Catalytic Asymmetric Propionate Aldol Reactions via Acyl Halide-Aldehyde Cyclocondensations

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Supporting Information

General Information: Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature and are reported as follows: $[\alpha]_\lambda$ (*c* g/100mL). Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. ^{1}H NMR spectra were recorded on Bruker Avance-300 (300 MHz) or DMX-500 (500 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (C**H**Cl_3: δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), integration. ^{13}C NMR spectra were recorded on a Bruker Avance-300 (75 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm). Mass spectra were obtained on a VG-7070 or Fisons Autospec high resolution magnetic sector mass spectrometer.

Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Flash chromatography was performed as previously described on EM silica gel 60 (230-240 mesh).[1] Alkynyl and aryl lactones were purified by flash chromatography using the following column packing procedure: the silica gel column is packed using 5% water/5% MeOH in ether and then is flushed with the eluting solvent mixture (hexanes/ethyl acetate). Analytical gas liquid chromatography (GLC) was performed on a Hewlet-Packard 5890 Series II gas chromatograph with a flame ionization detector and split mode capillary injection system, using a Chiraldex™ G-TA column (20 m x 0.25 mm) (Advanced Separation Technologies Inc.). Hydrogen was used as the carrier gas at the indicated pressures. Analytical high performance liquid chromatograph (HPLC) was performed on a Hewlett Packard 1100 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp, 190-600 nm), using a Daicel Chiralcel™ OD-H column (250 × 4.6 mm) (Daicel Inc.). HPLC grade isopropanol and hexanes were used as the eluting solvents.

All experiments were carried out under a nitrogen atmosphere in oven or flame-dried glassware using standard inert atmosphere techniques for introducing reagents and solvents. Dichloromethane (CH_2Cl_2) and *N*, *N*-diisopropylethylamine (DIEA) were distilled from CaH_2 under N_2. The catalyst comlex **1** was prepared according to the published procedure.[2] Aldehydes **2a**,**d**, and **g** were purchased from Aldrich Chemical Co. and used as received. Aldehydes **2b**,**c**,**e**,**f**, and **h** were prepared according to the published procedure.[3] All other commercially obtained reagents were used as received.

General procedure for asymmetric AAC reaction using catalyst 1. To a solution of 58 mg of aluminum complex **1** (0.10 mmol) in 5 mL of CH_2Cl_2 at –50 °C was added 280 μL of di(isopropyl)ethylamine (1.6 mmol), 140 μL of propionyl bromide (1.5 mmol), and aldehyde (1.0 mmol) in succession via syringe. The reaction was stirred until complete as monitored by TLC (~2-72 h; typically 30 h). The reaction mixture was poured into saturated aqueous NH_4Cl and extracted with ethyl acetate. The organic portions were dried (Na_2SO_4) and concentrated, and the crude product mixture was purified by flash chromatography (hexanes:ethyl acetate) or by bulb-to-bulb distillation. Lactones **3b-h** and **5** were purified by flash chromatography using the following column packing procedure: the silica gel column is packed using 5% water/5% MeOH in ether and then is flushed with the eluting solvent mixture (hexanes/ethyl acetate).

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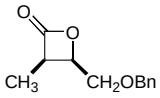
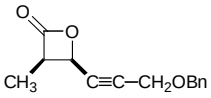
1 Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

2 Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742-9743.

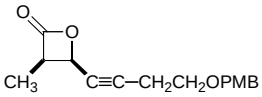
3 Journet, M.; Cai, D.; DiMichele, L. M.; Larsen, R. D. *Tetrahedron Lett.* **1998**, *39*, 6427-6428.



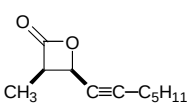
3-(*R*)-Methyl-4-(*R*)-(Benzyloxylmethyl)oxetan-2-one (3a): The General Procedure was followed employing 150 μL of benzyloxylacetaldehyde (1.0 mmol) and the reaction was stirred 48 h at –30 °C. Purification by flash chromatography (20% of ethyl acetate in hexane) gave 160 mg (78%) of the title compound. $[\alpha]_D$ -21.0^0 (*c* 2.3, $CHCl_3$). IR (thin film): 3075, 1824, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.28-39 (m, 5H), 4.71 (dt, J =6.6, 5.5 Hz, 1 H), 4.60-4.62 (d, J = 6.0Hz, 2 H), 3.85-3.86 (dq, J = 7.5, 6.0 Hz, 1 H), 3.77-3.79 (d, J= 6.0 Hz, 2 H), 1.40-1.42 (d, J = 4.5 Hz, CH_3 of the diastereomer 0.065 H), 1.31-1.32 (d, J = 7.5Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 137.4, 128.6(2C), 128.1, 127.9(2C), 73.8, 73.1, 68.1, 47.4, 8.2. HRMS *m/z* calcd for $C_{12}H_{14}O_3$: 190.0994; found 190.0983. Separation of the enantiomers by chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 10 % *i*-PrOH, 90 % hexane, T_r: 10.0 min (*R, S*), 12,2 min (*S, R*), 13.2 min (*R, R*), 31.4 min (*S, S*)] provided the enantiomer ratio and diastereomer ratios: (*R, R*):(*S, S*) = 97:3 (94% ee), *cis*:*trans* = 88:12 (76% de).



3-(*R*)-Methyl-4-(*R*)-(3-benzyloxylpropynyl)oxetan-2-one (3b): The General Procedure was followed employing 174 mg of 4-benzyloxyl-2-butynal (1.0 mmol) and the reaction was stirred 30 h at –50 °C. Purification by flash chromatography (20% ethyl acetate in hexanes) gave 196 mg (85%) of the title compound. $[\alpha]_D$ -7.50^0 (*c* 2.6, $CHCl_3$). IR (thin film): 3075, 2242, 1832, 1100 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.28-39 (m, 5H), 5.21-5.24 (dt, J =6.0, 2.0 Hz, 1 H), 4.62 (s, 2 H), 4.28-4.29 (d, J = 2.0 Hz, 2 H), 3.90-3.95 (dq, J= 7.5, 6.0 Hz, 1 H), 1.450-1.475(d, J = 7.5Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 137.1, 128.7(2C), 128.2(2C), 88.8, 78.9, 72.0, 64.6, 57.3, 50.0, 10.7.). HRMS
m/z calcd for $C_{14}H_{14}O_3$: 230.0943; found 230.0934. Separation of the enantiomers by chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 10 % *i*-PrOH, 90 % hexane, T_r: 11.6 min (*S, R*), 13.2 min (*R, R*), 17.8 min (*S, S*), 18.1 min (*R, S*)] provided the enantiomer and diastereomer ratios: (*R, R*):(*S, S*) = 97:3 (94 % ee), *cis*:*trans* = 90:10 (80% de).



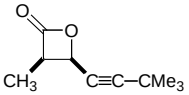
3-(*R*)-Methyl-4-(*R*)-[4-(*p*-methoxybenzyloxy)butynyl]oxetan-2-one (3c): The General Procedure was followed employing 218 mg of 5-[(*p*-methoxy)benzyloxyl]-2-pentynal (1.0 mmol) and the reaction was stirred 30 h at –50 °C. Purification by flash chromatography (20% ethyl acetate in hexane) gave 235 mg (86%) of the title compound. $[\alpha]_D$ -8.75^0 (*c* 2.4, $CHCl_3$). IR (thin film): 3075, 2245, 1832, 1100 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.25-7.27 (d, J = 6.5HZ, 2H), 6.88-6.90 (d, J = 6.5HZ, 2H), 5.13-5.17 (dt, J =6.0, 2.0 Hz, 1 H), 4.49 (s, 2 H), 3.80-3.87 (dq, J= 7.5, 6.0 Hz, 1 H), 3.82 (s, 3 H), 3.57-3.62 (t, J = 6.5 Hz, 2 H), 2.58-2.63 (td, J = 6.5, 2.0 Hz, 2 H), 1.395-1.410(d, J = 7.5Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 159.5, 130.1, 129.6(2C), 114.0(2C), 90.1, 73.8, 73.0, 67.7, 65.2, 55.5, 49.8, 20.6, 10.7). MS (EI, 70 eV): *m/z* 274(M^+), 241 (M^+-CH_3OH, H), 230 (M^+-CO_2), 121 ($[ArCH_2]$)$^+$. HRMS *m/z* calcd for $C_{16}H_{18}O_4$: 274.1205; found 274.1207. Separation of the stereoisomers by chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 10 % *i*-PrOH, 90 % hexane, T_r: 13.8 min (*R, R*), 16.8 min (*S, S*), 17.2 min (*S, R*), 20.2 min (*R, S*)] provided the enantiomer and diastereomer ratios: (*R, R*):(*S, S*) = 95:5 (90 % ee), *cis*:*trans* = 87.5:12.5 (75% de).



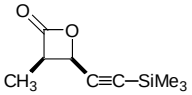
3-(*R*)-Methyl-4-(*R*)-(heptynyl)oxetan-2-one (3d): The General Procedure was followed employing 124 mg of octynal (1.0 mmol) and the reaction was stirred 30 h at –50 °C. Purification by flash chromatography (5% ethyl acetate in hexane) gave 152 mg (85%) of the title compound. $[\alpha]_D$ -3.8^0 (*c* 2.5, $CHCl_3$). IR (thin film): 2935, 2244, 1835, 1102 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.14-5.17 (dt, J =6.0, 2.0 Hz, 1 H), 3.81-3.86 (dq, J= 7.5, 6.0 Hz, 1 H), 2.27-2.33 (td, J = 6.5, 2.0 Hz, 2 H), 1.50-1.58 (m, 2H), 1.40-1.43 (d, J = 7.5 Hz, 3 H), 1.26-1.39 (m, 4 H), 0.86-0.93 (t, J = 7.5 Hz). ^{13}C

NMR (75 MHz, $CDCl_3$): δ 171.8, 94.2, 72.7, 65.3, 49.7, 31.1, 28.1, 22.3, 18.9, 14.1, 10.6). HRMS m/z calcd for $C_{11}H_{16}O_2$: 180.1150; found 180.1146.

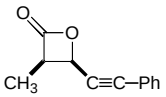
To assay stereoisomeric purity, lactone **3d** was converted to *N*-benzyl-2-(*R*)-methyl-3-(*R*)-hydroxy-4-decynamide. To a solution of lactone **3d** in THF was added benzyalamine at ambient temperature. The reaction was stirred 16 h at ambient temperature and the volatles were evaporated in vacuo to afford the title benzyl amide as a colorless glass. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.36 (m, 5 H), 6.35 (s, 1 H), 4.63-4.66 (dt,
J =3.5, 2.0 Hz, 1 H), 4.47-4.49 (d, J = 6.0 Hz, 2 H), 3.30-3.50 (br, 1 H), 2.58-2.62 (dq, J= 7.5, 3.5 Hz, 1 H), 2.15-2.20 (td, J = 6.5, 2.0 Hz, 2 H), 1.44-1.50 (m, 2H), 1.30-1.33 (d, J = 7.5 Hz, 3 H), 1.17-1.36 (m, 4 H), 0.87-0.92 (t, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8, 138.3, 128.7(2C), 127.8, 127.5(2C), 86.7, 78.6, 64.2, 45.7, 43.4, 31.1, 29.7, 28.4, 22.2, 18.7, 14.1, 12.7). MS (EI, 70 eV): *m/z* 287 (M^+), 270,163, 106, 91. Separation of the stereoisomers by chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 8 % *i*-PrOH, 92 % hexane, T_r: 8.53 min (*R, R*), 12.8 min (*S, S*), 14.5 min (*S, R*)] provided the enantiomer and diastereomer ratios: (*R, R*):(*S, S*) = 96:4 (93 % ee), *cis*:*trans* = 97.5:2.5 (95% de).



3-(*R*)-Methyl-4-(*R*)-(3,3-dimethyl-butynyl)oxetan-2-one (3e): The General Procedure was followed employing 110 mg of 4,4-dimethyl-pentynal (1.0 mmol) and the reaction was stirred 20 h at –50 °C. Purification by flash chromatography (5% of ethyl acetate in hexane) gave 150 mg (90%) of the title compound. $[\alpha]_D$ -11.3^0 (*c* 2.7, $CHCl_3$). IR (thin film): 2972, 2243, 1836, 1140, 1092 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.14-5.16 (d, J =6.0 Hz, 1 H), 3.81-3.86 (dq, J= 7.5, 6.0 Hz, 1 H), 1.39-1.42 (d, J = 7.5 Hz, 3 H), 1.26 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 101.9, 71.3, 65.2, 49.6, 30.7, 10.4. MS (EI, 70 eV):*m/z* 122 (M^+-CO_2), 107 (M^+-CO_2, CH_3). HRMS *m/z* calcd for C_9H_{14} (M^+-CO_2): 122.1096; found 122.1092. Separation of the stereoisomers by chiral GC [Chiraldex™ G-TA column, 20 m x 0.25 mm, flow rate 0.5 mL/min, method: 100 °C for 10min, ramp @ 5.0 °C/min to 130 °C for 12.0 min, ramp @ 10.0 °C/min to 160 °C for 15.0 min, T_r: 15.6 min (*S, R*), 20.5 min (*R, R*), 22.0 min (*S, S*),] provided the enantiomer and diastereomer ratios: (*R, R*):(*S, S*) = 95:5 (90 % ee), *cis*:*trans* = >99:1 (>98% de).

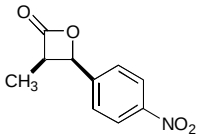


3-(*R*)-Methyl-4-(*R*)-(trimethylsilylethynyl)oxetan-2-one (3f): The General Procedure was followed employing 128 mg of trimethylsilylpropynal (1.0 mmol), 290 mg of catalyst **1** (0.05 mmol, 5 mol%), 200 μL of Hunig's base (1.2 mmol, 1.2 eq.), and 100 μL of propionylbromide (1.1 mmol, 1.1 eq.) in 5.0 mL of CH_2Cl_2 and the reaction was stirred for 2 h at –78 °C. Purification by bulb-to-bulb distillation gave 168 mg (90%) of the title compound. $[\alpha]_D$ -11.9^0 (*c* 2.6, $CHCl_3$). IR (thin film): 2963, 2174, 1838, 1252, 1140, 1083 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.12-5.14 (d, J =6.0 Hz, 1 H), 3.84-3.89 (dq, J= 7.5, 6.0 Hz, 1 H), 1.42-1.45 (d, J = 7.5 Hz, 3 H), 0.22 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 98.6, 97.0, 64.7, 49.8, 8.7, -0.35). MS (EI, 70 eV): *m/z* 167 (M^+-CH_3), 138 (M^+-CO_2), 123 (M^+-$SiMe_3$, H). HRMS *m/z* calcd for $C_8H_{11}O_2Si$ (M^+-CH_3): 167.0528; found 167.0533. Separation of the stereoisomers by chiral GC [Chiraldex™ G-TA column, 20 m x 0.25 mm, flow rate 0.5 mL/min, method: 100 °C for 10min, ramp @ 5.0 °C/min to 130 °C for 12.0 min, ramp @ 10.0 °C/min to 160 °C for 15.0 min, T_r: 11.2 min (*S, R*), 11.7 min (*R, R*), 11.9 min (*S, S*),] provided the enantiomer and diastereomer ratios: (*R, R*):(*S, S*) = 96.5:3.5 (93 % ee), *cis*:*trans* = >99:1 (>98% de).

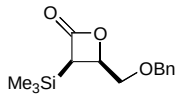


3-(*R*)-Methyl-4-(*R*)-(2-phenylethynyl)oxetan-2-one (3g): The General Procedure was followed employing 130 mg of 3-Phenylpropynal (1.0 mmol) and the reaction was stirred 12 h at –50 °C. Purification by flash chromatography (10% ethylacetate in hexane) gave 155 mg (83%) of the title compound. $[\alpha]_D$ –37.5° (*c* 2.4, $CHCl_3$). IR (thin film): 2232, 2200, 1836, 1490, 1140, 758 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.51 (m, 5 H), 5.38-5.40 (d, J =6.0 Hz, 1 H), 3.93-4.00 (dq, J= 6.0, 7.5 Hz, 1 H), 1.51-1.54 (d, J = 7.5 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 132.1, 129.6, 128.6, 92.2,

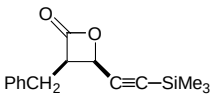
81.2, 65.2, 50.3, 10.7. MS (EI, 70 eV): *m/z* 186 (M^+). HRMS *m/z* calcd for $C_{12}H_{10}O_2$: 186.0680; found 186.0675. Separation of the stereoisomers by chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 5 % *i*-PrOH, 95 % hexane, T_r: 9.7 min (*R, R*), 16.9 min (*S, S*), minor diastereomers not detected] provided the enantiomer and diastereomer ratios: (*R, R*):(*S, S*) = 95.5:4.5 (91 % ee), *cis*:*trans* = >99:1 (>98% de).



