SUPPLEMENTARY MATERIAL

Total Synthesis of N^{14}-Desacetoxytubulysin H.

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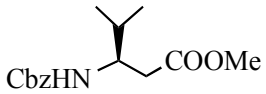
Experimental procedures and spectral data for all new compounds, including copies of ^{1}H and ^{13}C NMR spectra.

General: All reactions involving moisture sensitive reagents were conducted in oven-dried glassware under a nitrogen or argon atmosphere. Anhydrous solvents were obtained through standard laboratory protocols. Analytical thin-layer chromatography (TLC) was preformed on SiO_2 60 F-254 plates available from Merck. Visualization was accomplished by UV irradiation at 254 nm, or by staining with any one of the following reagents: iodine, 5% phosphomolybdic acid hydrate in ethanol, ninhydrin (0.3% w/v in glacial acetic acid/*n*-butyl alcohol 3:97), Vaughn's reagent (4.8 g of $(NH_4)_6Mo_7O_{24}\bullet 4H_2O$ and 0.2 g of $Ce(SO_4)_2\bullet 4H_2O$ in 10 mL of conc. H_2SO_4 and 90 mL of H_2O), or *para*-anisaldehyde (7.5 mL of *para*-anisaldehyde, 25 mL of conc. H_2SO_4, and 7.5 mL of acetic acid in 675 mL of 95% ethanol). Flash column chromatography was performed using SiO_2 60 (particle size 0.040-0.055 mm, 230-400 mesh, EM science distributed by Fisher Scientific).

Melting points were obtained on a Meltemp II™ capillary melting point apparatus fitted with a Fluke 51™ digital thermometer and are not corrected. Specific rotations of chiral compounds were obtained at the designated concentration and temperature on a Perkin Elmer 241 polarimeter using a 1 dm cell. Infrared spectra were collected on a Nicolet Avatar™ 360 FT–IR spectrometer from thin films deposited onto NaCl plates. Proton and carbon NMR spectra were obtained on Bruker Avance™ 300 and 500 MHz NMR spectrometers. Chemical shifts are reported as δ values in parts per million (ppm) as referenced to residual solvent. ^{1}H NMR spectra are tabulated as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), number of protons, and coupling constant(s). Mass spectra were obtained at the University of Pittsburgh Mass Spectrometry facility. A Varian HPLC system

equipped with Gilson 215 Liquid Handler and fraction collector was used for preparative HPLC purification. A Varian Dynamax Microsorb C18 column (250 mm × 10 mm, or 250 mm × 21.4 mm, 60 Å) was used. LC-MS analysis was performed on an Agilent 1100 instrument, using an analytical C18 column (Waters Xterra MS 100 × 4.6 mm, 3.5 μm, 0.4 mL/min).

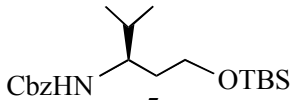


4

(*R*)-Methyl 3-(benzyloxycarbonylamino)-4-methylpentanoate (4).[1] To a solution of Cbz-Val-OH (1.0 g, 4.1 mmol) and triethylamine (0.60 mL, 4.3 mmol) in anhydrous THF (15 mL) cooled to -20 ºC was added isobutyl chloroformate (0.66 mL, 5.1 mmol) dropwise over 5 min, and the resulting white suspension was stirred further for 30 min. A diazomethane solution (~16.9 mmol) in ether (50 mL), which was prepared from Diazald (5.1 g, 24.0 mmol) using an Aldrich MiniDiazald apparatus and dried over potassium hydroxide (pellets) prior to use, was then introduced into the reaction mixture via cannula. The mixture was stirred further overnight, allowing the temperature to gradually rise to room temperature. Acetic acid was then added dropwise until there was no effervescence, and the mixture was diluted in ether (50 mL), washed with saturated sodium bicarbonate (30 mL) and brine (30 mL), dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (Et_2O/hexanes, 1:3) to give the diazoketone (0.96 g, 84%) as a yellow solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38-7.35 (m, 5 H), 5.41-5.38 (m, 2 H), 5.11 (s, 2 H), 4.15-4.14 (m, 1 H), 2.10 (octet, 1 H, J = 6.8 Hz), 1.00 (d, 3 H, J = 6.8 Hz), 0.90 (d, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.2, 156.3, 136.2, 128.4,

128.1, 128.0, 67.0, 62.8, 54.6, 31.0, 19.3, 17.2; IR (KBr, cm^{-1}) 3324, 2965, 2107, 1713, 1632, 1525, 1366, 1232.

To a solution of the above diazoketone (0.91 g, 3.3 mmol) in anhydrous methanol (15 mL) cooled at -35 ºC was added a solution of silver benzoate (80 mg, 0.35 mmol) in freshly distilled (over CaH_2) triethylamine (1 mL). The reaction flask was wrapped with aluminum foil to keep it dark, and the mixture was stirred overnight, during which time it gradually warmed up to room temperature. The solvent was concentrated under vacuum, and the residue was dissolved in ethyl acetate (60 mL), washed with saturated sodium bicarbonate (30 mL) and brine (30 mL), dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (Et_2O/hexanes, 1:3) to give **4** (0.77 g, 83%; or 70% for three steps) as a white solid: Mp 44.5-45.5 ºC; $[\alpha]_D^{23}$ -22.7 (*c* 2.2, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37-7.30 (m, 5 H), 5.16 (d, 1 H, *J* = 8.7 Hz), 5.10 (s, 2 H), 3.88-3.79 (m, 1 H), 3.66 (s, 3 H), 2.55-2.52 (m, 2 H), 1.85 (octet, 1 H, *J* = 6.8 Hz), 0.93 (d, 6 H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.2, 156.0, 136.5, 128.5, 128.0, 66.6, 53.6, 51.7, 36.8, 31.6, 19.3, 18.5; IR (film, cm^{-1}) 3338, 2961, 1731, 1531, 1239; HRMS (EI) calcd for $C_{15}H_{21}NO_4$ 279.1471, found 279.1478.



