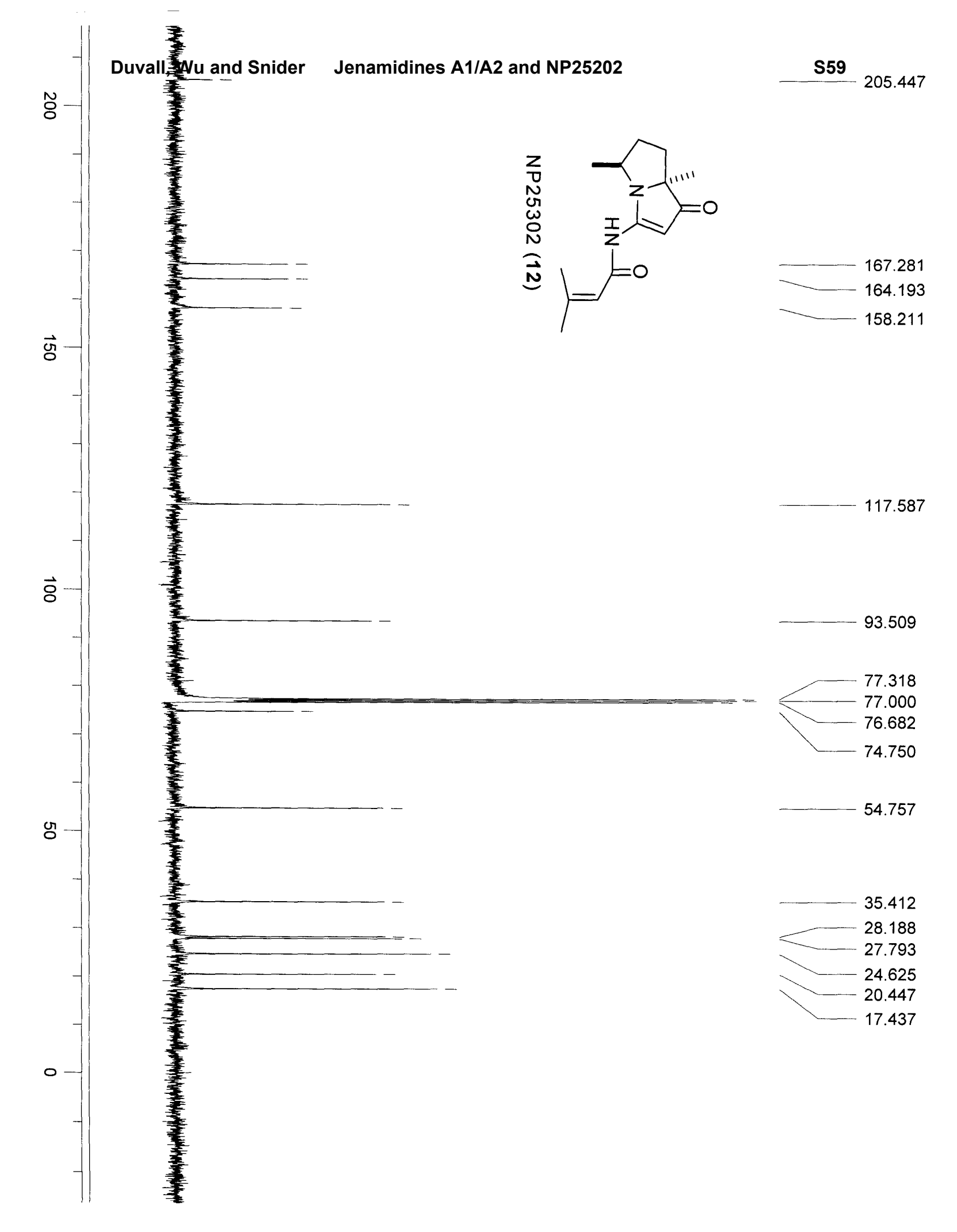


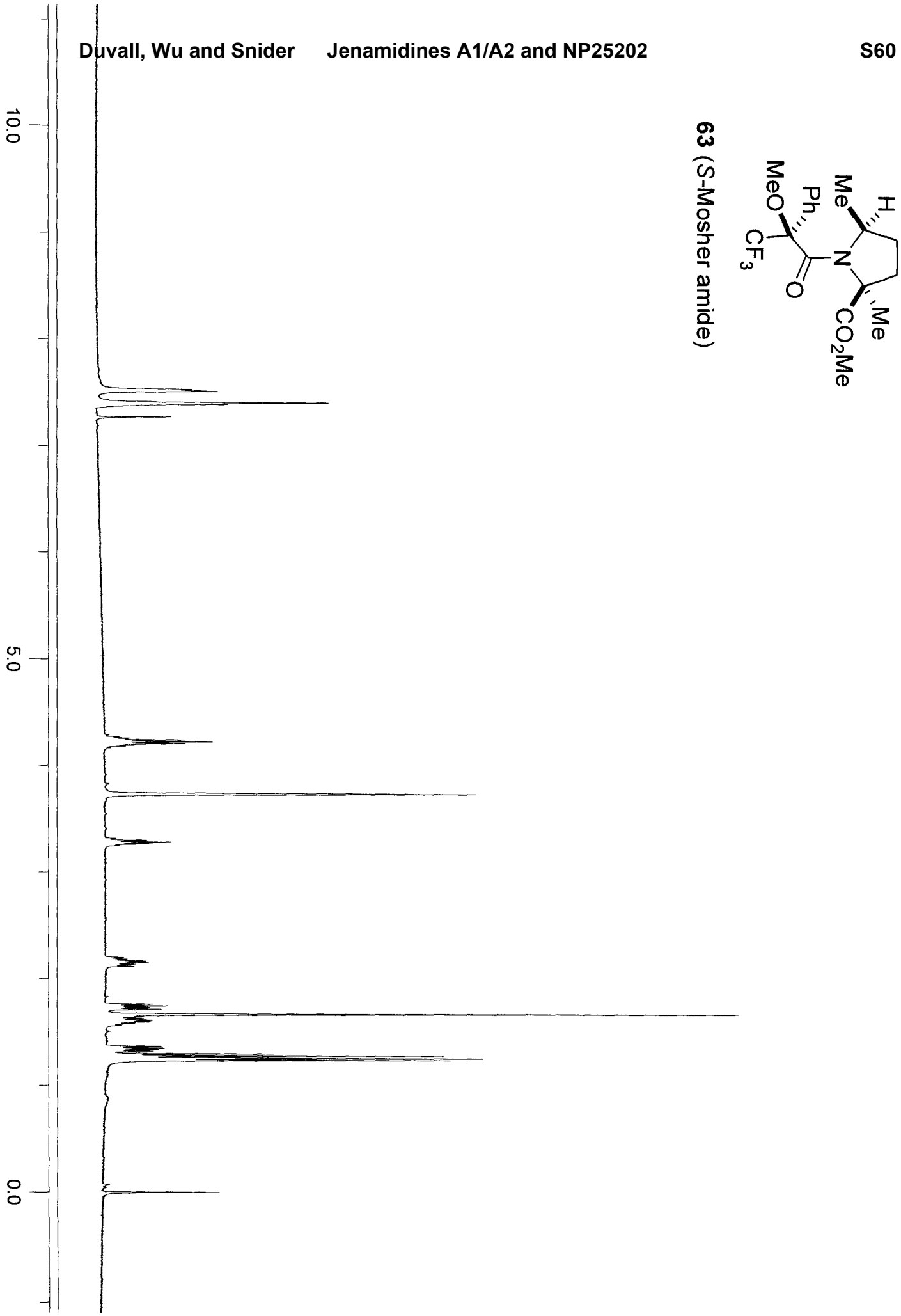
46

195.805
170.621
166.152
90.675
79.921
77.318
77.000
76.682
75.291
53.862
35.324
29.210
28.526
24.442
17.250