3-(*R*)-Methyl-4-(*R*)-(4´-nitrophenyl)oxetan-2-one (3h): The General Procedure was followed employing 151 mg of 4-nitrobenzaldehyde (1.0 mmol) and the reaction was stirred 20 h at –30 °C. Purification by flash chromatography (20% of ethyl acetate in hexane) gave 186 mg (90%) of the title compound (99% ee and 99% de, determined by HPLC and ^{1}H NMR of the purified product). $[\alpha]_D$ –129° (*c* 1.3, $CHCl_3$). IR (thin film): cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28-31 (d, J = 7.5 Hz, 2 H), 7.50-7.525 (d, J = 7.5 Hz, 2 H), 5.74-5.77 (d, J = 6.0Hz, 1 H), 4.14-4.24 (dq, J = 7.5, 6.0 Hz, 1 H), 0.93-0.95 (d, J = 7.5 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 148.2, 142.2, 126.8(2C), 124.1(2C), 74.2, 50.9, 9.9. MS (EI, 70 eV): *m/z* 287 (M^+). HRMS *m/z* calcd for $C_{18}H_{25}NO_2$: 287.1885; found 287.1894. Separation of the stereoisomers by chiral GC [Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 15 % *i*-PrOH, 85 % hexane, T_r: 12.8 min (*R, R*), 15.5 min (*S, S*), other diastereomers could not be detected] provided the enantiomer and diastereomer ratios: (*R, R*):(*S, S*) = 99.5:0.5 (99 % ee), *cis:trans* >99:1 (>98% de).

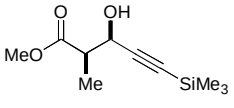


3-(*S*)-Trimethylsilyl-4-(*R*)-(benzyloxylmethyl)oxetan-2-one (4): To a –40 °C solution of 58 mg of catalyst **1** (0.10 mmol, 10 mol%) in 5 mL of CH_2Cl_2 was added 150 μL of benzyloxylacetaldehyde (1.0 mmol, 1.0 eq.) and 130 mg of trimethysilylketene (1.1 mmol, 1.1eq.) and the reaction was for 12 hrs. The solvent was evaporated in vacuo and the crude reaction mixture was subjected to flash chromatography (5% of ethylacetate in hexane) to afford 238 mg (90%) of the title compound (86% ee and 92%). $[\alpha]_D$ –5.7° (*c* 2.3, $CHCl_3$). IR (thin film): 3031, 2958, 1804 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-39 (m, 5H), 4.74-4.80 (dt, J =6.0, 4.5 Hz, 1 H), 4.59-4.61 (d, J = 6.0Hz, 2 H), 3.77-3.79 (d, J = 5.0 Hz, 2 H), 3.39-3.41 (d, J = 6.0 Hz, 1 H), 0.19 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 137.3, 128.6, 128.2, 73.8, 72.0, 69.8, 45.4, -0.94). MS (EI, 70 eV): *m/z* 264 (M^+), 206, 179, 91. HRMS *m/z* calcd for $C_{14}H_{20}O_3Si$: 264.1182; found 264.1180. Separation of the stereoisomers by chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 5 % *i*-PrOH, 95 % hexane, T_r: 12.0 min (*S, R*), 19.1 min (*R, S*), 26.8 min (*R, R*)] provided the enantiomer and diastereomer ratios: (*S, R*):(*R, S*) = 93:7 (86 % ee), *cis*:*trans* = 96:4 (92% de).

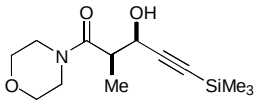


3-(*R*)-Benzyl-4-(*R*)-(trimethylsilylethynyl)oxetan-2-one (5): To a –50 °C solution of 58 mg of catalyst **1** (0.10 mmol, 10 mol%) in 5 mL of CH_2Cl_2 was added 128 mg of trimethylsilylpropynal (1.0 mmol, 1.0 eq.), 280 μL of Hunig's base (1.6 mmol, 1.6 eq.), and 320 mg of 3-phenylpropionylbromide (1.5 mmol, 1.5 eq.) and the reaction was stirred for 30 hrs. Purification by flash chromatography (5% of ethylacetate in hexane) gave 210 mg (86%) of the title compound (93% ee and 99% de, determined by HPLC of the purified product). $[\alpha]_D$ –140° (*c* 2.0, $CHCl_3$). IR (thin film): 3075, 2253, 1835, 1252, 1060 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.35 (m, 5H), 5.16-5.18 (d, J = 6.0 Hz, 1 H), 4.05-4.12 (dt, J = 6.0, 7.5 Hz, 1 H), 3.26-3.30 (dd, J= 7.5, 4.5 Hz, 2 H), 0.24 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$):
δ 169.9, 137.3, 128.9, 128.8, 127.1, 99.5, 97.3, 64.6, 56.3, 31.8, -0.35). MS (EI, 70 eV): *m/z* 258 (M^+). HRMS *m/z* calcd for $C_{15}H_{18}O_2Si$: 258.1076; found 258.1078. Separation of the stereoisomers by chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 5 % *i*-PrOH, 95 % hexane, T_r: 9.0 min (*R, R*), 12.1 min (*S, S*)]

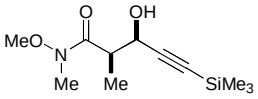
provided the enantiomer and diastereomer ratios: (*R, R*):(*S, S*) = 96.5:3.5 (93 % ee), *cis:trans* >99:1 (>98% de, other diastereomers could not be detected).



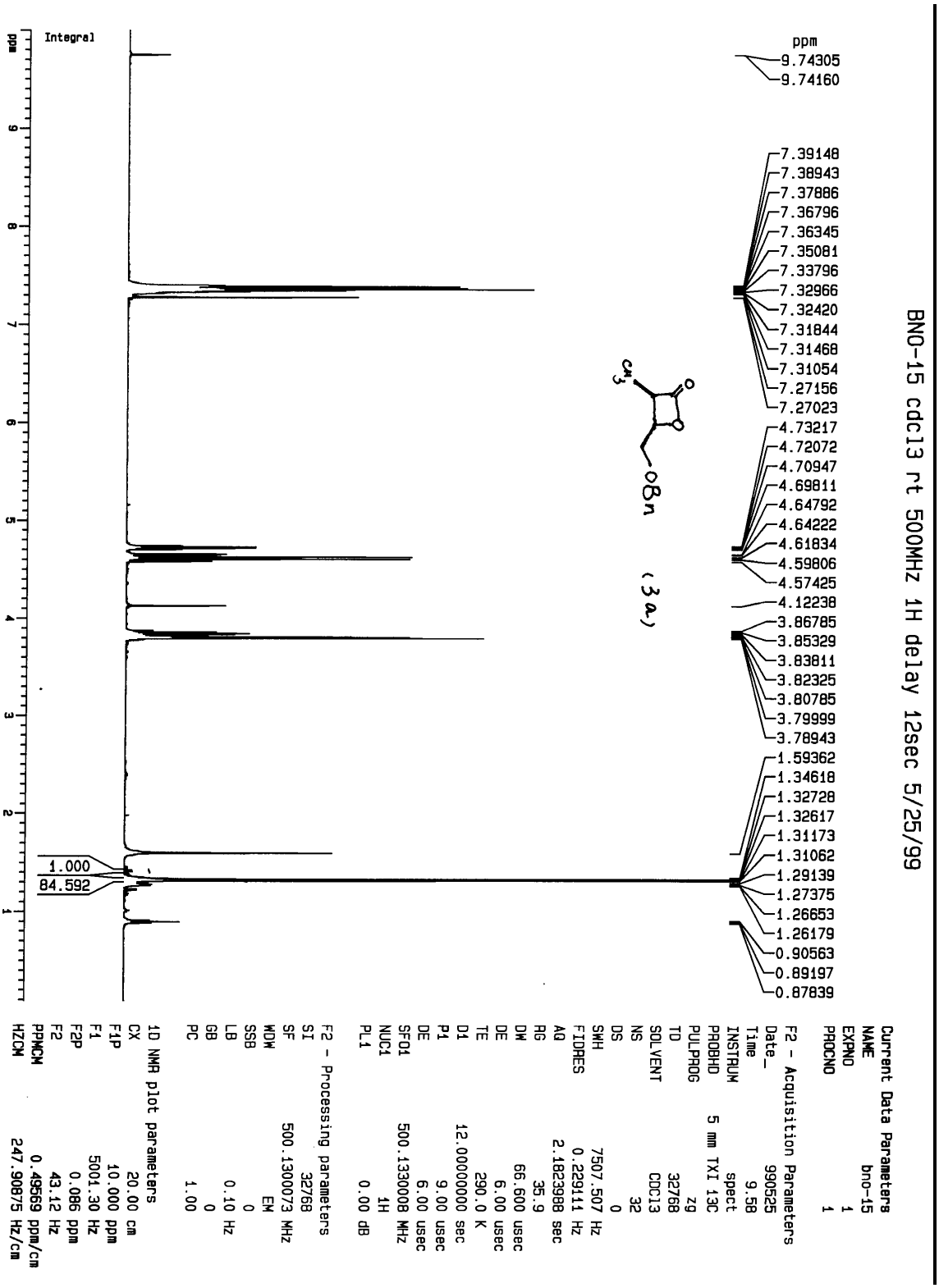
2-(*R*)-Methyl-3-(*R*)-hydroxy-5-trimethylsilyl-4-pentynoic acid, methyl ester (6). At –78 °C, 25mg of Na metal (1.1mmol, 1.1 eq) was dissolved in 2 mL of methanol. A solution of 182 mg of lactone **3f** (1.0mmol) was added and the reaction was stirred 10 min at –78 °C. Saturated aqueous NH_4Cl was added to the reaction mixture and the resulting mixture was allowed to warm to ambient temperature. The reaction mixture was extracted with ether (3 × 15mL) and the combined organic portions were washed with brine and dried ($MgSO_4$). The volatiles were evaporated in vacuo to afford 214 mg the title compound (100%) that did not require further purification. $[\alpha]_D$ +10.7° (*c* 2.3, $CHCl_3$). IR (neat) 3468, 2175, 1740, 1251, 845 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.62-4.63 (d, J =3.0 Hz, 1 H), 3.74 (s, 3 H), 2.95 (b, 1 H), 2.75-2.79 (dq, J= 3.0, 7.5 Hz, 1 H), 1.30-1.325 (d, J = 7.5 Hz, 3 H), 0.17 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6, 103.9, 90.8, 64.2, 52.2, 45.5, 11.9, -0.05. MS (EI, 70 eV): *m/z* 214 (M^+).



Morpholino-2-(*R*)-methyl-3-(*R*)-hydroxy-5-trimethylsilyl-4-pentynamide (7). To a solution of 182 mg of lactone **3f** (1.0mmol) in 1 mL of CH_2Cl_2 was added a solution of 87 mg of morphnine (1.0 mmol, 1.0 equiv) in 1 mL CH_2Cl_2 and the reaction was stirred 2 h at ambient temperature. The volatiles were evaporated in vacuo to afford 269 mg of the title amide (100%) that did not require further purification. $[\alpha]_D$ –5.0° (*c* 2.0, $CHCl_3$). IR (neat) 3400, 2250, 2170, 1621, 1251, 909, 733 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.77-4.78 (d, J =3.0 Hz, 1 H), 4.50 (b, 1 H), 3.50-3.70 (m, 8 H), 2.78-2.83 (dq, J= 3.0, 7.5 Hz, 1 H), 1.33-1.36 (d, J = 7.5 Hz, 3 H), 0.17 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6, 104.6, 89.6, 66.9, 66.8, 63.8, 46.4, 42.0, 40.6, 11.9, -0.03. MS (EI, 70 eV): *m/z* 269 (M^+). HRMS *m/z* calcd for $C_{13}H_{23}NO_3Si$: 269.1447; found 269.1447.