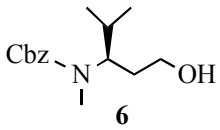
5

(*R*)-Benzyl 1-(*tert*-butyldimethylsilyloxy)-4-methylpentan-3-ylcarbamate (5).[2] To an ice-cooled solution of **4** (0.66 g, 2.4 mmol) in anhydrous THF (10 mL) was added dropwise lithium borohydride (2.0 M solution in THF, 1.8 mL, 3.6 mmol) over 5 min. A solution of methanol (0.20 mL, 4.8 mmol) in anhydrous THF (5 mL) was then added over

10 min, and the mixture was stirred further overnight, allowing the temperature to rise to room temperature. The solvent was concentrated under vacuum, and the residue was dissolved in ethyl acetate (70 mL), washed with hydrochloric acid (1 *N*, 20 mL x 2), saturated sodium bicarbonate (20 mL), and brine (20 mL), dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (EtOAc/hexanes, 1:1) to give the desired alcohol (0.42 g, 71%) as a white solid: Mp 52.0-53.0 ºC; $[\alpha]_D^{23}$ +12.1 (*c* 4.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38-7.37 (m, 5 H), 5.16, 5.10 (d_{AB}, 2 H, *J* = 12.1 Hz), 4.63 (d, 1 H, *J* = 8.8 Hz), 3.74-3.56 (m, 3 H), 2.95 (bs, 1 H), 1.90-1.70 (m, 2 H), 1.41-1.30 (m, 1 H), 0.96 (d, 3 H, *J* = 6.9 Hz), 0.93 (d, 3 H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.4, 136.3, 128.4, 128.0, 127.9, 66.7, 58.9, 52.9, 35.2, 32.0, 19.1, 17.9; IR (film, cm^{-1}) 3324, 2959, 2875, 1693, 1537, 1251, 1048.

To a solution of the alcohol (0.34 g, 1.4 mmol) and imidazole (0.18 g, 2.4 mmol) in anhydrous DMF (2 mL) was added a solution of *tert*-butyldimethylchlorosilane (0.32 g, 2.1 mmol) in anhydrous THF (2 mL). The mixture was stirred further overnight, diluted in water (10 mL), and extracted with ether (20 mL x 3). The combined organic layers were washed with hydrochloric acid (1 *N*, 20 mL), saturated sodium bicarbonate (20 mL), and brine (20 mL), dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (Et_2O/hexanes, 1:7) to give **5** (0.49 g, 99%) as a colorless oil: $[\alpha]_D^{23}$ +6.6 (*c* 5.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36-7.35 (m, 5 H), 5.13, 5.07 (d_{AB}, 2 H, *J* = 12.4 Hz), 5.01 (d, 1 H, *J* = 9.4 Hz), 3.74-3.60 (m, 3 H), 1.89-1.72 (m, 2 H), 1.61-1.49 (m, 1 H), 0.95-0.90 (m, 6 H), 0.90 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.2, 136.8, 128.4, 127.8, 66.3, 60.6, 54.2, 34.5, 31.8, 25.8,

18.8, 18.1, 18.0, -5.5; IR (film, cm^{-1}) 3333, 2958, 2858, 1699, 1537, 1255, 1096, 836, 776; MS (APCI) *m*/*z* 366 ($[M+H]^+$).

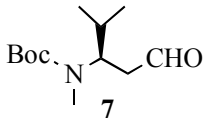


6

(*R*)-Benzyl 1-hydrox-4-methylpentan-3-yl(methyl)carbamate (6). To an ice-cooled solution of **5** (0.40 g, 1.1 mmol) in anhydrous THF (2 mL) was added a solution of NaHMDS (0.28 g, 1.5 mmol) in THF (1 mL). The reaction mixture was stirred for 20 min before iodomethane (0.1 mL, 1.6 mmol) was added. The mixture was stirred overnight, while the temperature was allowed to rise to room temperature. The solution was diluted with ethyl acetate (60 mL), washed with hydrochloric acid (1 *N*, 10 mL) and brine (10 mL), dried (Na_2SO_4), concentrated under vacuum, and purified by chromatography on SiO_2 (Et_2O/hexanes, 1:8) to give the methylated product (0.40 g, 96%) as a colorless oil: $[\alpha]_D^{23}$ +5.2 (*c* 2.2, CH_2Cl_2); NMR analysis ($CDCl_3$) showed a mixture of rotamers at room temperature; ^1H NMR (DMSO-d_6, 338 K, 300 MHz) δ 7.34-7.33 (m, 5 H), 5.09, 5.04 (d_{AB}, 2 H, *J* = 12.6 Hz), 3.69 (dt, 1 H, *J* = 10.0, 4.0 Hz), 3.51-3.44 (m, 2 H), 2.70 (s, 3 H), 1.80-1.62 (m, 3 H), 0.89 (d, 3 H, *J* = 6.6 Hz), 0.85 (s, 9 H), 0.77 (d, 3 H, *J* = 6.7 Hz), 0.00 (s, 6 H); ^{13}C NMR (DMSO-d_6, 338 K, 75 MHz) δ 155.6, 137.3, 127.8, 127.2, 126.8, 65.6, 59.8, 58.7, 31.9, 29.7, 28.8, 25.4, 19.5, 19.1, 17.4, -5.9; IR (film, cm^{-1}) 2957, 2857, 1701, 1471, 1252, 1098, 835; HRMS (EI) calcd for $C_{21}H_{37}NO_3Si$ 379.2543, found 379.2536.

To a solution of the above methylated product (0.40 g, 0.28 mmol) in THF (2 mL) was added tetrabutylammonium fluoride (1.0 M solution in THF, 0.34 mL, 0.34 mmol).

The reaction mixture was stirred at room temperature for 4 h, diluted with ethyl acetate (40 mL), washed with brine (10 mL), dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (EtOAc/hexanes, 1:1) to give **6** (0.27 g, 96%) as a colorless oil: $[\alpha]_D^{23}$ -13.1 (*c* 2.8, CH_2Cl_2); NMR analysis ($CDCl_3$) showed a mixture of rotamers at room temperature; ^{1}H NMR (DMSO-d_6, 333 K, 300 MHz) δ 7.35-7.30 (m, 5 H), 5.08 (s, 2 H), 4.10 (bs, 1 H), 3.68 (dt, 1 H, *J* = 10.2, 3.5 Hz), 3.47-3.25 (m, 2 H), 2.70 (s, 3 H), 1.78-1.55 (m, 3 H), 0.89 (d, 3 H, *J* = 6.3 Hz), 0.77 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR (DMSO-d_6, 333 K, 75 MHz) δ 155.8, 137.1, 127.9, 127.2, 126.8, 65.6, 58.9, 58.2, 32.1, 29.7, 28.6, 19.6, 19.2; IR (film, cm^{-1}) 3466, 2961, 2875, 1694, 1682, 1455, 1338; HRMS (EI) calcd for $C_{15}H_{23}NO_3$ 265.1678, found 265.1677.