200
150
100
50
0

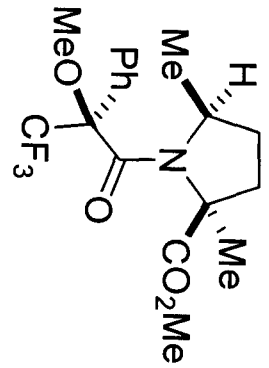

10.0
5.0
0.0
NP25302 (12)
N
HN
O
O

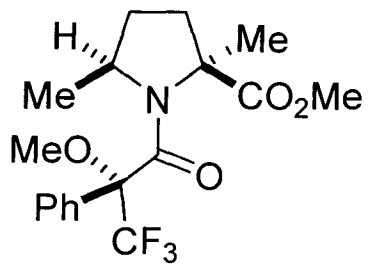

205.447
167.281
164.193
158.211
117.587
93.509
77.318
77.000
76.682
74.750
54.757
35.412
28.188
27.793
24.625
20.447
17.437
200
150
100
50
0
NP25302 (12)
N
HN
O
O



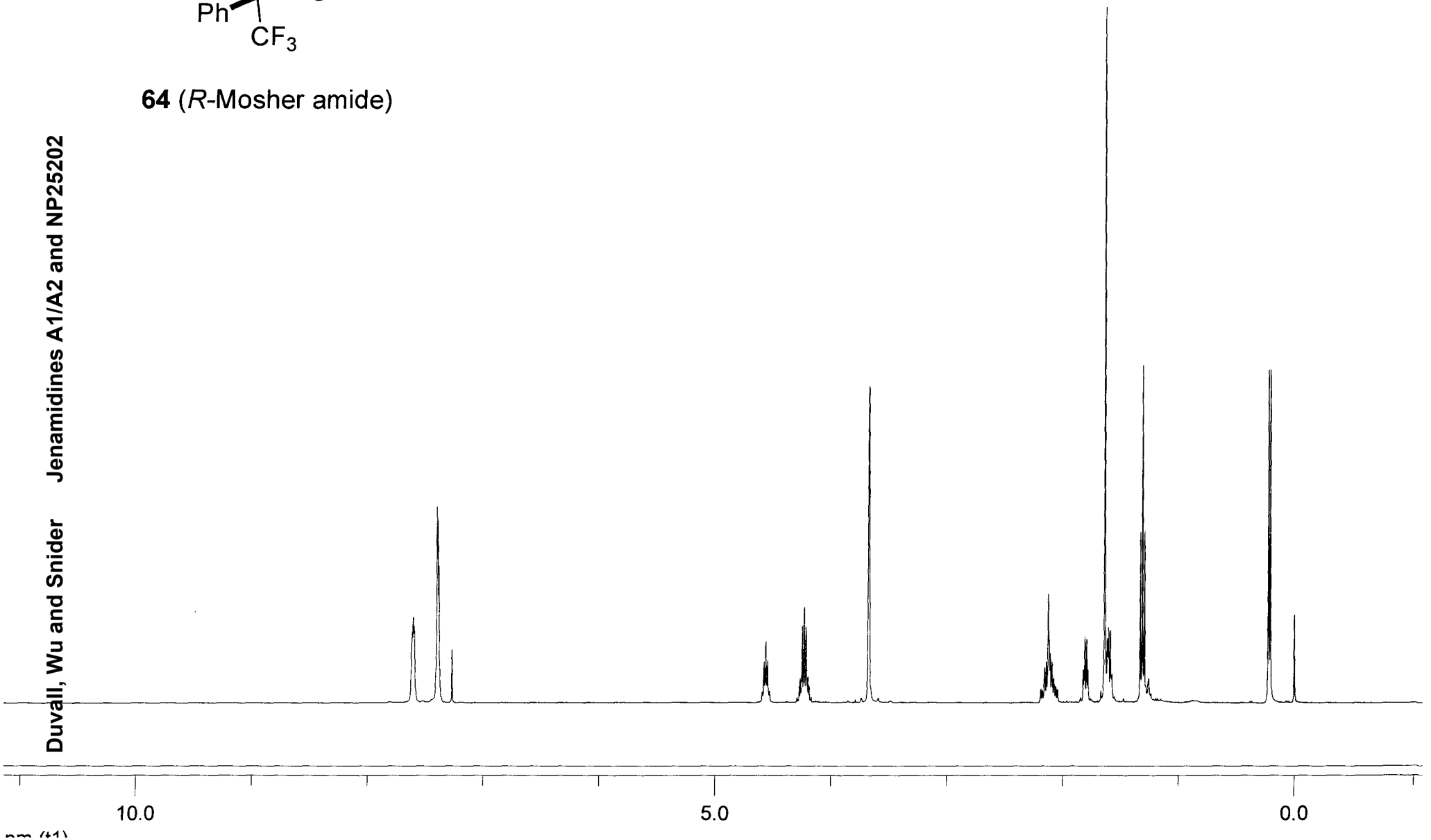
63 (S-Mosher amide)