***N*-Methoxy-*N*-methyl-2-(*R*)-methyl-3-(*R*)-hydroxy-5-trimethylsilyl-4-pentynamide (8).** To a solution of 180 mg of lactone **3f** (1.0mmol) and 250 μL of diisopropylethylamine (1.5 mmol, 1.5 equiv) in 2 mL of CH_2Cl_2 was added 150mg of *N,O*-dimethylhydroxyamine•HCl salt (1.5 mmol, 1.5 equiv)and the reaction was stirred 10 h at ambient temperature. A saturated aqueous solution of NH_4Cl was added and the resuting mixture was extracted with ether (3 × 15mL). The combined organic portions were washed with brine and dried ($MgSO_4$). The volatiles were evaporated in vacuo and the crude product mixture was subjected to flash chromatography (10% ethyl acetate in hexane) to afford 235 mg of amide **8** (97%) as a colorless oil. $[\alpha]_D$ –16° (*c* 2.8, $CHCl_3$). IR (neat) 3404, 2248, 2175, 1640, 1251, 845 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.67-4.69 (d, J =3.0 Hz, 1 H), 3.72 (s, 3 H), 3.18 (s, 3 H), 3.02 (b, 1 H), 3.02-3.04 (dq, J= 3.0, 7.5 Hz, 1 H), 1.32-1.34 (d, J = 7.5 Hz, 3 H), 0.15 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.6, 104.3, 89.8, 63.8, 61.8, 40.7, 32.0, 11.6, -0.02. MS (EI, 70 eV): *m/z* 244 (M^++1), 228 (M^+–Me), 226 (M^+–OH). HRMS *m/z* calcd for $C_{10}H_{18}NO_3Si$ (M^+–Me): 228.1056; found 228.1057.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7.38943
7.37886
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7.36345
7.35081
7.33796
7.32966
7.32420
7.31844
7.31468
7.31054
7.27156
7.27023
4.73217
4.72072
4.70947
4.69811
4.64792
4.64222
4.61834
4.59806
4.57425
4.12238
3.86785
3.85329
3.83811
3.82325
3.80785
3.79999
3.78943
1.59362
1.34618
1.32728
1.32617
1.31173
1.31062
1.29139
1.27375
1.26653
1.26179
0.90563
0.89197
0.87839
CH3
OBn
(3a)
Integral
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84.592
Current Data Parameters
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EXPNO 1
PROCNO 1
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Time 9.58
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PROBHD 5 mm TXI 13C
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TD 32768
SOLVENT CDCl3
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DS 0
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FIDRES 0.229111 Hz
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RG 35.9
DW 66.600 usec
DE 6.00 usec
TE 290.0 K
D1 12.00000000 sec
P1 9.00 usec
DE 6.00 usec
SFO1 500.1330008 MHz
NUC1 1H
PL1 0.00 dB
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WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00
1D NMR plot parameters
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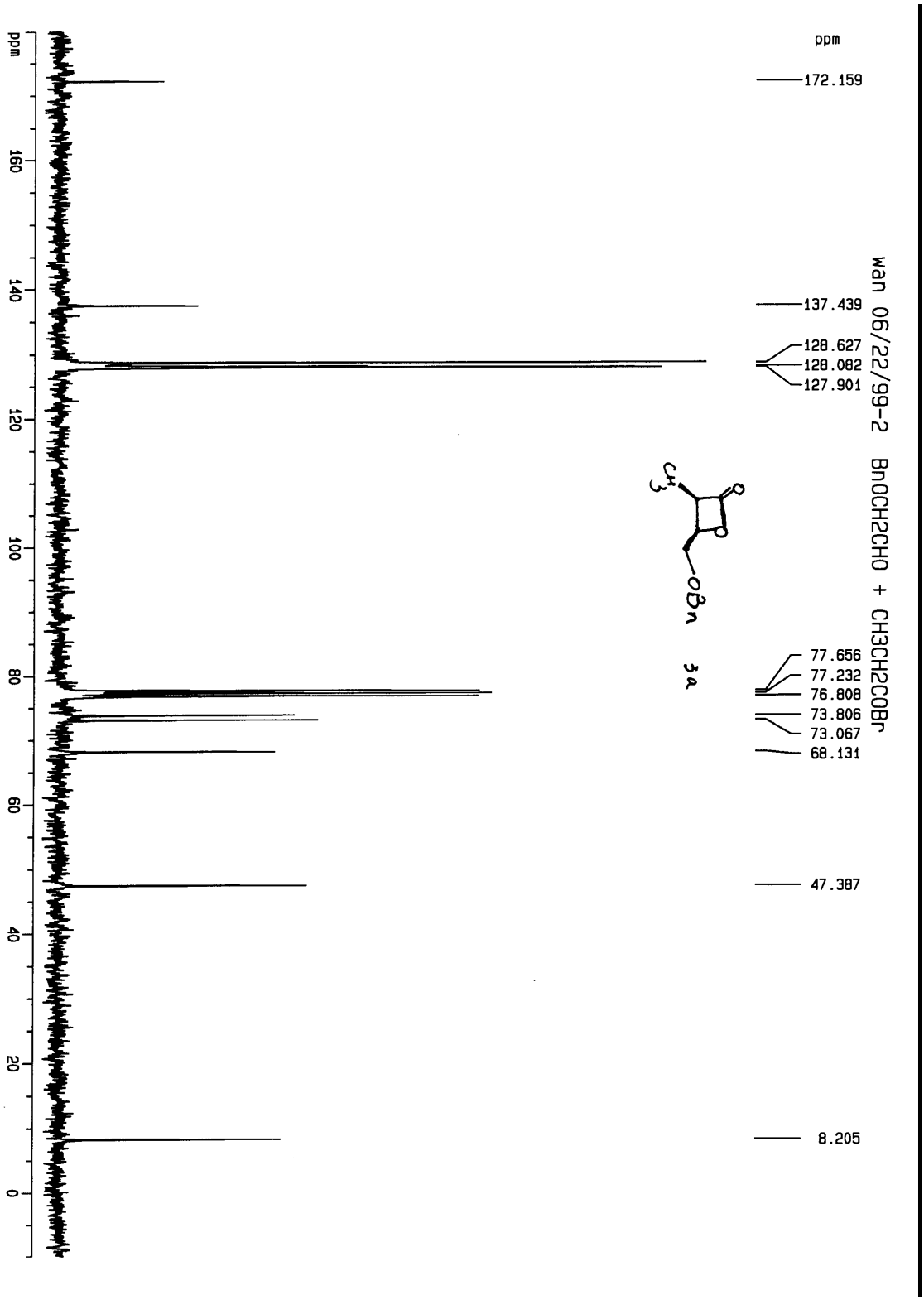
F1 5001.30 Hz
F2P 0.086 ppm
F2 43.12 Hz
PPMCM 0.49569 ppm/cm
HZCM 247.90875 Hz/cm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73.806
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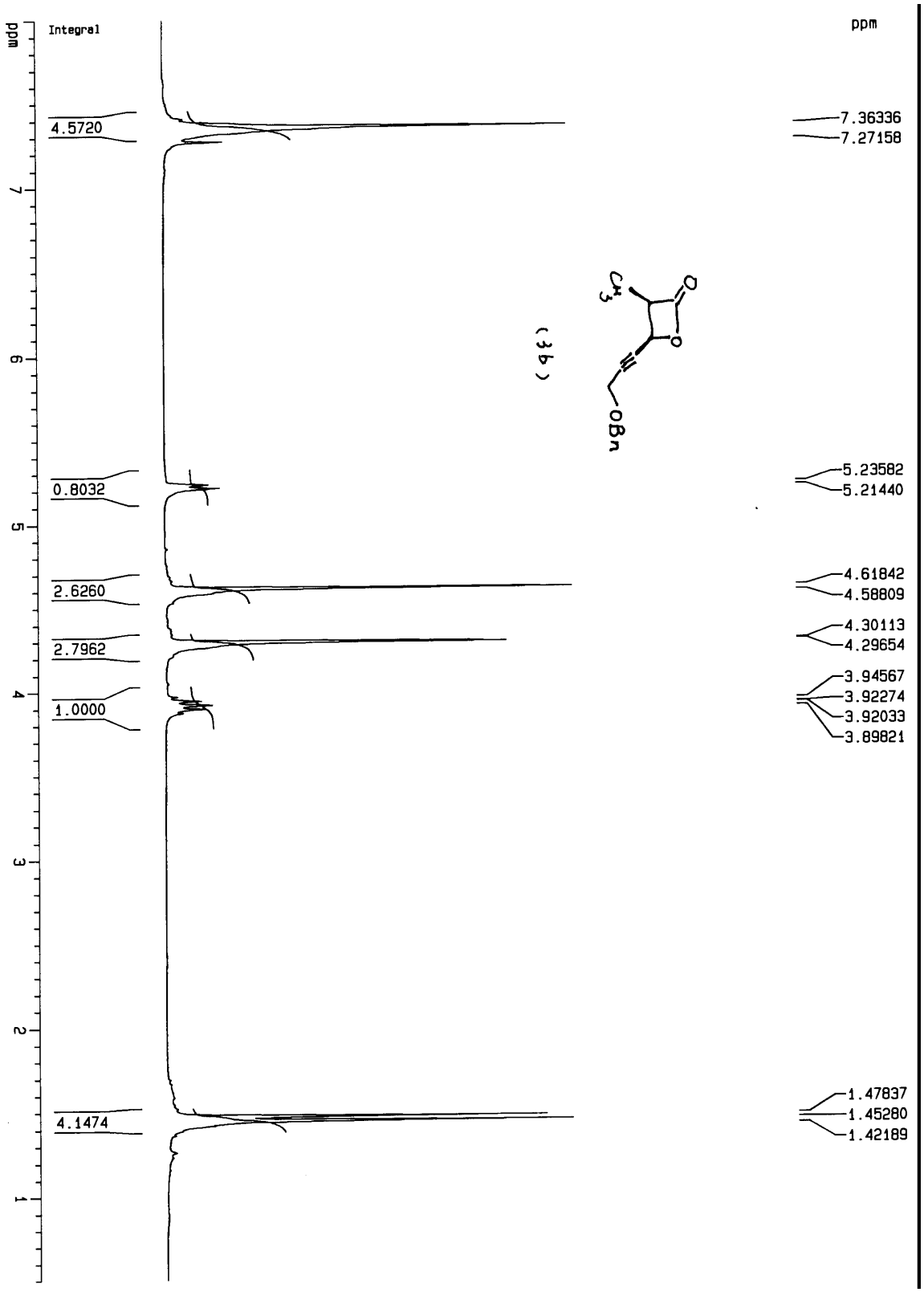
8.205
wan 06/22/99-2 BnOCH2CHO + CH3CH2COBr
OBn
3a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5.21440
4.61842
4.58809
4.30113
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3.92274
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1.45280
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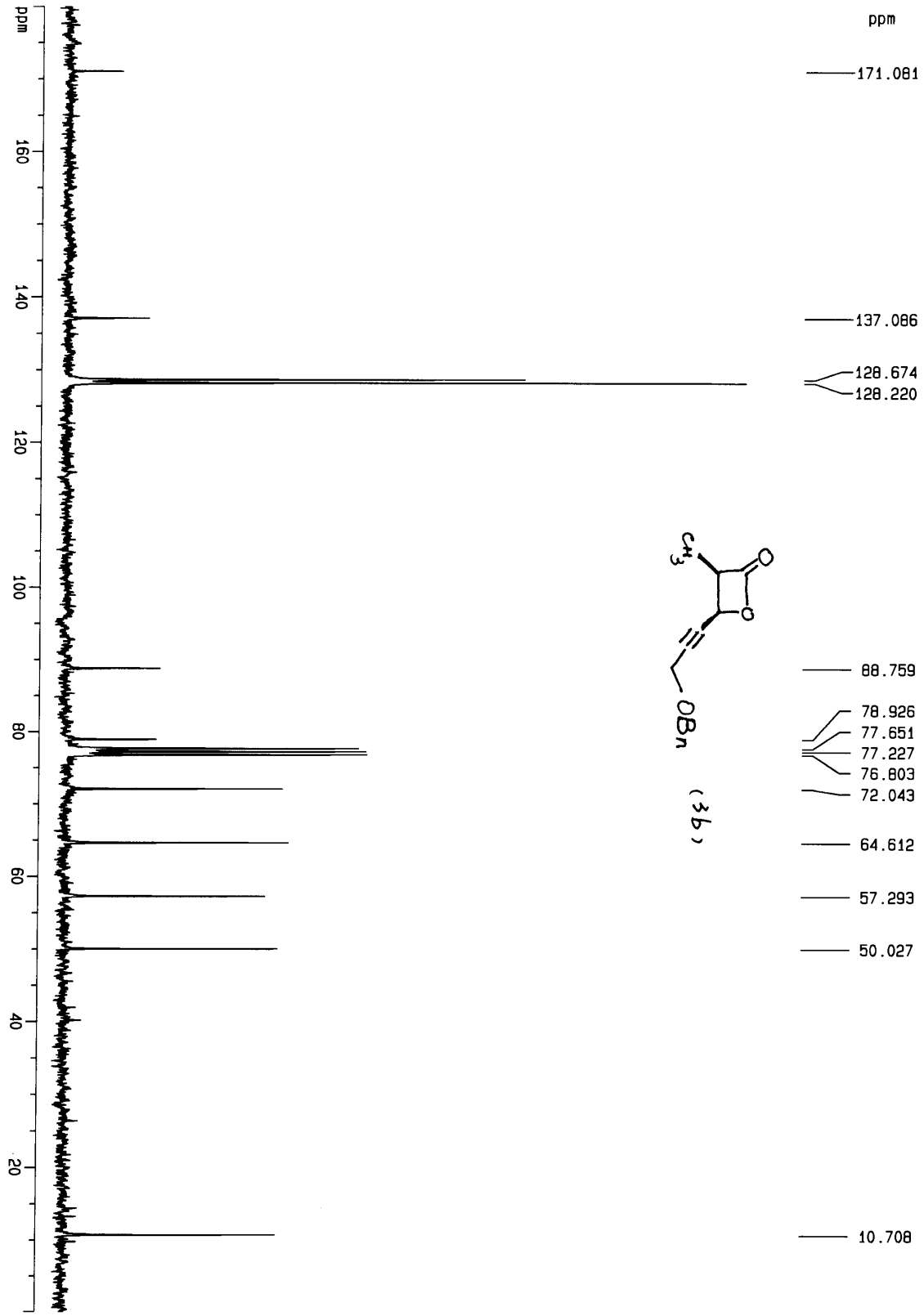
OBn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120
100
80
60
40
20
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128.220
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77.227
76.803
72.043
64.612
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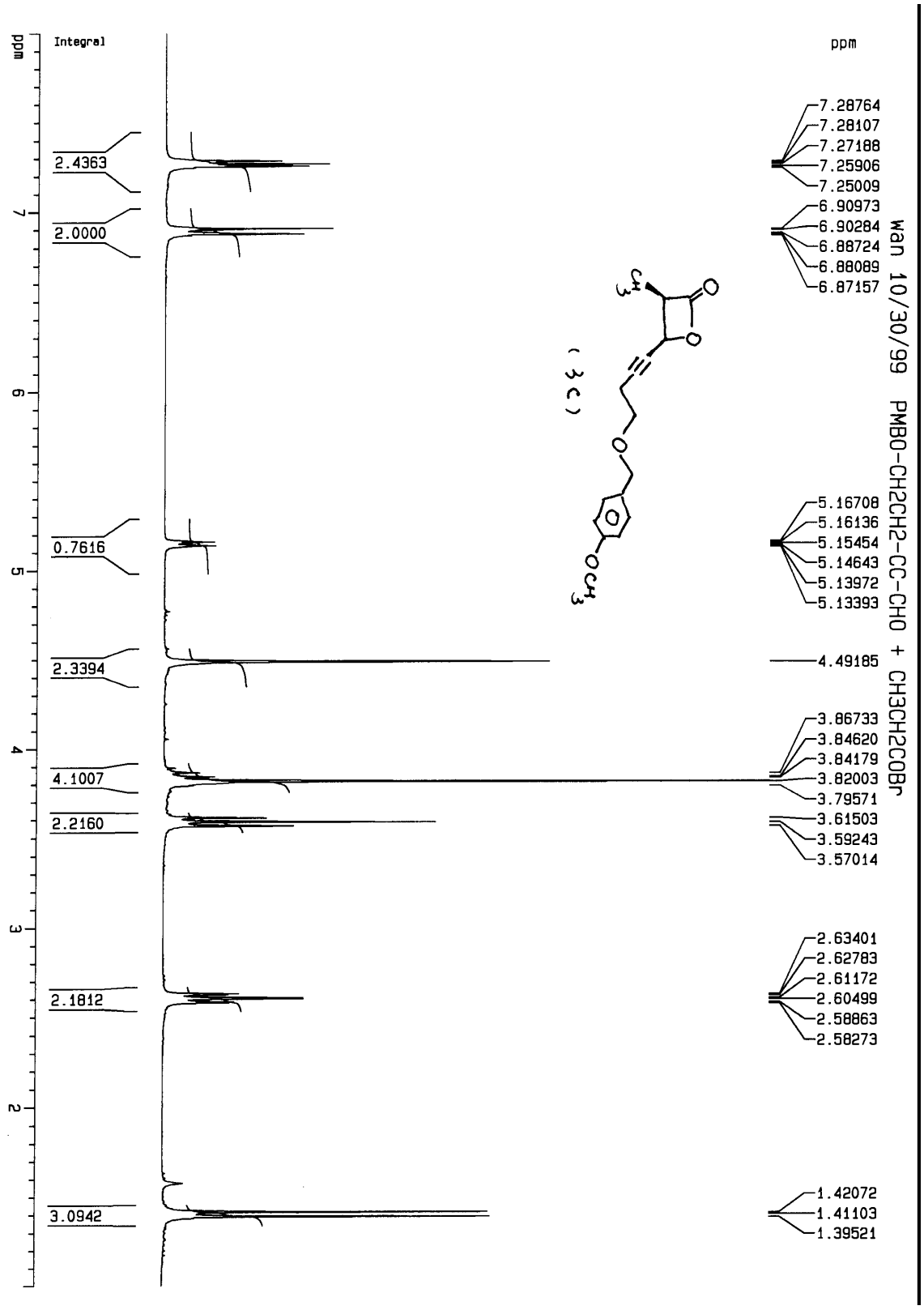
50.027
10.708
CH3
OBn
(3b)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7.25009
6.90973
6.90284
6.88724
6.88089
6.87157
5.16708
5.16136
5.15454
5.14643
5.13972
5.13393
4.49185
3.86733
3.84620
3.84179
3.82003
3.79571
3.61503
3.59243
3.57014
2.63401
2.62783
2.61172
2.60499
2.58863
2.58273
1.42072
1.41103
1.39521
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2.0000
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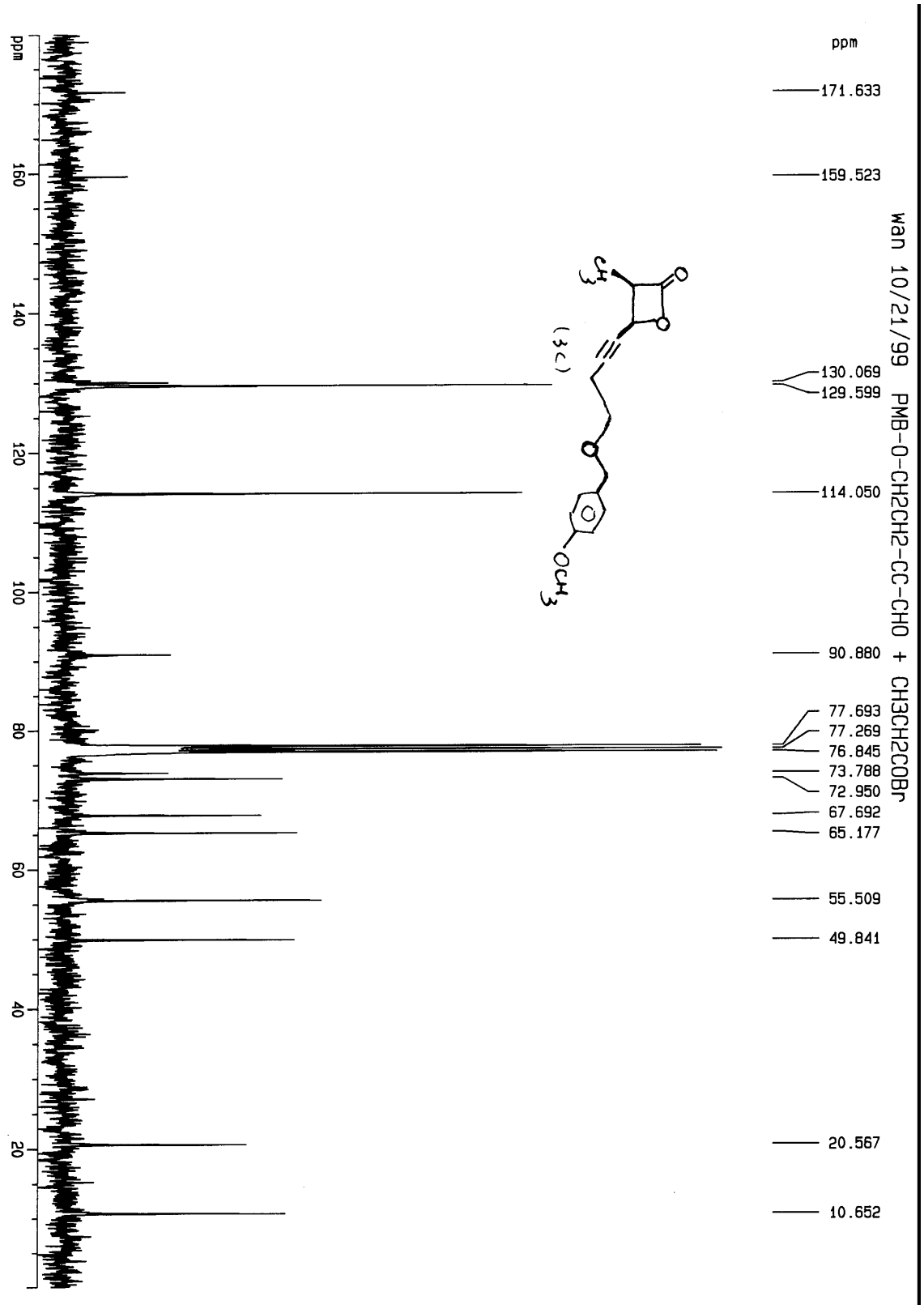
4.1007
2.2160
2.1812
3.0942
(3 c)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140
120
100
80
60
40
20
(3c)
OCH3
CH3
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129.599
114.050
90.880
77.693
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73.788
72.950
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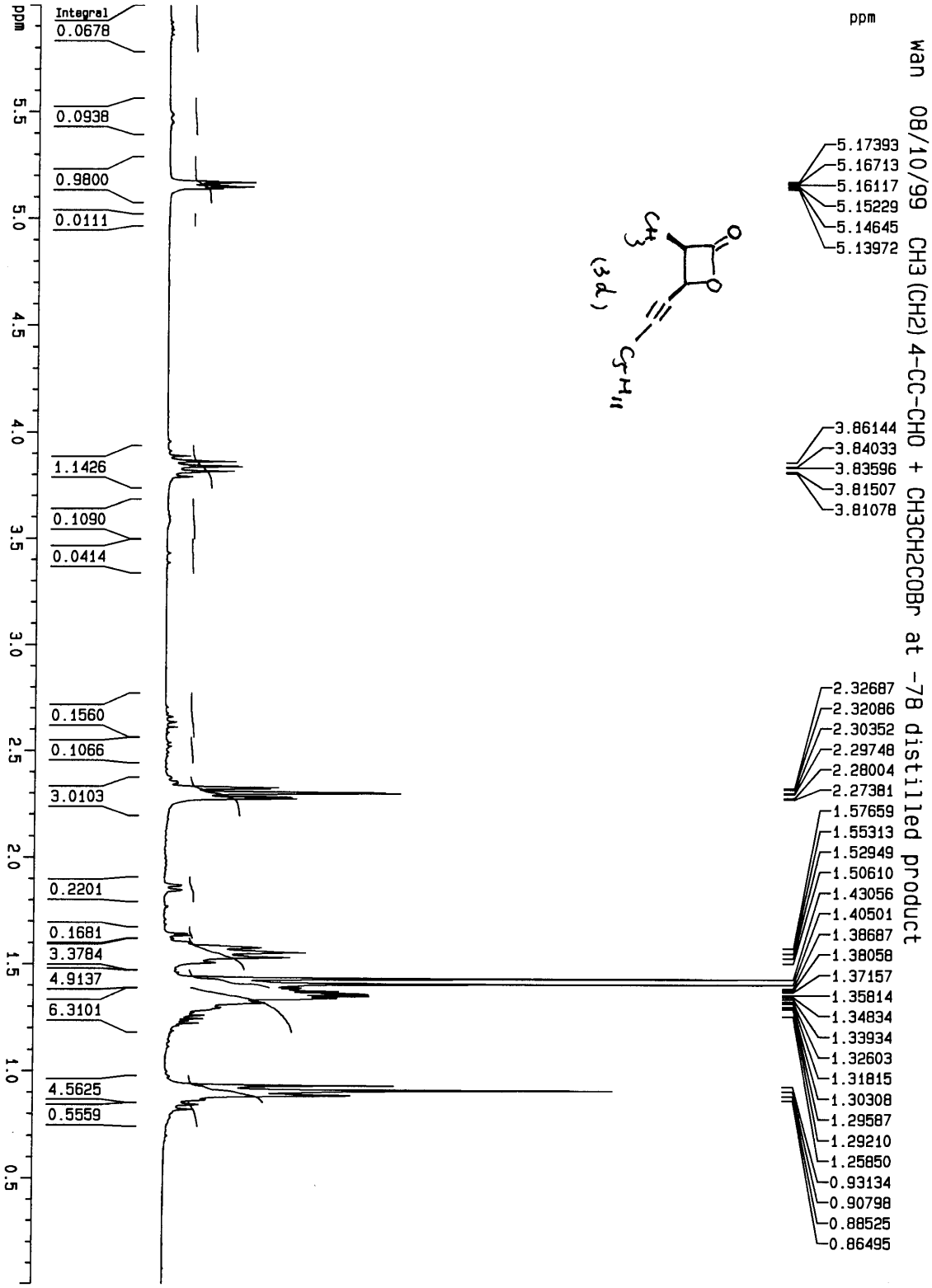
55.509
49.841
20.567
10.652
wan 10/21/99 PMB-O-CH2CH2-CC-CHO + CH3CH2COBr