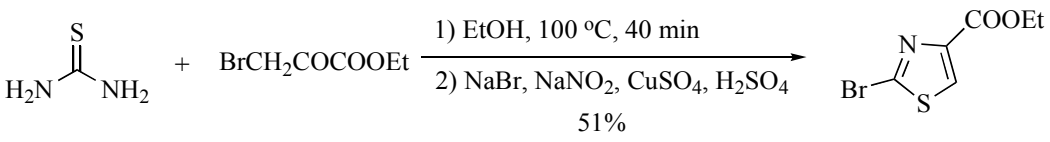


7

(*R*)-3-((*tert*-Butoxycarbonyl)methyl)amino-4-methylpentanal (7). A mixture of **6** (0.73 g, 2.7 mmol), di-*tert*-butyldicarbonate (0.72 g, 3.2 mmol), and palladium on activated carbon (5% Pd, 78 mg) in methanol (15 mL) was stirred under a hydrogen balloon at room temperature overnight. The solvent was concentrated under vacuum, and the residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:1) to give the Boc-protected amino alcohol (0.58 g, 92%) as a colorless oil: $[\alpha]_D^{23}$ -22.3 (*c* 3.2, CH_2Cl_2). Major rotamer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.87-3.79 (m, 1 H), 3.61-3.51 (m, 1 H), 3.42-3.31 (m, 1 H), 2.61 (s, 3 H), 2.03-1.84 (m, 1 H), 1.73-1.61 (m, 1 H), 1.46 (s, 9 H), 1.39-1.25 (m, 1 H), 0.96 (d, 3 H, *J* = 6.5 Hz), 0.88 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.0, 79.9, 58.9, 57.4, 31.8, 30.0, 28.4, 20.1. Characteristic signals

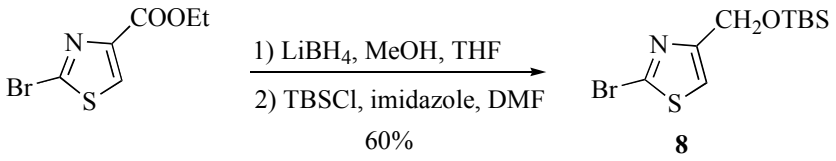
of the minor rotamer: ^{13}C NMR ($CDCl_3$, 75 MHz) δ 59.8, 32.2, 30.6, 27.9; IR (film, cm^{-1}) 3454, 2968, 1694, 1393, 1177, 1047; HRMS (EI) calcd for $C_{12}H_{25}NO_3$ 231.1834, found 231.1830.

To a mixture of Dess-Martin periodinane (1.19 g, 2.8 mmol) in anhydrous dichloromethane (6 mL) was added dropwise a solution of the above Boc-protected amino alcohol (0.57 g, 2.4 mmol) in dichloromethane (8 mL). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed, and the residue was dissolved in ether (70 mL), washed with a mixture of sodium hydroxide (1.0 *N*, 10 mL) and sodium thiosulfate (1.0 M, 10 mL), saturated sodium bicarbonate (10 mL), and brine (10 mL), dried (Na_2SO_4), concentrated under vacuum, and purified by chromatography on SiO_2 (Et_2O/hexanes, 1:2) to give **7** (0.50 g, 89%) as a colorless oil: $[\alpha]_D^{23}$ -75.9 (*c* 2.8, CH_2Cl_2). ^{1}H NMR analysis at room temperature showed a 1.2:1 mixture of rotamers. Major rotamer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.67 (bs, 1 H), 4.32 (dt, 1 H, J = 10.6, 4.3 Hz), 2.66 (s, 3 H), 2.62-2.43 (m, 2 H), 1.83-1.72 (m, 1 H), 1.44 (s, 9 H), 0.96 (d, 3 H, J = 6.4 Hz), 0.90 (d, 3 H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.6, 156.1, 79.6, 56.7, 44.9, 30.4, 29.1, 28.3, 20.0, 19.2. Characteristic signals of the minor rotamer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.65 (s, 1 H), 4.10 (dt, 1 H, J = 10.0, 4.9 Hz), 2.72 (s, 3 H), 1.47 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.8, 155.6, 80.0, 57.8, 30.8, 28.9, 28.4, 20.1, 19.4; IR (film, cm^{-1}) 2971, 2726, 1726, 1688, 1366, 1153; HRMS (EI) calcd for $C_{12}H_{23}NO_3$ 229.1678, found 229.1674; calcd for $C_9H_{16}NO_3$ (M-C_3H_7) 186.1130, found 186.1130.



Ethyl 2-bromothiazole-4-carboxylate. The procedure by Kelly et al.[3] was slightly modified. To a mixture of thiourea (6.60 g, 86.8 mmol) in ethanol (5 mL) was added dropwise a solution of ethyl bromopyruvate (80-85% purity, 19.5 g, ~85.0 mmol) in ethanol (5 mL). The reaction mixture was heated slowly to 100 ºC and kept at that temperature for 40 min to give a clear brown solution. Upon cooling to room temperature a yellow precipitate was formed, and dissolved in sulfuric acid (9 *N*, 400 mL). The solution was transferred into a 1000 mL three-necked bottle equipped with a mechanical stirrer, an addition funnel, and a gas outlet with an inverted wide-mouth funnel suspended just above a sodium hydroxide solution (4 *N*, 100 mL). The solution was cooled in an ice bath, and cupric sulfate pentahydrate (25.0 g, 0.10 mol) and sodium bromide (30.8 g, 0.30 mol) were added portionwise. A solution of sodium nitrite (8.8 g, 0.13 mol) in water (50 mL) was then added dropwise over 1 h. ***CAUTION****: Red gas, presumably a mixture of Br_2 and HBr, was formed once sodium nitrite was introduced. The reaction must be performed in a well-ventilated hood.* Stirring was continued for 4 h, during which time the bath temperature gradually rose to room temperature. The mixture was diluted with water (200 mL) and extracted with ether (200 mL x 4). The combined organic layers were concentrated to about 300 mL, washed with saturated sodium bicarbonate (100 mL x 2) and brine (100 mL), dried (Na_2SO_4), concentrated under vacuum, and purified by chromatography on SiO_2 (EtOAc/hexanes, 1:8) to give the thiazole ester (10.2 g, 51% for two steps) as a yellow solid: Mp 68.2-69.5 ºC (lit.[3] 68.5-69.2 ºC); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12 (s, 1 H), 4.41 (q, 2 H, J = 7.1 Hz), 1.39 (t, 3 H, J = 7.1 Hz); ^{13}C NMR

($CDCl_3$, 75 MHz) δ 160.1, 147.2, 136.8, 130.8, 61.8, 14.2; IR (KBr, cm^{-1}) 3090, 2986, 1717, 1488, 1478, 1431, 1329, 1224, 1121, 1011, 774; MS (ESI) *m*/*z* 260 ($[M+Na]^+$), 258.

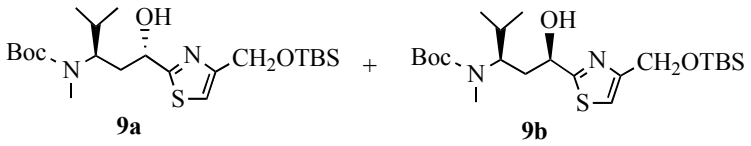


8

2-Bromo-4-((*tert*-butyldimethylsilyloxy)methyl)thiazole (8).[2] To an ice-cooled solution of ethyl 2-bromothiazole-4-carboxylate (10.2 g, 43.2 mmol) in anhydrous THF (50 mL) was added dropwise lithium borohydride (2.0 M solution in THF, 33.0 mL, 66.0 mmol) over 20 min. A solution of methanol (2.7 mL, 66.7 mmol) in anhydrous THF (10 mL) was then added over 30 min, and the mixture was stirred further overnight, allowing the temperature to rise to room temperature. The solvent was concentrated under vacuum, and the residue was dissolved in ethyl acetate (70 mL), washed with hydrochloric acid (1 *N*, 30 mL x 2), saturated sodium bicarbonate (30 mL), and brine (30 mL), dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (EtOAc/hexanes, 1:3) to give the corresponding alcohol (6.3 g, 75%) as a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.18 (t, 1 H, *J* = 0.9 Hz), 4.74 (d, 2 H, *J* = 0.9 Hz), 3.02 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.7, 136.4, 118.6, 60.4; IR (film, cm^{-1}) 3368, 2927, 1416, 1013.