63 (S-Mosher amide)

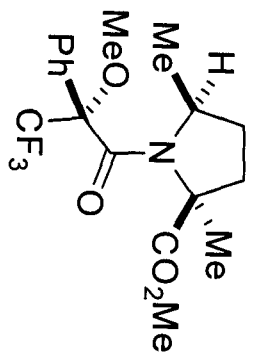


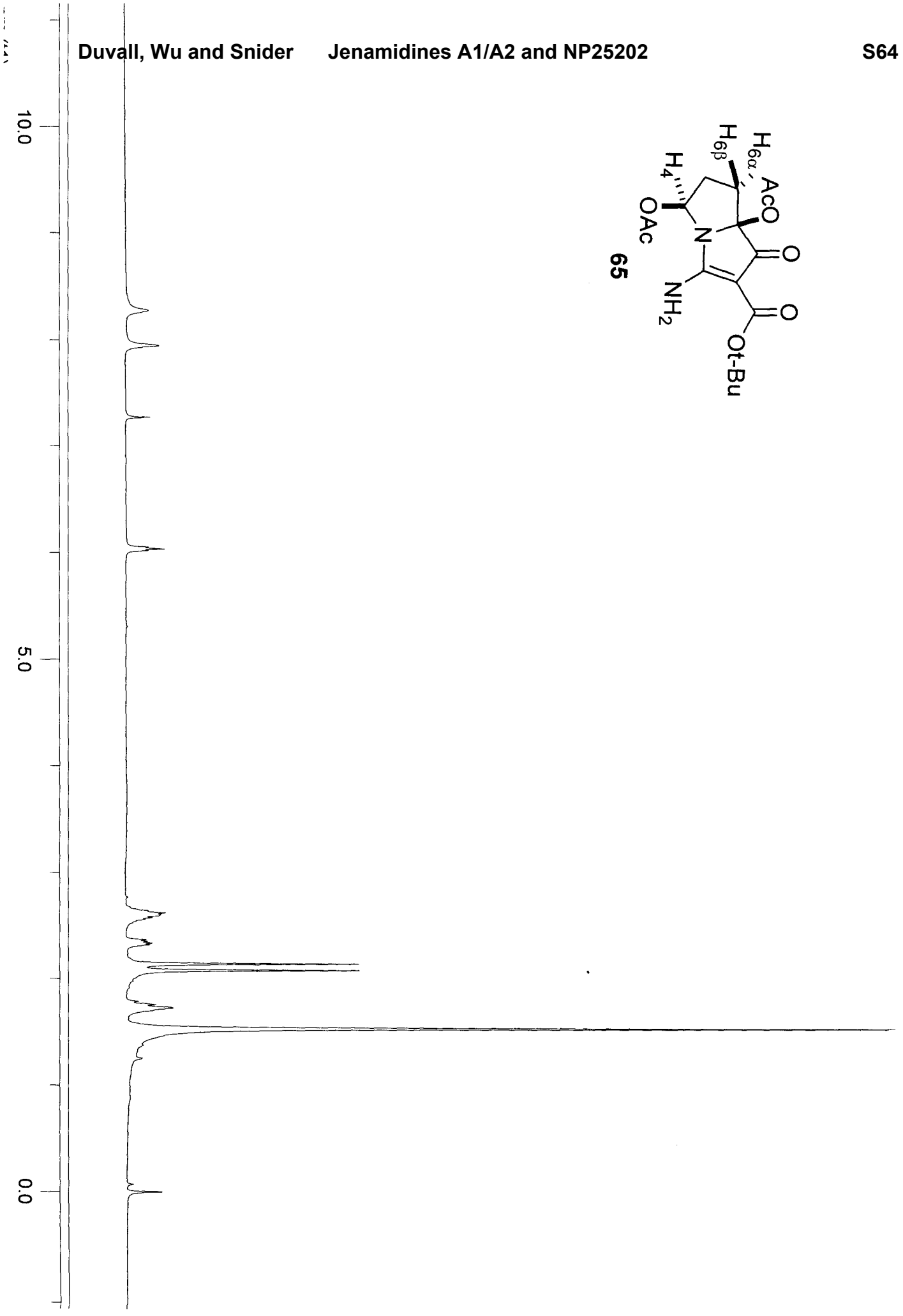


64 (*R*-Mosher amide)

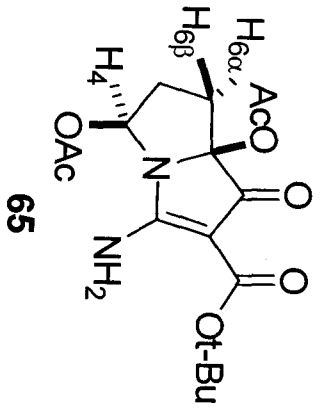


64 (*R*-Mosher amide)