wan 08/10/99 CH3(CH2)4-CC-CHO + CH3CH2COBr at -78 distilled product
ppm
Integral
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0.9800
0.0111
1.1426
0.1090
0.0414
0.1560
0.1066
3.0103
0.2201
0.1681
3.3784
4.9137
6.3101
4.5625
0.5559
5.17393
5.16713
5.16117
5.15229
5.14645
5.13972
3.86144
3.84033
3.83596
3.81507
3.81078
2.32687
2.32086
2.30352
2.29748
2.28004
2.27381
1.57659
1.55313
1.52949
1.50610
1.43056
1.40501
1.38687
1.38058
1.37157
1.35814
1.34834
1.33934
1.32603
1.31815
1.30308
1.29587
1.29210
1.25850
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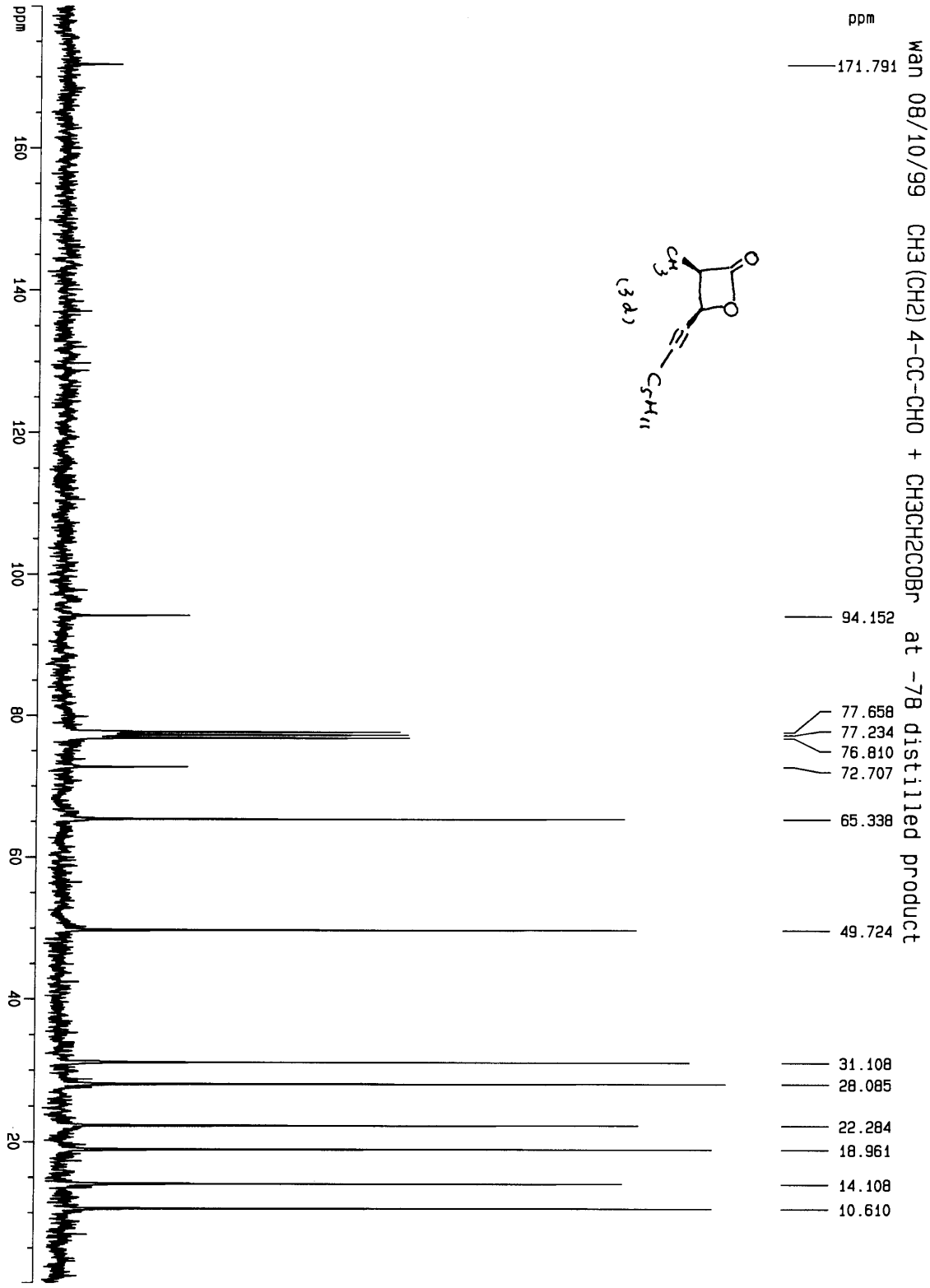
0.90798
0.88525
0.86495
(3d)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120
100
80
60
40
20
ppm
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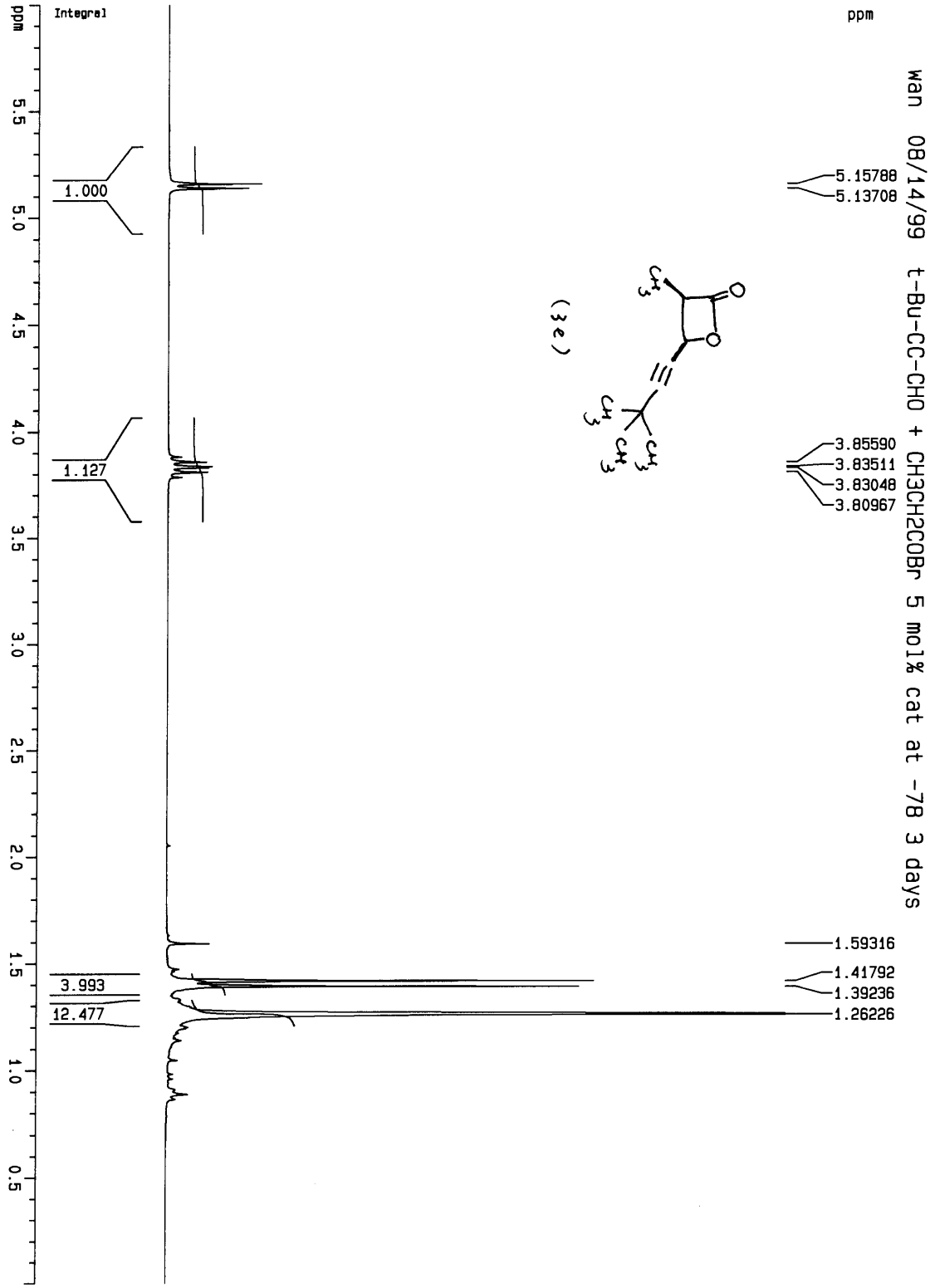
77.234
76.810
72.707
65.338
49.724
31.108
28.085
22.284
18.961
14.108
10.610
wan 08/10/99 CH3(CH2)4-CC-CHO + CH3CH2COBr at -78 distilled product
(3d)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Integral
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3.83511
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3.80967
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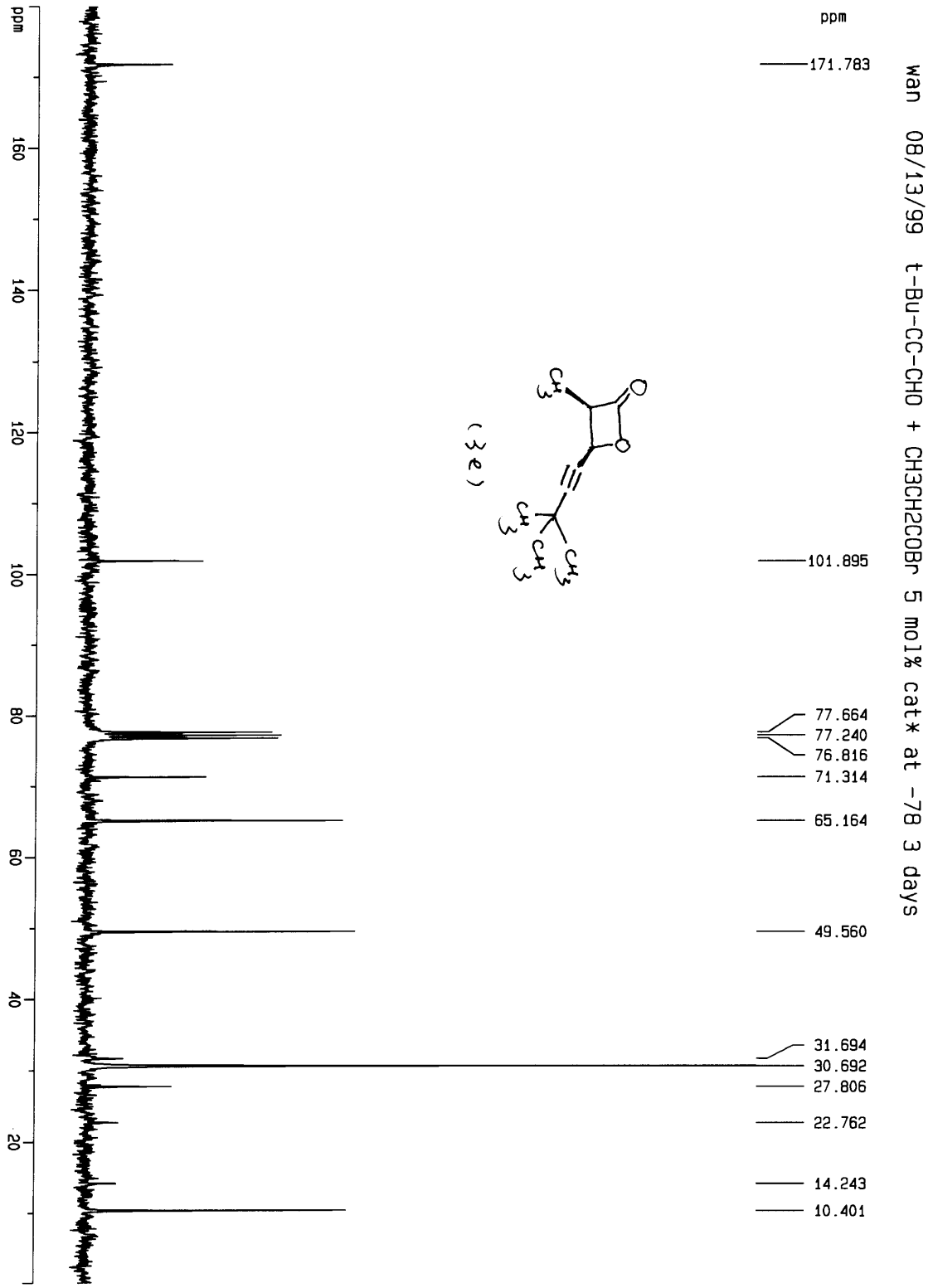