To a solution of the above alcohol (6.3 g, 32.5 mmol) and imidazole (2.4 g, 40.0 mmol) in anhydrous DMF (30 mL) was added a solution of *tert*-butyldimethylchlorosilane (6.0 g, 40.0 mmol) in anhydrous THF (20 mL) over 30 min. The reaction mixture was stirred overnight, diluted with water (30 mL), and extracted with ether (50 mL x 4). The combined organic layers were washed with hydrochloric acid

(1 *N*, 30 mL), saturated sodium bicarbonate (30 mL), and brine (30 mL), dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (EtOAc/hexanes, 1:10) to give **8** (8.0 g, 60% for two steps) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.14 (t, 1 H, *J* = 1.4 Hz), 4.82 (d, 2 H, *J* = 1.4 Hz), 0.94 (s, 9 H), 0.11 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.6, 135.5, 117.2, 62.0, 25.8, 18.3, -5.4; IR (film, cm^{-1}) 2954, 2929, 2857, 1424, 1257, 1138, 1105, 1014, 838, 778.



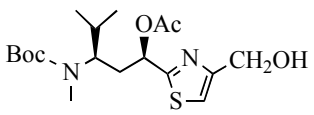
9a **9b**

***tert*-Butyl (1*S*,3*R*)- and (1*R*,3*R*)-1-(4-((*tert*-butyldimethylsilyloxy)methyl)thiazol-2-yl)-1-hydroxy-4-methylpentan-3-yl(methyl)carbamate (9a and 9b)**. To an ice-cooled solution of **8** (0.62 g, 2.0 mmol) in anhydrous THF (10 mL) was added dropwise *sec*-butylmagnesium chloride (1.7 M, 1.2 mL, 2.0 mmol) in THF. The reaction mixture was stirred for 30 min, treated dropwise over 10 min with a solution of **7** (0.23 g, 1.0 mmol) in anhydrous THF (5 mL), and stirred overnight, while the temperature was allowed to gradually warm up to room temperature. The reaction was then quenched by the addition of saturated ammonium chloride (10 mL), and the mixture was extracted with ethyl acetate (30 mL x 2). The combined organic layers were washed with hydrochloric acid (1 *N*, 10 mL), saturated sodium bicarbonate (10 mL), and brine (10 mL), dried (Na_2SO_4), concentrated under vacuum, and purified by chromatography on SiO_2 (Et_2O/hexanes, 1:3) to give **9a** (90 mg, 20%) and **9b** (0.18 g, 40%) as colorless oils.

(1*S*,3*R*)-Isomer **9a**: R_f = 0.32 (EtOAc/hexanes, 1:3); $[\alpha]_D^{23}$ -62.1 (*c* 1.2, CH_2Cl_2). ^{1}H NMR analysis at room temperature showed a 2.6:1 mixture of rotamers. Major rotamer:

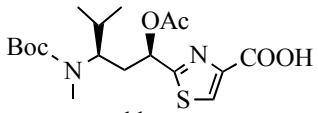
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.06 (s, 1 H), 5.04-4.92 (m, 1 H), 4.87-4.74 (m, 3 H), 3.83 (dt, 1 H, *J* = 10.5, 3.3 Hz), 2.41-2.19 (m, 2 H), 2.34 (s, 3 H), 1.80-1.68 (m, 1 H), 1.40 (s, 9 H), 1.00 (d, 3 H, *J* = 6.5 Hz), 0.94 (s, 9 H), 0.83 (d, 3 H, *J* = 6.5 Hz), 0.11 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.5, 157.6, 156.8, 113.1, 80.1, 70.7, 62.3, 58.0, 35.7, 30.2, 28.5, 25.9, 20.3, 19.7, 18.4, -5.3, -5.4. Characteristic signals of the minor rotamer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.13 (s, 1 H), 2.56 (s, 3 H), 1.42 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.6; IR (film, cm^{-1}) 3400, 2959, 2930, 2858, 1693, 1667, 1472, 1366, 1256, 1152, 1101, 839, 777; MS (ESI) *m/z* 481 ([M+Na]$^+$), 459 ([M+H]$^+$).

(1*R*,3*R*)-Isomer **9b**: R_f = 0.53 (EtOAc/hexanes, 1:3); $[\alpha]_D^{23}$ -12.0 (*c* 2.5, CH_2Cl_2). NMR analysis at room temperature showed a 6:1 mixture of rotamers. Major rotamer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.11 (t, 1 H, *J* = 1.2 Hz), 4.98 (d, 1 H, *J* = 3.4 Hz), 4.82 (d, 2 H, *J* = 1.1 Hz), 4.67 (dt, 1 H, *J* = 10.8, 3.1 Hz), 3.95 (dt, 1 H, *J* = 11.2, 3.2 Hz), 2.72 (s, 3 H), 2.03 (dt, 1 H, *J* = 13.0, 2.7 Hz), 1.92 (dt, 1 H, *J* = 12.4, 3.5 Hz), 1.77-1.67 (m, 1 H), 1.46 (s, 9 H), 0.94 (d, 3 H, *J* = 6.5 Hz), 0.93 (s, 9 H), 0.90 (d, 3 H, *J* = 6.5 Hz), 0.10 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.9, 158.4, 156.7, 113.1, 80.5, 69.1, 62.3, 57.7, 37.9, 29.7, 28.3, 28.1, 25.9, 20.1, 18.3, -5.4. Characteristic signals of the minor rotamer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.75 (s, 3 H), 1.50 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.4, 20.2; IR (film, cm^{-1}) 3400, 2959, 2930, 2858, 1693, 1662, 1472, 1366, 1256, 1136, 1102, 839, 778; HRMS (EI) calcd for $C_{22}H_{42}N_2O_4SSi$ 458.2635, found 458.2638.