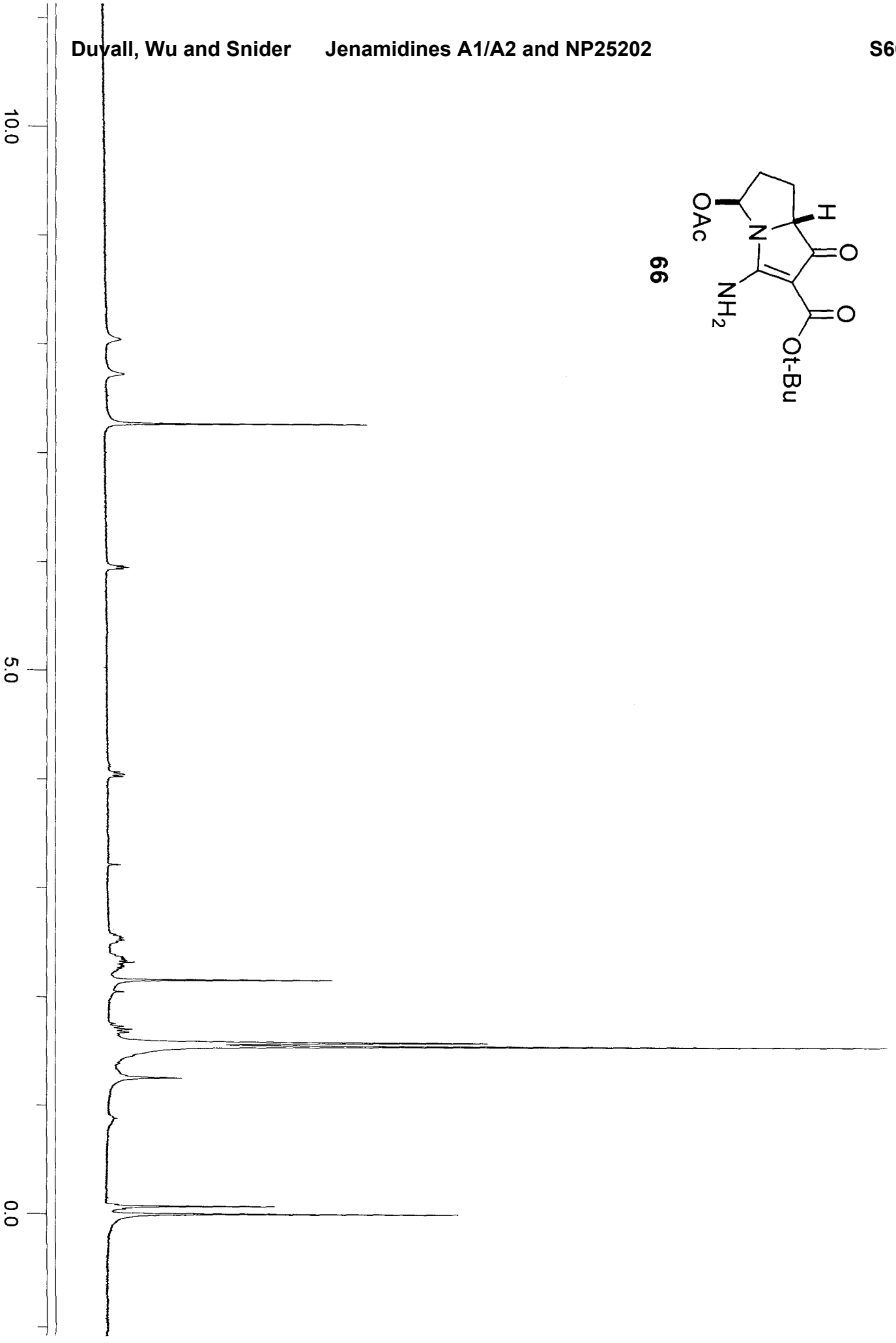
65



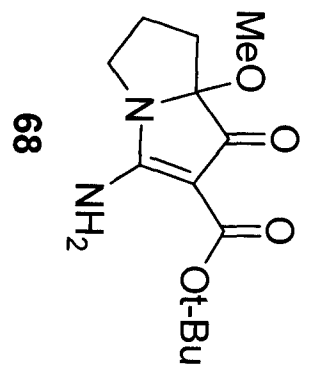
65

184.982
173.176
171.282
168.247
165.201
97.613
88.185
84.202
80.430
77.318
77.000
76.682
32.162
31.868
28.427
21.262
20.972