1.41792
1.39236
1.26226
1.000
1.127
3.993
12.477
(3e)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77.240
76.816
71.314
65.164
49.560
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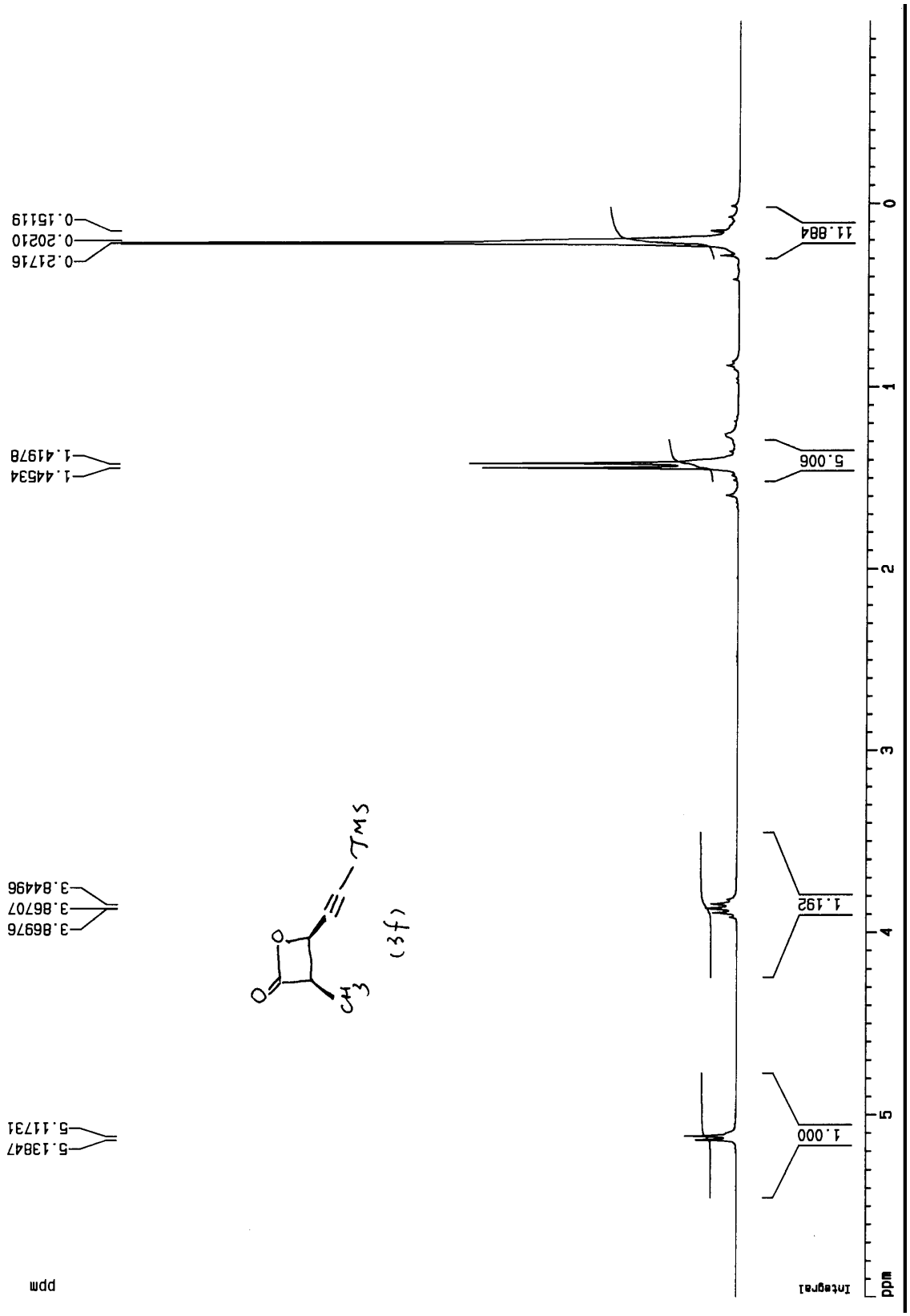
22.762
14.243
10.401
ppm
160
140
120
100
80
60
40
20
(3e)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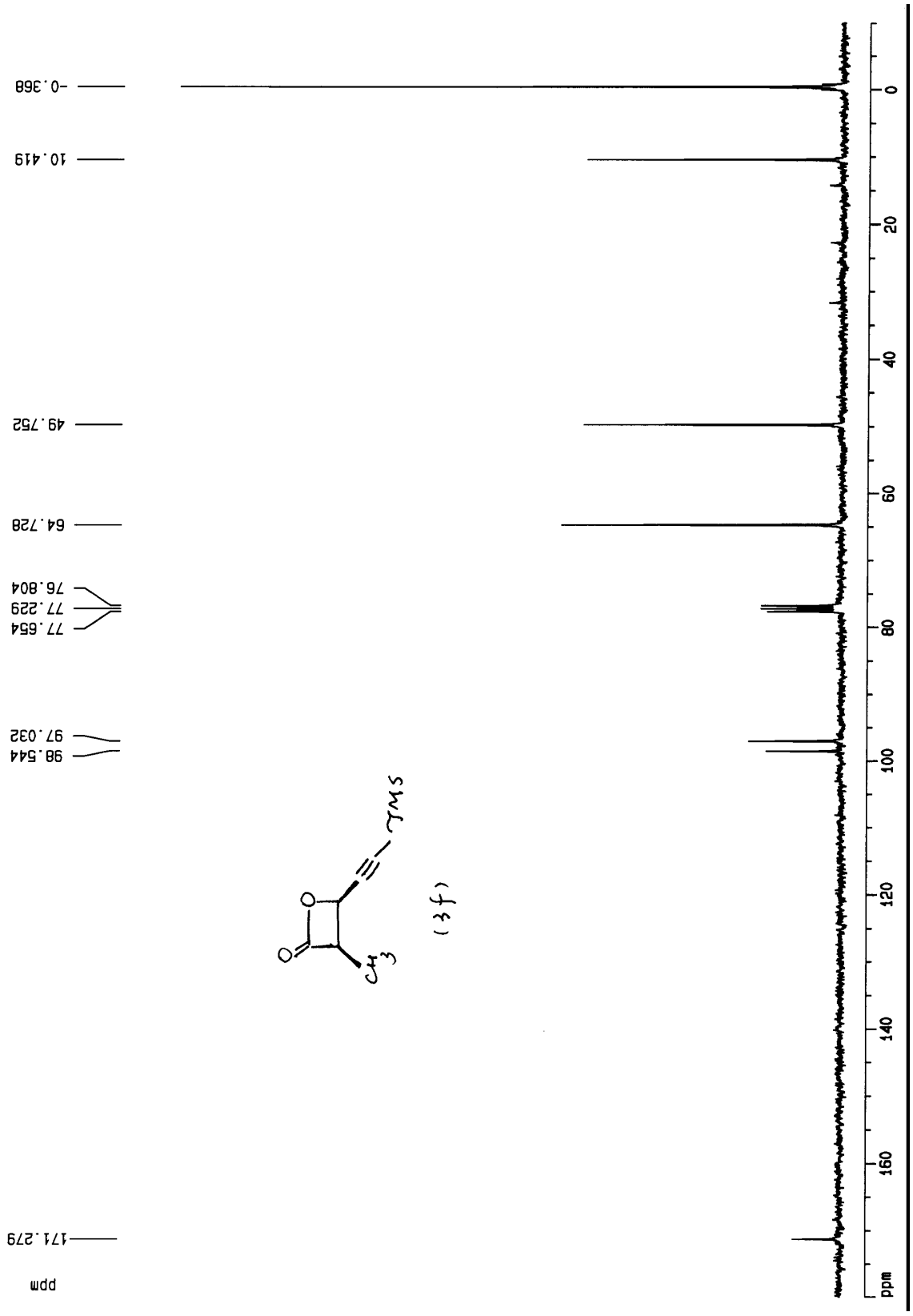
0.20210
0.15119
TMS
CH3
(3f)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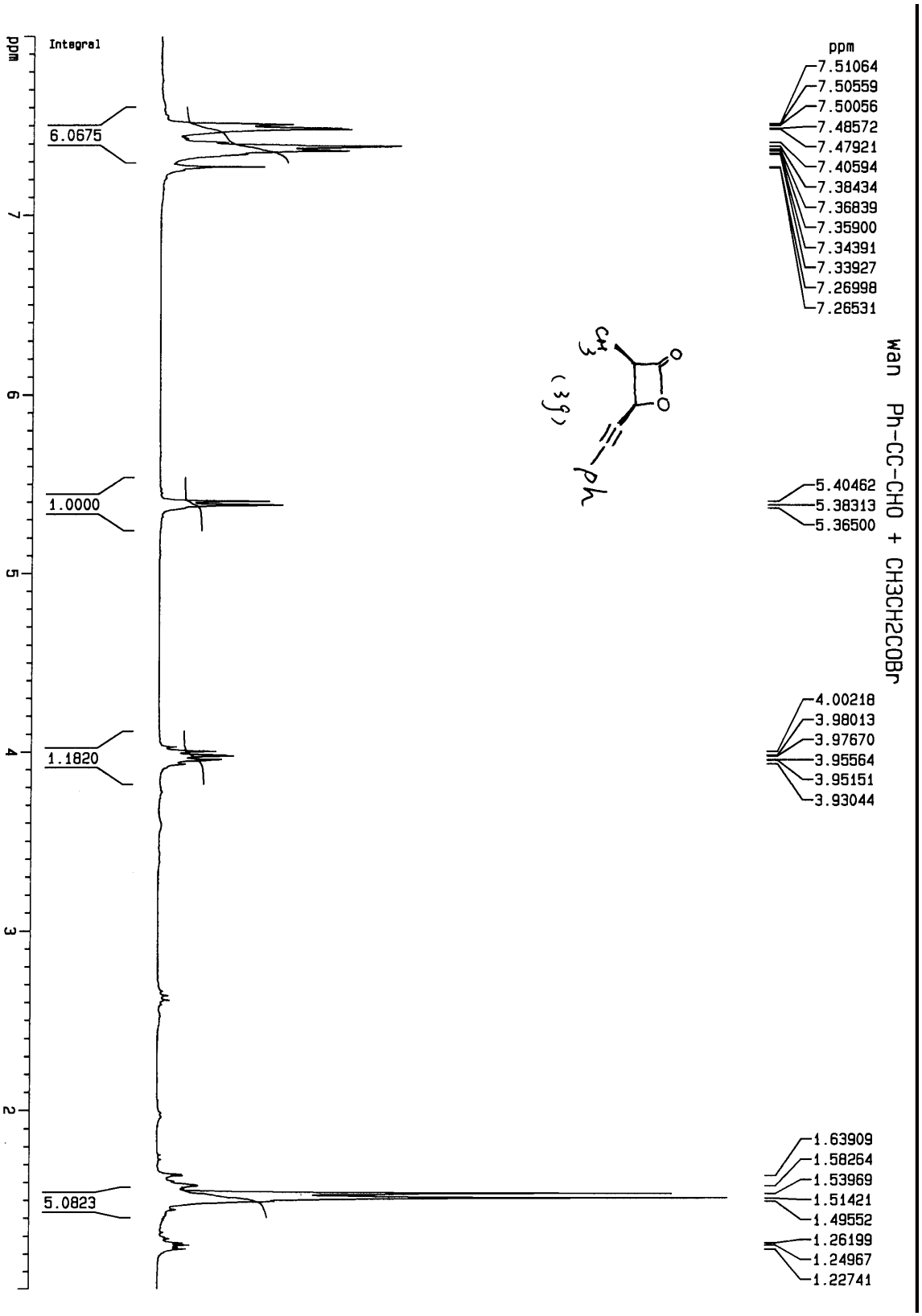
20
40
60
80
100
120
140
160
TMS
CH3
O
O
(3f)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7.34391
7.33927
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5.40462
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5.36500
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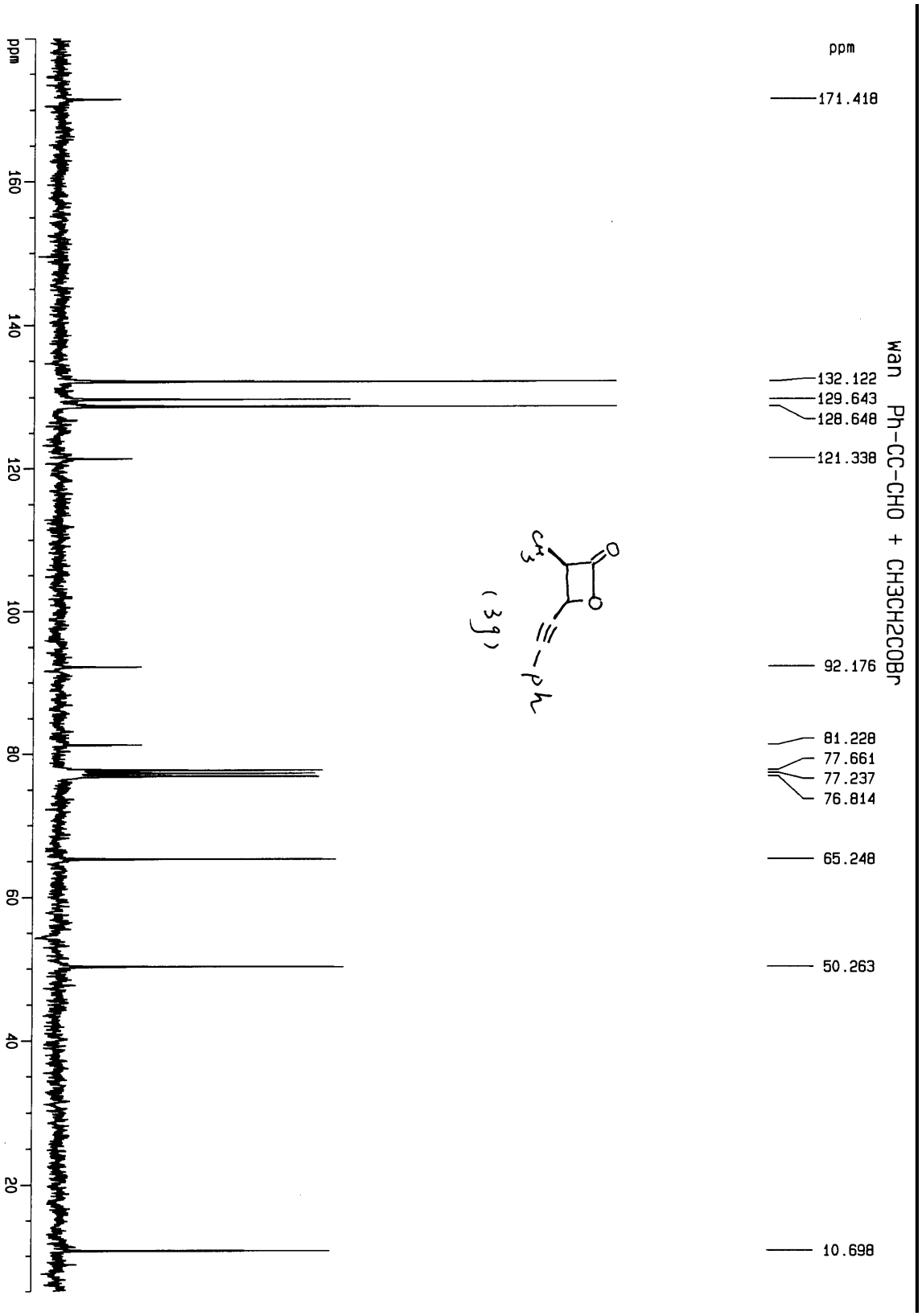
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140
120
100
80
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40
20
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77.237
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65.248
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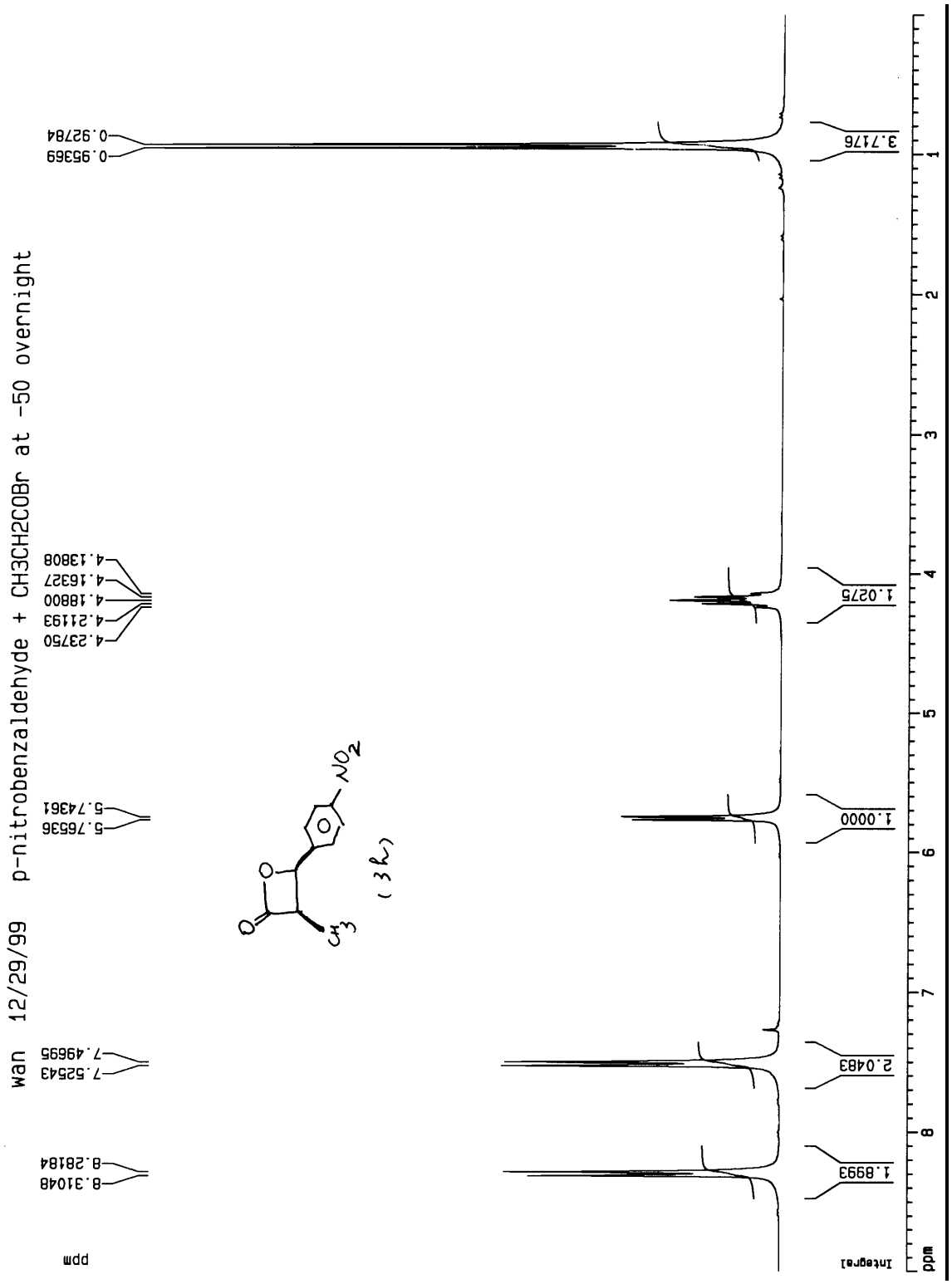
10.698
wan Ph-CC-CHO + CH3CH2COBr
(39)