10

(1*R*,3*R*)-3-(*tert*-Butoxycarbonyl(methyl)amino)-1-(4-(hydroxymethyl)thiazol-2-yl)-4-methylpentyl acetate (10). To an ice-cooled solution of **9b** (85 mg, 0.18 mmol) and triethylamine (0.10 mL, 0.72 mmol) in dichloromethane (4 mL) was added acetyl chloride (0.05 mL, 0.70 mmol). The reaction mixture was stirred for 3 h and allowed to gradually warm up to room temperature. The solution was diluted with ether (40 mL), washed with saturated sodium bicarbonate (10 mL x 2) and brine (10 mL), dried (Na_2SO_4), and concentrated to give the ester as a yellow oil which was used without further purification. A solution of this oil in THF (1 mL) was treated with tetrabutylammonium fluoride (1.0 M solution in THF, 1.0 mL, 1.0 mmol) at room temperature overnight, diluted with ethyl acetate (40 mL), washed with brine (10 mL), dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (EtOAc/hexanes, 1:1) to give **10** (45 mg, 63% for two steps) as a colorless oil: $[\alpha]_D^{23}$ +15.1 (*c* 1.5, CH_2Cl_2). ^{1}H NMR analysis at room temperature showed a 2:1 mixture of rotamers. Major rotamer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.14 (s, 1 H), 5.83 (dd, 1 H, *J* = 11.6, 2.8 Hz), 4.74 (s, 2 H), 4.07 (dt, 1 H, *J* = 11.1, 3.6 Hz), 2.80 (bs, 1 H), 2.69 (s, 3 H), 2.33 (ddd, 1 H, *J* = 14.9, 11.5, 3.6 Hz), 2.14 (s, 3 H), 2.02 (ddd, 1 H, *J* = 14.7, 12.0, 2.8 Hz), 1.72-1.64 (m, 1 H), 1.44 (s, 9 H), 0.97 (d, 3 H, *J* = 6.6 Hz), 0.86 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.8, 170.2, 156.3, 156.2, 114.7, 79.3, 70.5, 69.3, 60.9, 56.3, 34.9, 30.4, 28.3, 28.0, 20.9, 19.9, 19.5. Characteristic signals of the minor rotamer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.15 (s, 1 H), 5.91 (dd, 1 H, *J* = 9.0, 3.9 Hz), 3.84-3.69 (m, 1 H), 2.97 (bs, 1 H), 2.62 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.9, 169.5, 156.4, 115.0, 79.7, 60.8, 30.7, 28.4, 21.0, 20.2, 19.7; IR (film, cm^{-1}) 3434, 2971, 1755, 1689, 1367, 1223, 1157; HRMS (ESI) calcd for $C_{18}H_{30}N_2O_5NaS$ (M+Na) 409.1773, found 409.1780.

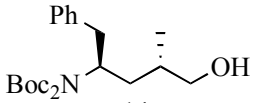


11

2-((1*R*,3*R*)-1-Acetoxy-3-(*tert*-butoxycarbonyl(methyl)amino)-4-methylpentyl)-thiazole-4-carboxylic acid (11). Dess-Martin periodinane (48 mg, 0.11 mmol) was added to a solution of **10** (30 mg, 0.08 mmol) in anhydrous dichloromethane (2 mL). The reaction mixture was stirred at room temperature for 6 h, diluted with ether (30 mL), washed with a mixture of sodium hydroxide (1.0 *N*, 5 mL) and sodium thiosulfate (1.0 M, 5 mL), saturated sodium bicarbonate (10 mL), and brine (10 mL), dried (Na_2SO_4), and concentrated under vacuum to give the crude aldehyde (29 mg, 99%) as a colorless oil. ^{1}H NMR analysis at room temperature showed a 2.5:1 mixture of rotamers. Major rotamer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.99 (s, 1 H), 8.13 (s, 1 H), 5.87 (dd, 1 H, *J* = 11.6, 2.9 Hz), 4.14-4.04 (m, 1 H), 2.70 (s, 3 H), 2.41-2.31 (m, 1 H), 2.16 (s, 3 H), 2.13-2.07 (m, 1 H), 1.76-1.64 (m, 1 H), 1.43 (s, 9 H), 0.98 (d, 3 H, *J* = 6.6 Hz), 0.86 (d, 3 H, *J* = 6.6 Hz). Characteristic signals of the minor rotamer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.00 (s, 1 H), 8.14 (s, 1 H), 5.94 (dd, 1 H, *J* = 9.8, 2.9 Hz).

A solution of this crude aldehyde (29 mg, 0.08 mmol) in *tert*-butyl alcohol (2 mL) was treated with a solution of 2-methyl-2-butene in THF (2 M, 0.3 mL, 0.60 mmol), followed by the dropwise addition of a mixture of sodium chlorite (39 mg, 0.43 mmol) and sodium dihydrogenphosphate monohydrate (0.13 g, 0.97 mmol) in water (1.0 mL). The reaction mixture was stirred further at room temperature for 6 h, diluted with hydrochloric acid (0.1 *N*, 10 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were dried (Na_2SO_4), concentrated under vacuum, and purified

by chromatography on SiO_2 (CH_2Cl_2/MeOH/AcOH, 95:5:0.5) to give **11** (28 mg, 90% for two steps) as a colorless oil: $[\alpha]_D^{23}$ +5.0 (*c* 1.1, CH_2Cl_2). ^{1}H NMR analysis at room temperature showed a 2:1 mixture of rotamers. Major rotamer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (bs, 1 H), 5.89 (d, 1 H, *J* = 10.4 Hz), 4.10 (t, 1 H, *J* = 10.8 Hz), 2.70 (s, 3 H), 2.32-2.23 (m, 1 H), 2.17 (s, 3 H), 1.71-1.66 (m, 1 H), 1.44 (s, 9 H), 0.97 (d, 3 H, *J* = 6.3 Hz), 0.86 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.5, 170.1, 163.4, 156.4, 146.9, 128.2, 79.5, 69.5, 65.8, 56.5, 34.8, 30.5, 28.4, 20.8, 20.6, 20.0, 19.5, 15.2; Characteristic signals of the minor rotamer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.98-5.95 (m, 1 H), 3.81-3.75 (m, 1 H), 2.64 (s, 3 H), 2.11 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.9, 170.6, 169.4, 156.5, 80.0, 70.7, 30.7, 29.7, 28.5, 20.9, 20.3, 19.7; IR (film, cm^{-1}) 3119, 2972, 1744, 1689, 1484, 1391, 1368, 1221, 1158; HRMS (ESI) calcd for $C_{18}H_{28}N_2O_6NaS$ (M+Na) 423.1566, found 423.1608.