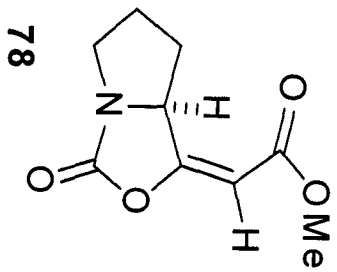
200
150
100
50
0



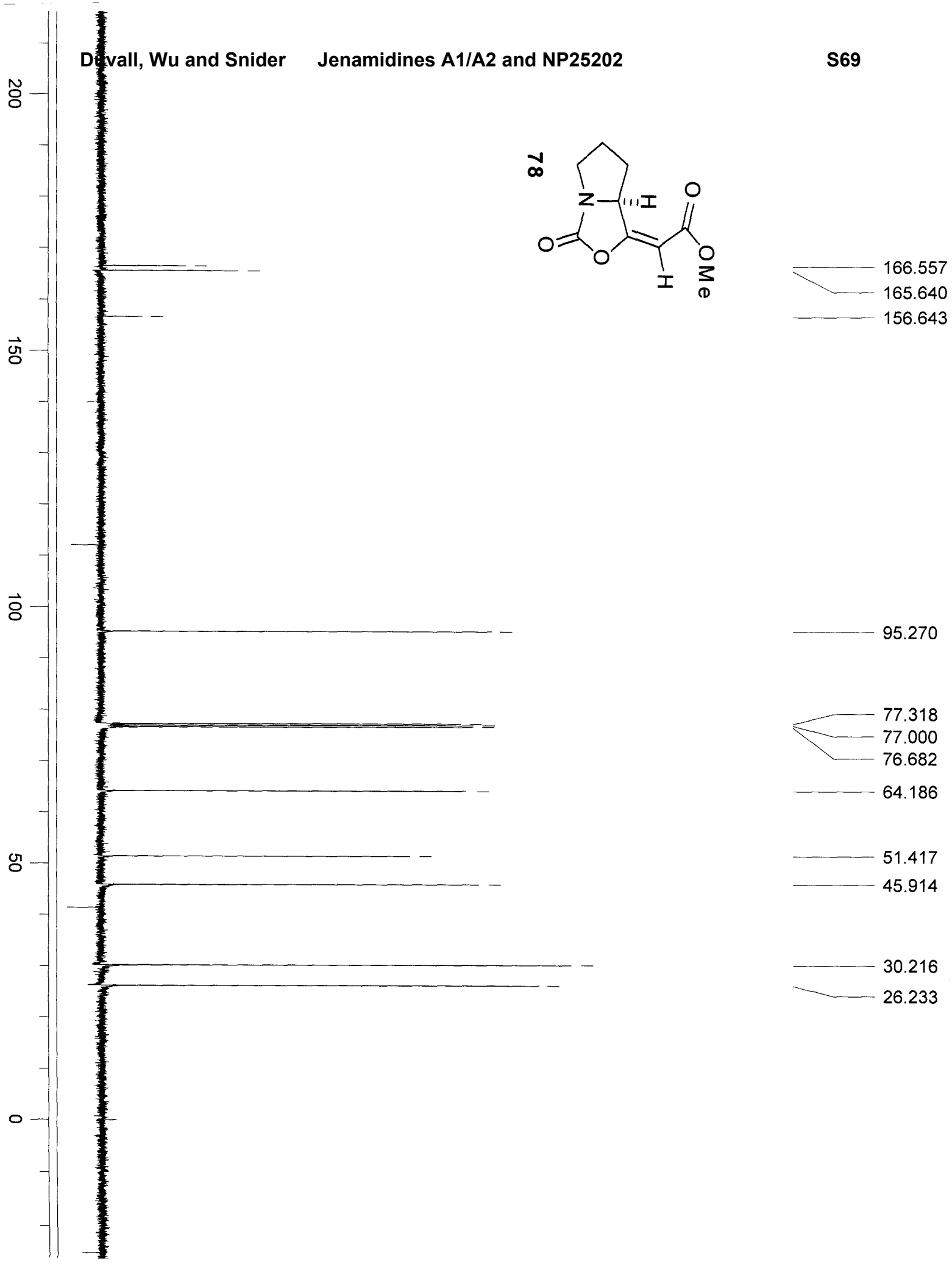
66

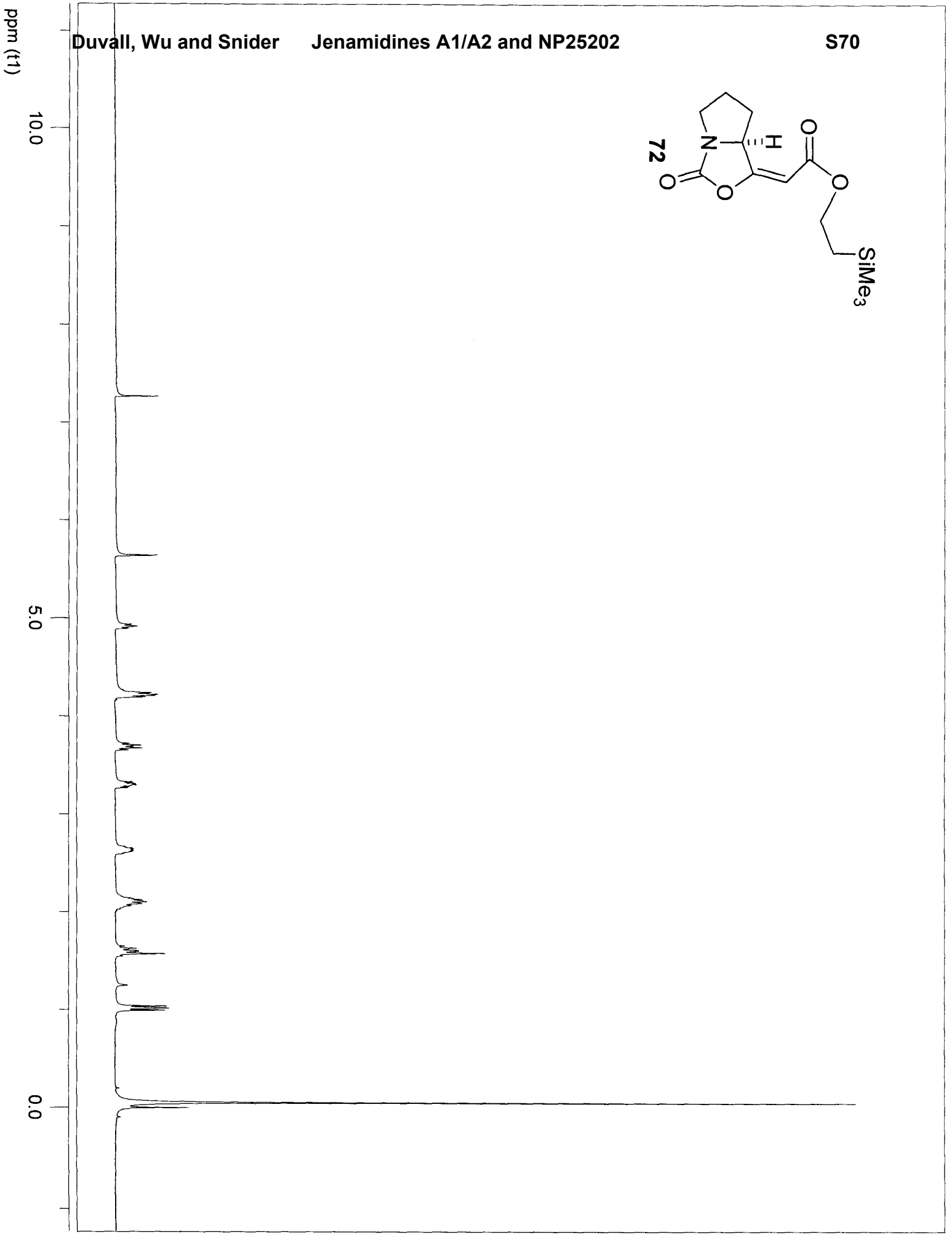


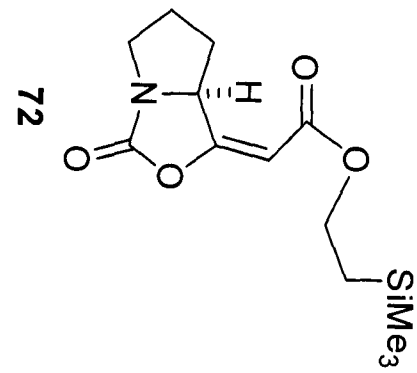
68


78
N
H
O
O
O
OMe
H

ppm (t1)
10.0
5.0
0.0


78
N
H
O
O
O
OMe
H
166.557
165.640
156.643
95.270
77.318
77.000
76.682
64.186
51.417
45.914
30.216
26.233
200
150
100
50
0


ppm (t1)
10.0
5.0
0.0
72
N
H
O
O
O
O
O
SiMe3



200
150
100
50
0

166.352
165.291
156.781
95.889
77.318
77.000
76.683
64.192
62.609
45.948
30.319
26.252
17.337
-1.513