wan 12/29/99 p-nitrobenzaldehyde + CH3CH2COBr at -50 overnight
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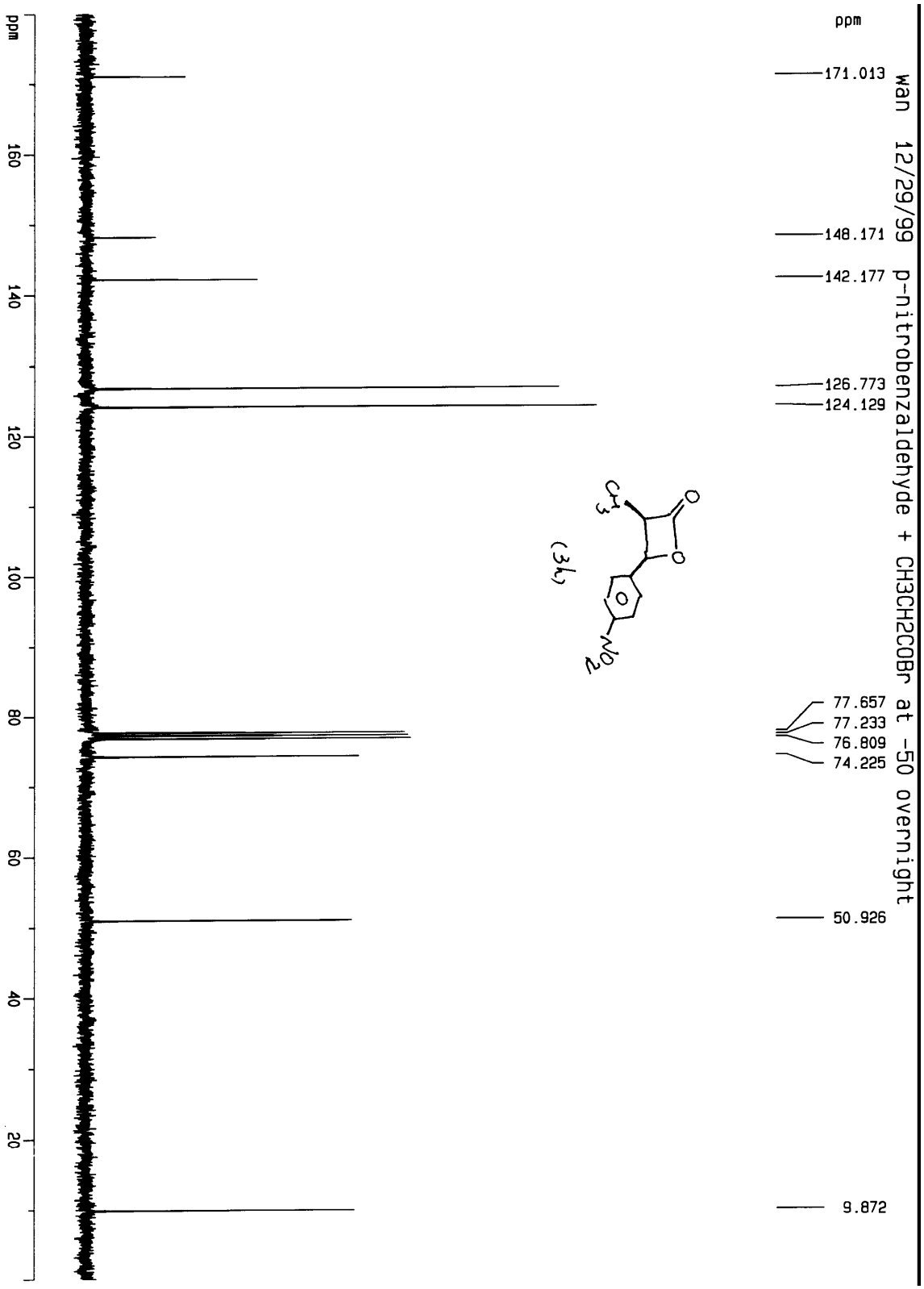
7.52543
7.49695
5.76536
5.74361
4.23750
4.21193
4.18800
4.16327
4.13808
0.95369
0.92784
3.7176
1.0275
1.0000
2.0483
1.8993
Integral
ppm
(3k)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140
120
100
80
60
40
20
ppm
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77.657
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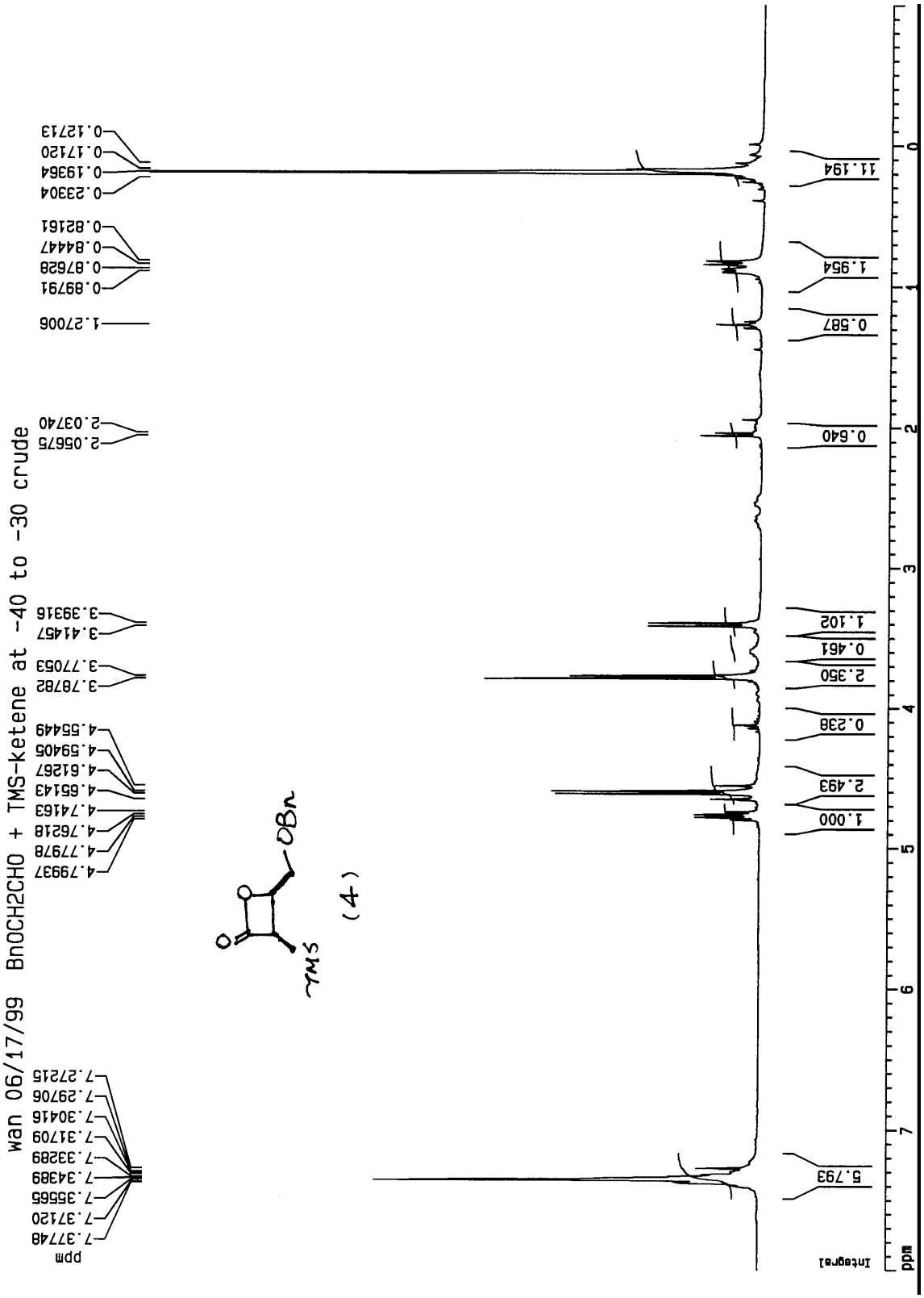
wan 12/29/99 p-nitrobenzaldehyde + CH3CH2COBr at -50 overnight
(3k)
CH3
O
O
NO2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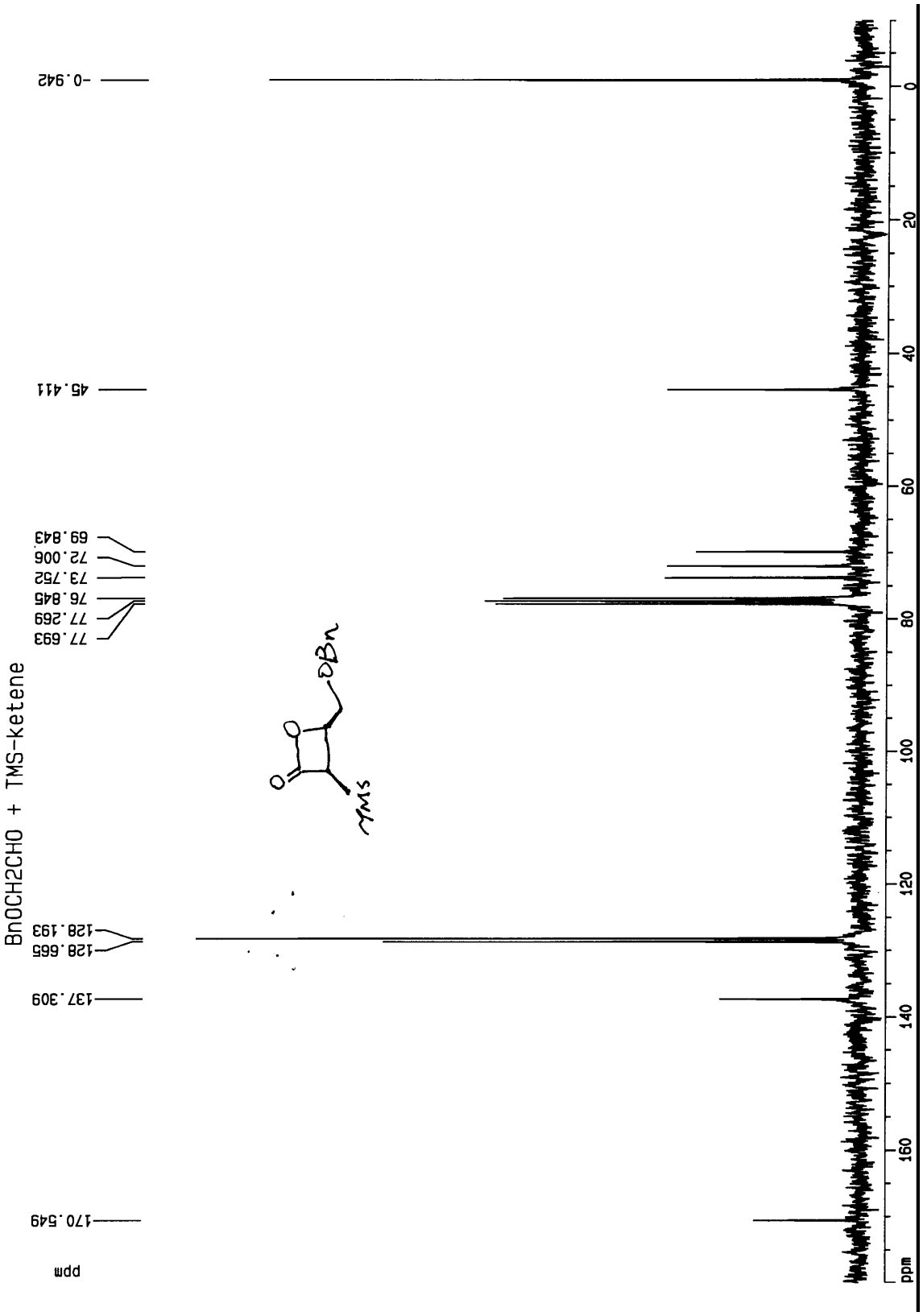
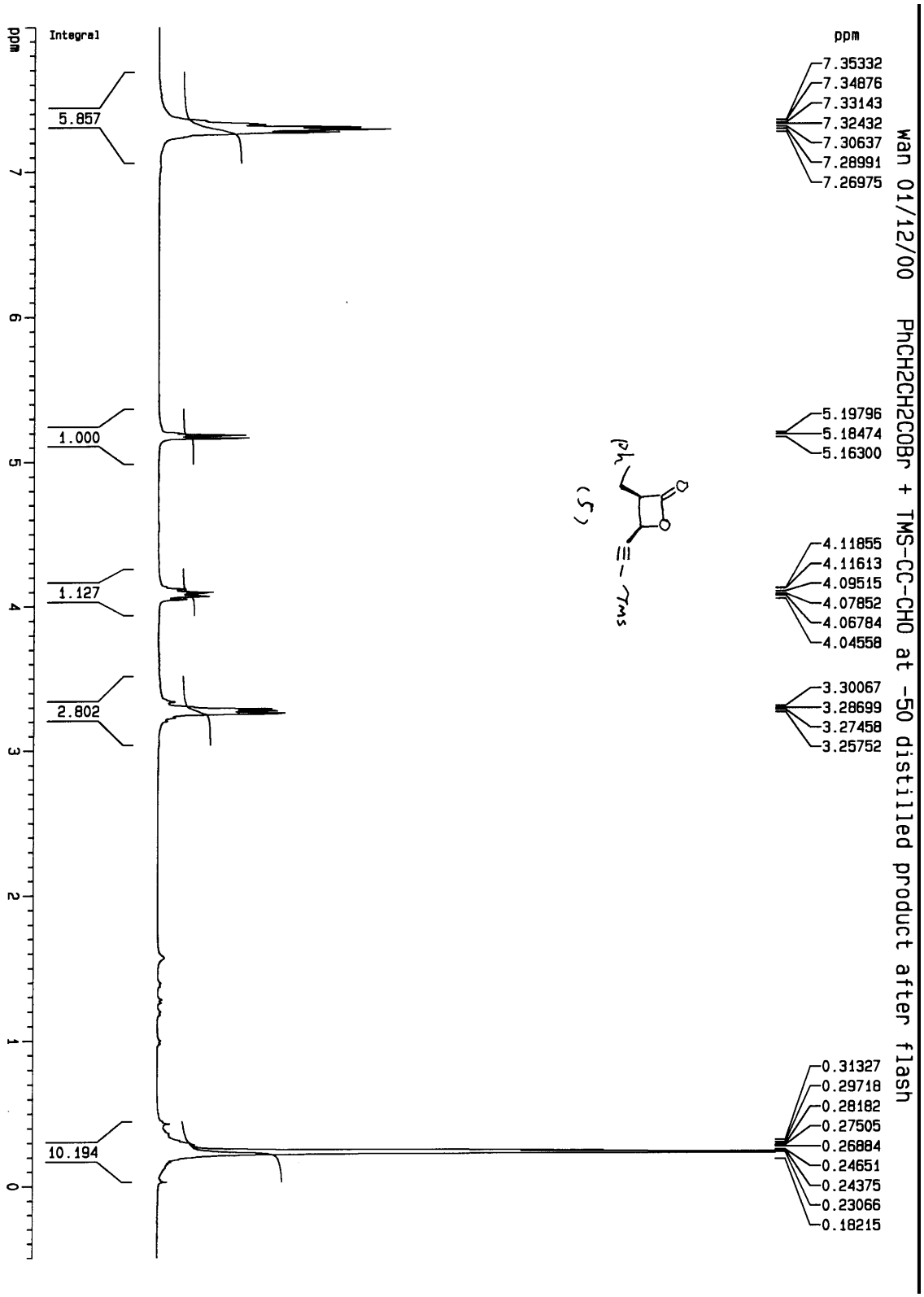
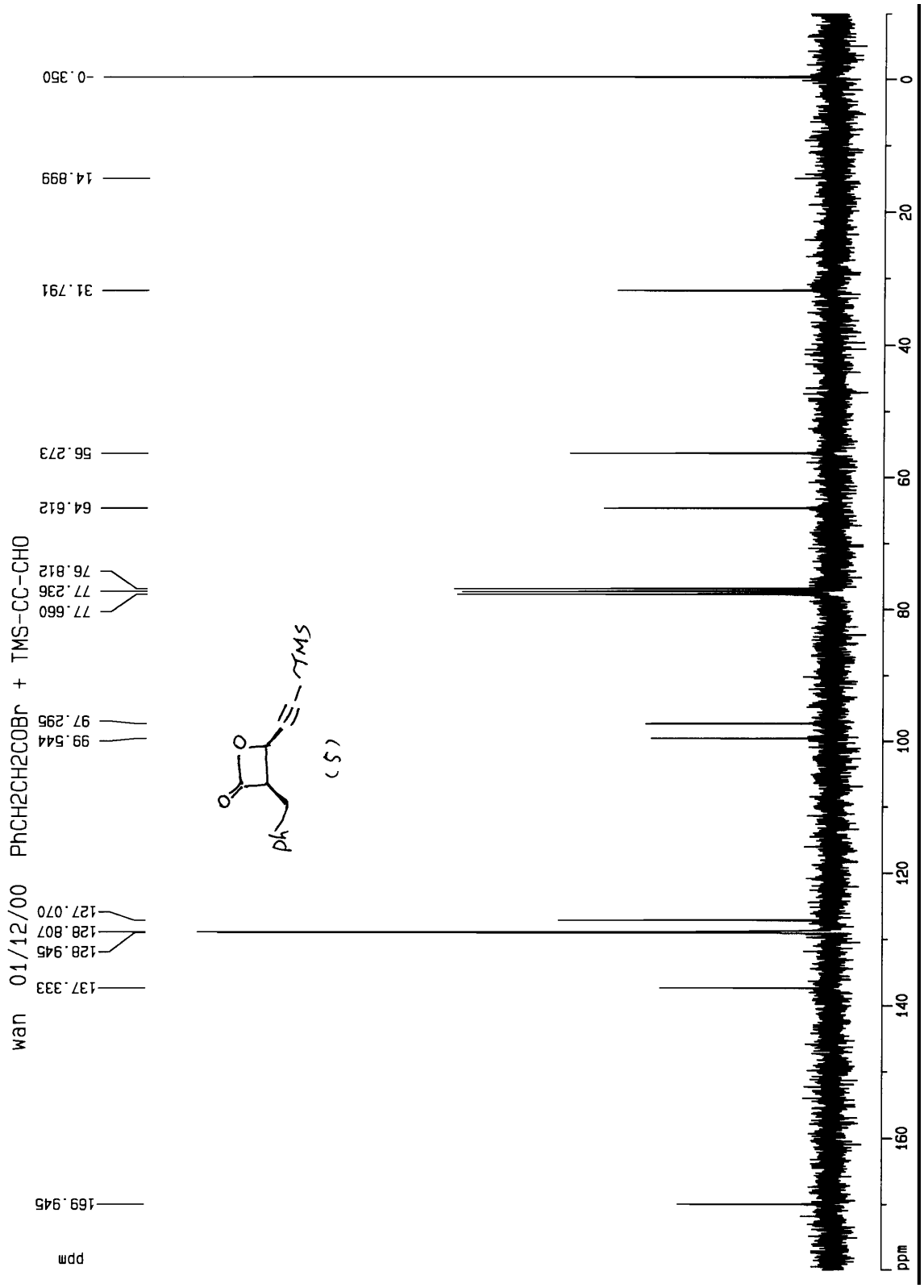
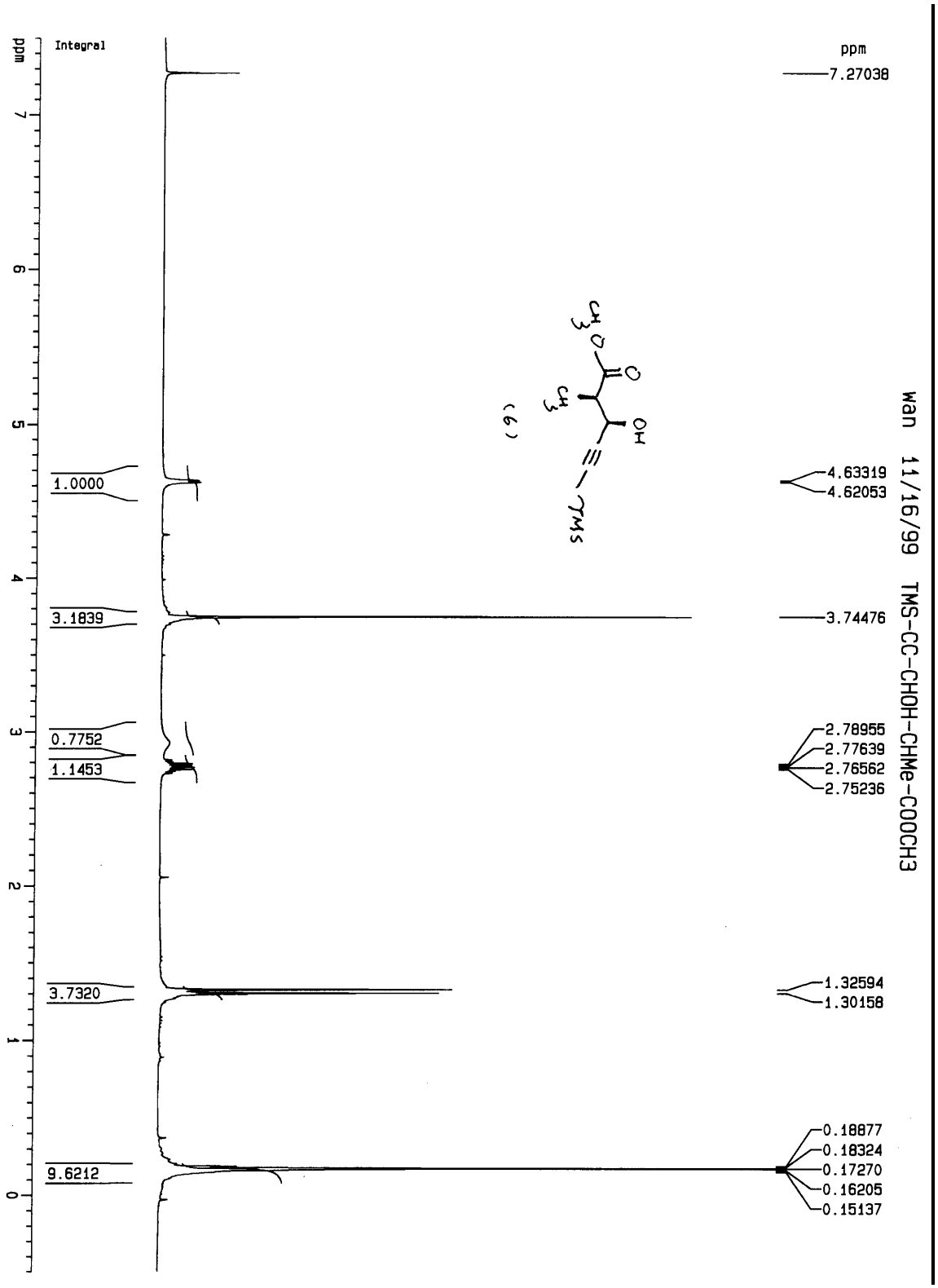
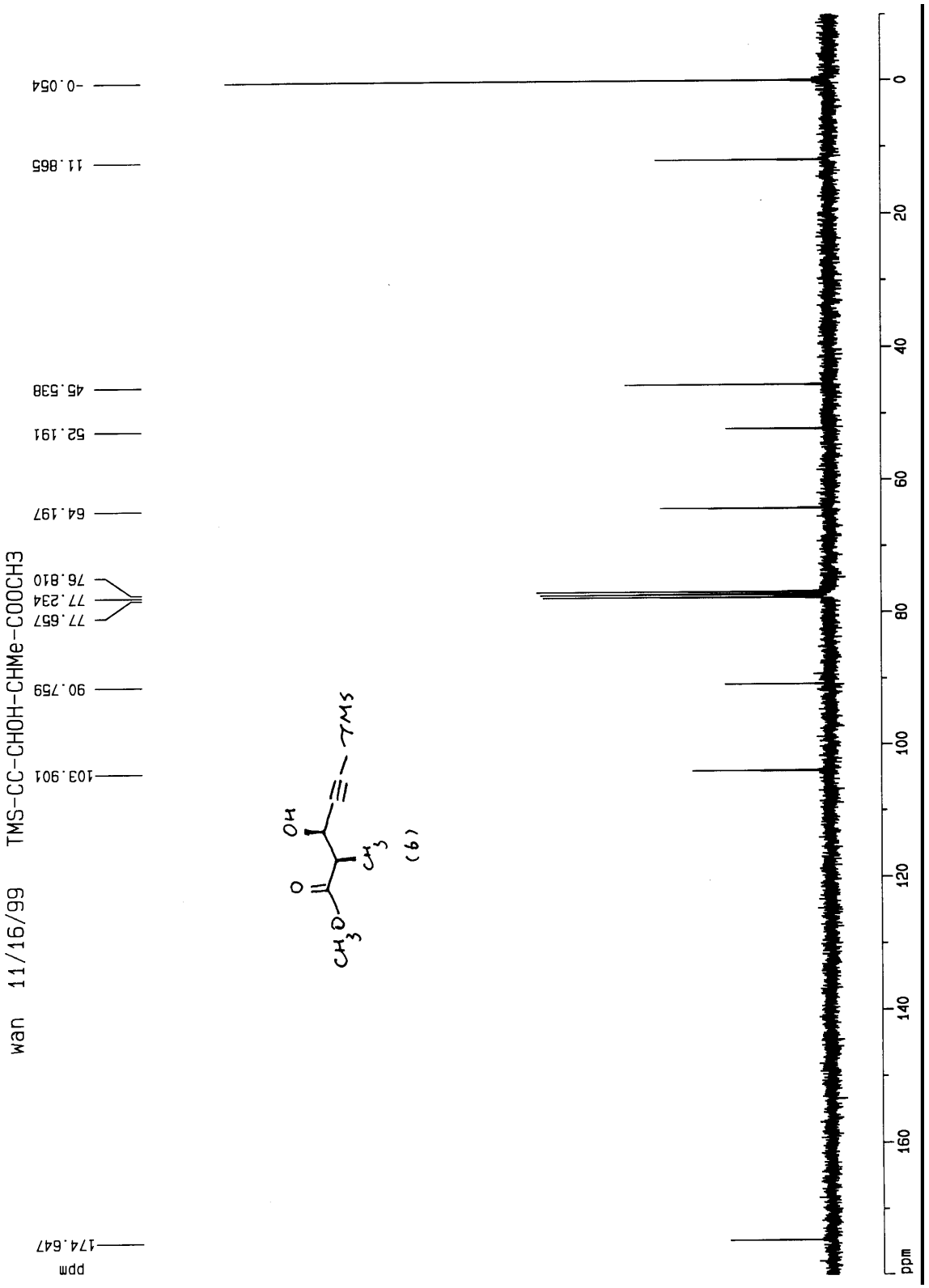
4.76218
4.74163
4.65143
4.61267
4.59405
4.55449
3.78782
3.77053
3.41457
3.39316
2.05675
2.03740
1.27006
0.89791
0.87628
0.84447
0.82161
0.23304
0.19364
0.17120
0.12713
Integral
11.194
1.954
0.587
0.640
1.102
0.461
2.350
0.238
2.493
1.000
5.793
ppm
OBn
TMS
(4)