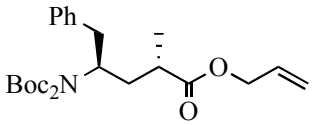


14

Di-*tert*-butyl (2*R*,4*S*)-5-hydroxy-4-methyl-1-phenylpentan-2-yliminodicarbonate (14). To a solution of **12**[4] (1.0 g, 1.9 mmol) in anhydrous THF (15 mL) cooled in a dry ice/acetone bath was added butyllithium (1.6 M solution in hexanes, 1.8 mL, 2.5 mmol) dropwise over 5 min. The reaction mixture was stirred for 30 min before a solution of di-*tert*-butyl dicarbonate (0.75 g, 3.3 mmol) in anhydrous THF (5 mL) was introduced in one portion. The solution was stirred further overnight, and the temperature was allowed to gradually rise to room temperature. The reaction was quenched with saturated ammonium chloride (10 mL), and extracted with ethyl acetate (30 mL x 2). The

combined organic layers were washed with hydrochloric acid (1 *N*, 10 mL) and brine (10 mL x 2), dried (Na_2SO_4), and concentrated under vacuum to give a colorless oil which was used without further purification.

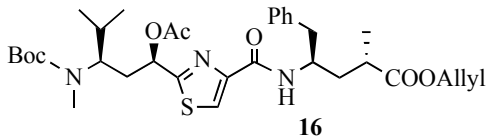
A solution of this oil in THF (2 mL) was treated with tetrabutylammonium fluoride (1.0 M solution in THF, 4.0 mL, 4.0 mmol) at room temperature overnight. The mixture was then diluted with ethyl acetate (70 mL), washed with brine (10 mL x 2), dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (EtOAc/hexanes, 1:1) to give **14** (0.44 g, 59% for two steps) as a colorless oil: $[\alpha]_D^{23}$ -69.2 (*c* 1.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28-7.15 (m, 5 H), 4.55-4.46 (m, 1 H), 3.56-3.44 (m, 2 H), 3.18 (dd, 1 H, *J* = 13.4 Hz, 9.7 Hz), 2.82 (dd, 1 H, *J* = 13.4, 5.9 Hz), 1.88-1.61 (m, 3 H), 1.40 (s, 18 H), 0.96 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.5, 139.0, 129.4, 128.2, 126.1, 81.9, 67.8, 57.5, 40.2, 36.3, 32.9, 27.9, 17.6; IR (film, cm^{-1}) 3436, 2978, 2932, 1738, 1699, 1346, 1145; MS (ESI) *m*/*z* 416 ($[M+Na]^+$); HRMS (ESI) calcd for $C_{22}H_{35}NO_5Na$ (M+Na) 416.2413, found 416.2435.



15

(2*S*,4*R*)-Allyl 4-(bis(*tert*-butoxycarbonyl)amino)-2-methyl-5-phenylpentanoate (15). Alcohol **14** (0.39 g, 1.0 mmol) was oxidized by the same two-step sequence as described for **10** to give the corresponding crude carboxylic acid (0.68 g) as a colorless oil. A solution of this oil in DMF (3 mL) was mixed with cesium carbonate (0.91 g, 2.8 mmol) and allyl bromide (1.0 mL, 11.5 mmol), stirred overnight, diluted in water (15 mL) and extracted with ethyl acetate (30 mL x 2). The combined organic layers were washed with

brine (15 mL x 2), dried (Na_2SO_4), concentrated under vacuum, and purified by chromatography on SiO_2 (EtOAc/hexanes, 1:7) to give **15** (0.36 g, 81% for three steps) as a colorless oil: $[\alpha]_D^{23}$ -26.7 (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27-7.17 (m, 5 H), 5.94-5.85 (m, 1 H), 5.32-5.18 (m, 2 H), 4.65-4.45 (m, 3 H), 3.16 (dd, 1 H, *J* = 13.4, 9.6 Hz), 2.83 (dd, 1 H, *J* = 13.5, 6.1 Hz), 2.54 (sextet, 1 H, *J* = 7.1 Hz), 2.05-2.00 (m, 2 H), 1.40 (s, 18 H), 1.20 (d, 3 H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.7, 153.1, 138.7, 132.5, 129.4, 128.2, 126.2, 117.8, 81.8, 65.0, 57.3, 40.0, 36.8, 36.3, 27.9, 18.3; IR (film, cm^{-1}) 2979, 2935, 1738, 1701, 1456, 1345, 1228, 1145; MS (ESI) *m*/*z* 470 ($[M+Na]^+$); HRMS (ESI) calcd for $C_{23}H_{37}NO_6Na$ (M+Na) 470.2519, found 470.2516.

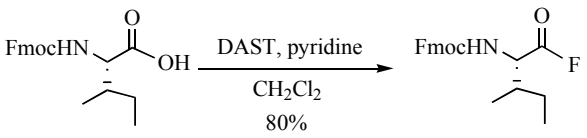


16

(2*S*,4*R*)-Allyl 4-(2-((1*R*,3*R*)-1-acetoxy-3-(*tert*-butoxycarbonyl(methyl)amino)-4-methylpentyl)thiazole-4-carboxamido)-2-methyl-5-phenylpentanoate (16). To a solution of **15** (0.20 g, 0.45 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1 mL, 13 mmol). The reaction mixture was stirred at room temperature for 2 h, diluted with ethyl acetate (60 mL), washed with saturated sodium bicarbonate (15 mL x 2), dried (Na_2SO_4), and concentrated under vacuum to give the crude amine (0.13 g, 100%) as a colorless oil: MS (ESI) *m*/*z* 248 ($[M+H]^+$).

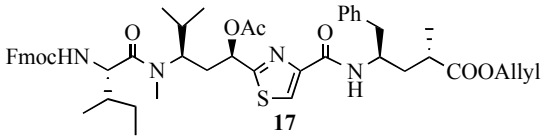
To a solution of **11** (82 mg, 0.21 mmol) and triethylamine (0.06 mL, 0.45 mmol) in anhydrous THF (4 mL) cooled to -20 ºC was added dropwise isobutyl chloroformate (0.05 mL, 0.37 mmol), and the resulting white suspension was stirred further for 30 min. A solution of the above crude amine (0.13 g, 0.45 mmol) in anhydrous THF (2 mL) was

then added via cannula, and the mixture was stirred overnight, allowing the temperature to gradually rise to room temperature. The mixture was then diluted with ethyl acetate (70 mL), washed with brine (15 mL x 2), dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (EtOAc/hexanes, 1:2) to give **16** (0.10 g, 76% for two steps) as a white solid: Mp 105.1-107.0 ºC; $[\alpha]_D^{23}$ +9.9 (*c* 0.81, CH_2Cl_2). ^{1}H NMR analysis at room temperature showed a 3:1 mixture of rotamers. Major rotamer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (s, 1 H), 7.31-7.25 (m, 5 H), 7.16 (d, 1 H, *J* = 9.2 Hz), 5.99-5.89 (m, 1 H), 5.84 (dd, 1 H, *J* = 11.7 Hz, 3.0 Hz), 5.32 (d, 1 H, *J* = 17.4 Hz), 5.23 (d, 1 H, *J* = 10.2 Hz), 4.59 (d, 2 H, *J* = 5.4 Hz), 4.50-4.43 (m, 1 H), 4.13 (dt, 1 H, *J* = 11.1, 3.9 Hz), 3.04-2.89 (m, 2 H), 2.76 (s, 3 H), 2.70 (m, 1 H), 2.38-2.29 (m, 1 H), 2.20 (s, 3 H), 2.12-2.01 (m, 2 H), 1.79-1.63 (m, 2 H), 1.49 (s, 9 H), 1.23 (d, 3 H, *J* = 7.0 Hz), 1.05 (d, 3 H, *J* = 6.7 Hz), 0.93 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.7, 170.4, 170.1, 160.3, 156.2, 150.0, 137.6, 132.3, 129.5, 128.4, 126.5, 123.2, 117.8, 79.4, 70.8, 69.2, 65.1, 56.4, 48.4, 41.1, 37.7, 36.6, 35.0, 30.4, 28.4, 20.8, 20.0, 19.6, 17.7. Characteristic signals of the minor rotamer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.71 (s, 3 H), 2.21 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4, 150.2, 137.7, 129.4, 123.1, 79.7, 48.5, 41.3, 37.8, 35.5, 30.6, 28.2, 20.9, 20.3, 19.7, 17.8; IR (film, cm^{-1}) 3391, 3306, 2971, 2933, 1735, 1686, 1540, 1367, 1164; HRMS (EI) calcd for $C_{33}H_{47}N_3O_7S$ 629.3135, found 629.3132.



Fmoc-Ile-F.[5] To a solution of Fmoc-Ile-OH (3.5 g, 10.0 mmol) and pyridine (0.81 mL, 10.0 mmol) in anhydrous dichloromethane (60 mL) was added via cannula a solution of

(diethylamino)sulfur trifluoride (1.6 mL, 12.1 mmol) in dichloromethane (10 mL) over 10 min. The reaction mixture was stirred at room temperature for 30 min, diluted with dichloromethane (40 mL), washed with ice-cold water (100 mL x 2), dried ($MgSO_4$), filtered, concentrated, and recrystallized from dichloromethane/hexanes to give the acyl fluoride (2.8 g, 80%) as a white solid: Mp 113.1-114.4 ºC (lit.[5b] 115-116 ºC); $[\alpha]_D^{23}$ +15.9 (*c* 0.51, EtOAc) (lit.[5b] $[\alpha]_D^{23}$ +15.6 (*c* 0.51, EtOAc)); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 (d, 2 H, *J* = 7.6 Hz), 7.61 (d, 2 H, *J* = 7.2 Hz), 7.43 (t, 2 H, *J* = 7.4 Hz), 7.34 (dt, 2 H, *J* = 7.4, 1.1 Hz), 5.27 (d, 1 H, *J* = 8.7 Hz), 4.55 (dd, 1 H, *J* = 8.7, 4.5 Hz), 4.48 (d, 2 H, *J* = 6.8 Hz), 4.25 (t, 1 H, *J* = 6.7 Hz), 2.05-1.95 (m, 1 H), 1.55-1.44 (m, 1 H), 1.35-1.21 (m, 1 H), 1.04 (d, 3 H, *J* = 6.8 Hz), 0.99 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.3 (d, *J* = 372.1 Hz), 155.9, 143.6, 143.5, 141.3, 127.8, 127.1, 124.9, 120.0, 67.2, 57.5 (d, *J* = 57.2 Hz), 47.1, 37.1, 25.0, 15.4, 11.4; ^{19}F NMR ($CDCl_3$, 282 MHz) δ ($CFCl_3$ as the external standard) 34.8; IR (film, cm^{-1}) 3324, 2968, 1843, 1705, 1520, 1451, 1256, 1082; MS (ESI) *m*/*z* 378 ($[M+Na]^+$).

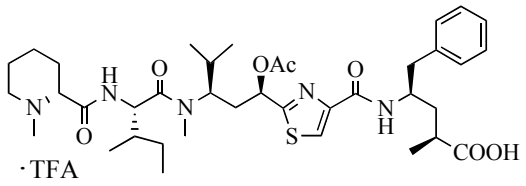


17

(2*S*,4*R*)-Allyl 4-(2-((5*S*,8*R*,10*R*)-5-*sec*-butyl-1-(9*H*-fluoren-9-yl)-8-isopropyl-7-methyl-3,6,12-trioxo-2,11-dioxa-4,7-diazatridecan-10-yl)thiazole-4-carboxamido)-2-methyl-5-phenylpentanoate (17). To a solution of **16** (53 mg, 84 μmol) in dichloromethane (2 mL) was added trifluoroacetic acid (0.3 mL, 3.9 mmol). The reaction mixture was stirred at room temperature for 10 h, diluted with ethyl acetate (60 mL), washed with saturated sodium bicarbonate (15 mL x 2), dried (Na_2SO_4), and concentrated

under vacuum to give the crude amine (56 mg) as a colorless oil: MS (ESI) *m*/*z* 552 ($[M+Na]^+$), 530 ($[M+H]^+$).

A solution of this amine (56 mg, 84 μmol) in anhydrous DMF (0.5 mL) was treated with diisopropylethylamine (0.05 mL, 0.28 mmol) and Fmoc-Ile-F (0.10 g, 0.28 mmol), stirred at room temperature for 18 h, diluted with ethyl acetate (50 mL), washed with saturated sodium bicarbonate (10 mL) and brine (10 mL), dried (Na_2SO_4), concentrated under vacuum, and purified by chromatography on SiO_2 (EtOAc/hexanes, 1:1) to give **17** (58 mg, 80%) as a colorless syrup: $[\alpha]_D^{23}$ +0.29 (*c* 0.70, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.02 (s, 1 H), 7.77 (d, 2 H, *J* = 7.4 Hz), 7.59 (d, 2 H, *J* = 6.8 Hz), 7.41 (t, 2 H, *J* = 7.3 Hz), 7.34-7.22 (m, 7 H), 7.11 (d, 1 H, *J* = 9.2 Hz), 5.94-5.82 (m, 1 H), 5.65 (d, 1 H, *J* = 9.3 Hz), 5.44 (d, 1 H, *J* = 9.6 Hz), 5.28 (dd, 1 H, *J* = 17.2, 1.4 Hz), 5.20 (d, 1 H, *J* = 10.4 Hz), 4.58-4.54 (m, 3 H), 4.44-4.32 (m, 3 H), 4.14 (t, 1 H, *J* = 7.0 Hz), 3.00 (s, 3 H), 2.96-2.86 (m, 2 H), 2.70-2.60 (m, 1 H), 2.38-2.31 (m, 1 H), 2.19 (s, 3 H), 2.11-2.00 (m, 3 H), 1.77-1.61 (m, 3 H), 1.20 (d, 3 H, *J* = 7.1 Hz), 1.04 (d, 3 H, *J* = 6.5 Hz), 1.00 (d, 3 H, *J* = 6.7 Hz), 0.94 (t, 3 H, *J* = 7.3 Hz), 0.83 (d, 3 H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.7, 173.6, 170.0, 169.9, 160.2, 156.3, 150.0, 143.9, 143.7, 141.3, 141.2, 137.5, 132.2, 129.6, 128.4, 127.6, 127.0, 126.5, 125.1, 125.0, 123.4, 119.9, 117.9, 69.5, 67.0, 65.1, 55.8, 48.3, 47.2, 41.0, 37.6, 37.3, 36.6, 34.6, 29.9, 29.6, 23.8, 20.8, 20.1, 19.5, 17.6, 16.0, 11.2; IR (film, cm^{-1}) 3291, 2966, 2935, 1717, 1645, 1538, 1495, 1410, 1222; MS (ESI) *m*/*z* 887 ($[M+Na]^+$), 865 ($[M+H]^+$).