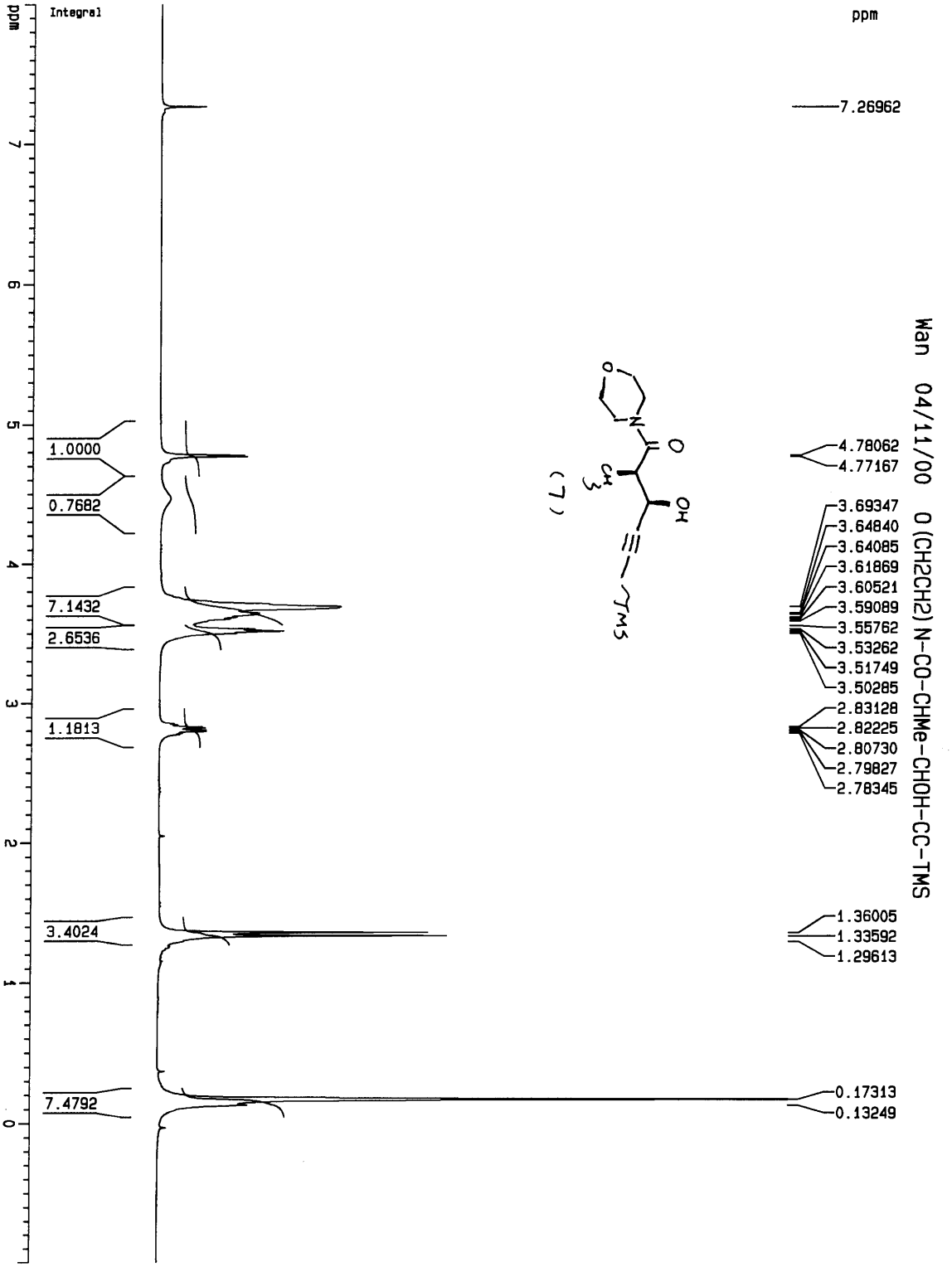

BnOCH2CHO + TMS-ketene
-0.942
45.411
69.843
72.006
73.752
76.845
77.269
77.693
128.193
128.665
137.309
170.549
ppm
0
20
40
60
80
100
120
140
160
ppm
OBn
TMS

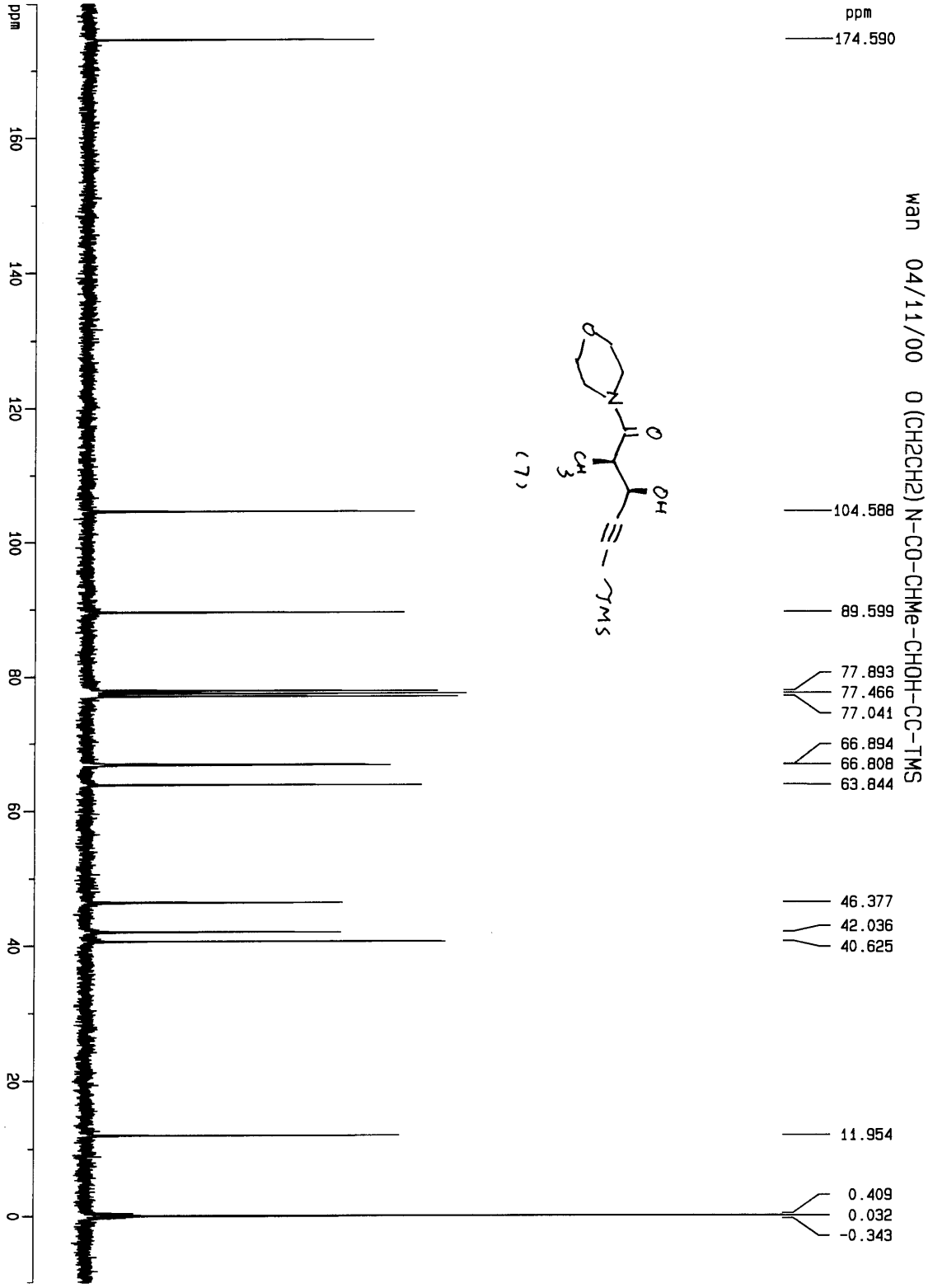

wan 01/12/00 PhCH2CH2COBr + TMS-CC-CHO at -50 distilled product after flash
ppm
7.35332
7.34876
7.33143
7.32432
7.30637
7.28991
7.26975
5.19796
5.18474
5.16300
4.11855
4.11613
4.09515
4.07852
4.06784
4.04558
3.30067
3.28699
3.27458
3.25752
0.31327
0.29718
0.28182
0.27505
0.26884
0.24651
0.24375
0.23066
0.18215
Integral
5.857
1.000
1.127
2.802
10.194
ppm
(S)

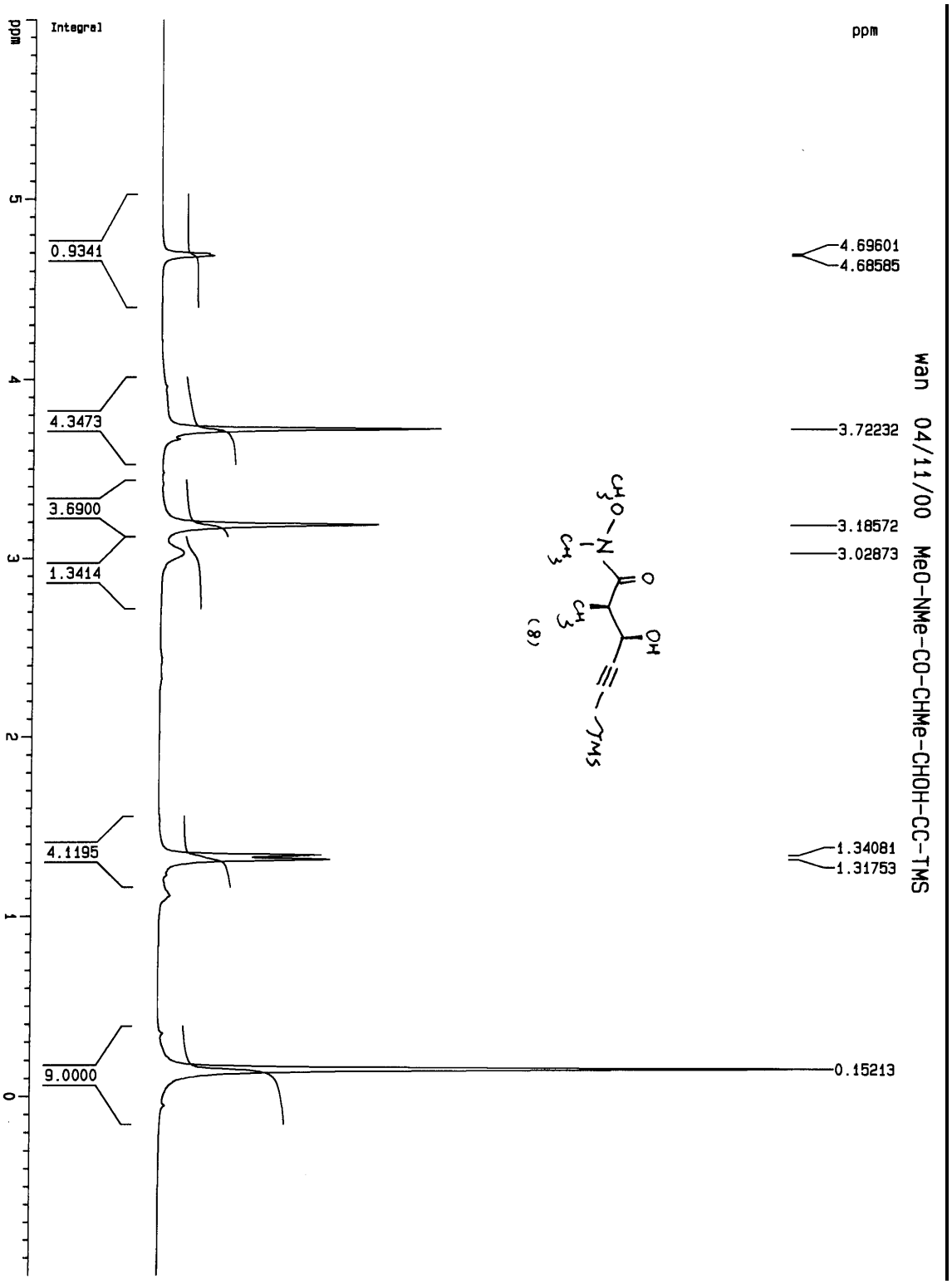

wan 01/12/00 PhCH2CH2COBr + TMS-CC-CHO
-0.350
14.899
31.791
56.273
64.612
76.812
77.236
77.660
97.295
99.544
127.070
128.807
128.945
137.333
169.945
ppm
0
20
40
60
80
100
120
140
160
ppm
TMS
Ph
O
O
(S)

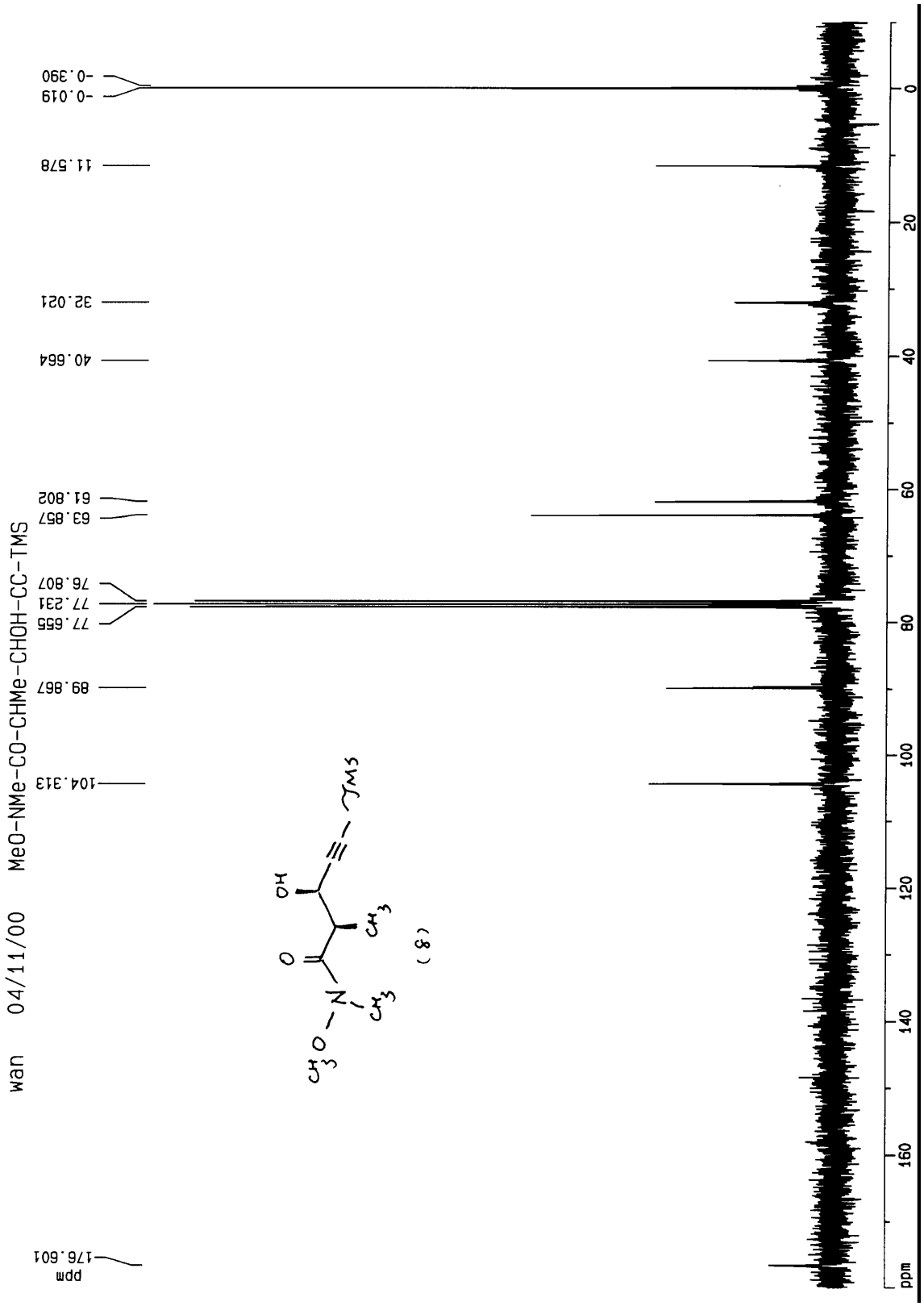

wan 11/16/99 TMS-CC-CHOH-CHMe-COOCH3
ppm
7.27038
4.63319
4.62053
3.74476
2.78955
2.77639
2.76562
2.75236
1.32594
1.30158
0.18877
0.18324
0.17270
0.16205
0.15137
Integral
1.0000
3.1839
0.7752
1.1453
3.7320
9.6212
(6)
TMS
OH


wan 11/16/99 TMS-CC-CHOH-CHMe-COOCH3
-0.054
11.865
45.538
52.191
64.197
76.810
77.234
77.657
90.759
103.901
174.647
ppm
0
20
40
60
80
100
120
140
160
ppm
TMS
OH
O
CH3O
CH3
(6)


Integral
ppm
7.26962
4.78062
4.77167
3.69347
3.64840
3.64085
3.61869
3.60521
3.59089
3.55762
3.53262
3.51749
3.50285
2.83128
2.82225
2.80730
2.79827
2.78345
1.36005
1.33592
1.29613
0.17313
0.13249
1.0000
0.7682
7.1432
2.6536
1.1813
3.4024
7.4792
Wan 04/11/00 O(CH2CH2)N-CO-CHMe-CHOH-CC-TMS
(7)


ppm
174.590
104.588
89.599
77.893
77.466
77.041
66.894
66.808
63.844
46.377
42.036
40.625
11.954
0.409
0.032
-0.343
wan 04/11/00 O(CH2CH2)N-CO-CHMe-CHOH-CC-TMS
(7)
CH3
OH
TMS
O
N
ppm
160
140
120
100
80
60
40
20
0


wan 04/11/00 MeO-NMe-CO-CHMe-CHOH-CC-TMS
ppm
Integral
4.69601
4.68585
3.72232
3.18572
3.02873
1.34081
1.31753
0.15213
0.9341
4.3473
3.6900
1.3414
4.1195
9.0000
(8)


wan 04/11/00 MeO-NMe-CO-CHMe-CHOH-CC-TMS
-0.390
-0.019
11.578
32.021
40.664
61.802
63.857
76.807
77.231
77.655
89.867
104.313
176.601
ppm
0
20
40
60
80
100
120
140
160
ppm
OH
O
TMS
(8)