1

***N*[14]-Desacetoxytubulysin H trifluoroacetic acid salt (1)**. To a solution of **17** (17 mg, 20 μmol) in dichloromethane (0.5 mL) was added tris(2-aminoethyl)amine (0.05 mL, 0.33 mmol). The reaction mixture was stirred at room temperature for 3 h, diluted with ethyl acetate (20 mL), washed with saturated sodium bicarbonate (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated under vacuum to give the crude amine (14 mg) as a colorless oil: MS (ESI) *m*/*z* 665 ($[M+Na]^+$), 643 ($[M+H]^+$).

To a mixture of *N*-methyl-D-pipecolinic acid (9 mg, 63 μmol) (prepared[6] from D-pipecolinic acid) and *N*,*N*'-dicyclohexylcarbodiimide (18 mg, 86 μmol) in anhydrous DMF (0.4 mL) was added pentafluorophenol (12 mg, 65 μmol). The reaction mixture was stirred at room temperature overnight, filtered through a 0.2 μm Millex micro-filter unit to give a clear solution, and added to the crude amine (14 mg, ~20 μmol). The reaction mixture was stirred at room temperature for 24 h, and purified by chromatography on SiO_2 (1:1 EtOAc/hexanes to wash out less polar impurities, followed by 2% MeOH in EtOAc to elute the product) to give the crude allyl ester of **1** (15 mg) as a yellow oil: MS (ESI) *m*/*z* 790 ($[M+Na]^+$), 768 ($[M+H]^+$).

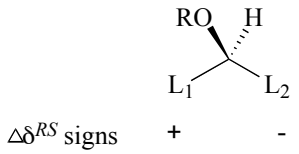
A solution of this allyl ester (15 mg, <20 μmol)), tetrakis(triphenylphosphine)palladium(0) (3 mg, 2.6 μmol) and dimedone (11 mg, 78 μmol) in THF (0.5 mL) under an Ar atmosphere was stirred at room temperature overnight. After evaporation of the volatiles, the residue was purified by chromatography on SiO_2 (1:1 EtOAc/hexanes to wash out less polar impurities, followed by 10% MeOH

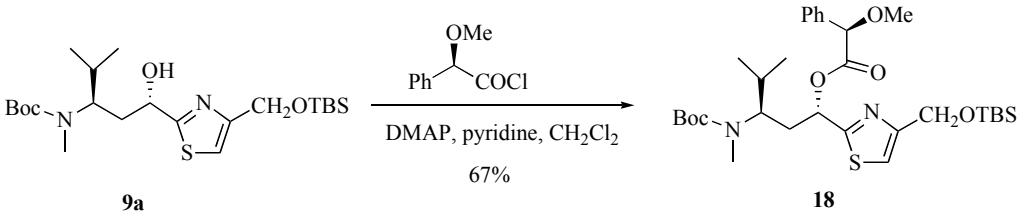
in CH_2Cl_2 to elute the product) to give a yellow oil. Further purification by semi-preparative HPLC (Dynamax Microsorb C-18 column, 250 mm × 10 mm; methanol/0.1% TFA in water; methanol gradient from 60% to 99% over 30 min; 2 mL/min) gave **1** (7.1 mg, 44% for three steps) as a colorless syrup: τ_R = 19.8 min; $[\alpha]_D^{23}$ -17.4 (*c* 0.46, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 8.63 (d, 1 H, *J* = 8.0 Hz), 8.09 (s, 1 H), 8.07 (bs, 1 H), 7.24-7.23 (m, 4 H), 7.19-7.16 (m, 1 H), 5.72 (dd, 1 H, *J* = 11.0, 2.5 Hz), 4.74-4.70 (m, 1 H), 4.42-4.36 (m, 2 H), 3.75 (dd, 1 H, *J* = 12.8, 3.8 Hz), 3.49-3.45 (m, 1 H), 3.12 (s, 3 H), 3.11-3.04 (m, 1 H), 2.90 (dd, 2 H, *J* = 6.8, 3.2 Hz), 2.74 (s, 3 H), 2.58-2.53 (m, 1 H), 2.39 (ddd, 1 H, *J* = 14.5, 11.5, 3.2 Hz), 2.33-2.28 (m, 1 H), 2.18-2.16 (m, 1 H), 2.15 (s, 3 H), 2.01 (ddd, 1 H, *J* = 14.0, 10.0, 4.0 Hz), 1.95-1.89 (m, 4 H), 1.81-1.74 (m, 2 H), 1.67 (ddd, 1 H, *J* = 14.4, 10.1, 4.5 Hz), 1.61-1.56 (m, 2 H), 1.23-1.20 (m, 1 H), 1.17 (d, 3 H, *J* = 7.0 Hz), 1.04 (d, 3 H, *J* = 6.5 Hz), 1.01 (d, 3 H, *J* = 7.0 Hz), 0.94 (t, 3 H, *J* = 7.2 Hz), 0.85 (d, 3 H, *J* = 7.0 Hz); ^{13}C NMR (CD_3OD, 75 MHz) δ 179.9, 174.6, 171.8, 171.6, 169.2, 162.8, 150.8, 139.5, 130.5, 129.3, 127.4, 125.1, 71.2, 68.0, 58.4, 56.2, 56.0, 50.7, 42.9, 42.2, 39.1, 37.8, 37.4, 35.6, 30.9, 30.2, 25.2, 24.0, 22.3, 20.8, 20.5, 20.3, 18.5, 16.2, 11.3; IR (film, cm^{-1}) 3258, 2964, 2929, 2877, 1735, 1676, 1546, 1373, 1446, 1373, 1204, 1134; MS (ESI) *m*/*z* 750 ($[M+Na]^+$), 728 ($[M+H]^+$); HRMS (EI) calcd for $C_{38}H_{55}N_5O_6S$ ($M–H_2O$) 709.3873, found 709.3863.

Determination of the Absolute Configurations of 9a and 9b

To determine the absolute configurations of **9a** and **9b**, a double derivatization of each epimer with (*R*)- and (*S*)-α-phenylacetic acid (MPA) was performed. The ^{1}H NMR spectra of both ester derivatives were recorded, and the $\Delta\delta^{RS}$ (δ^R - δ^S) for the hydrogens

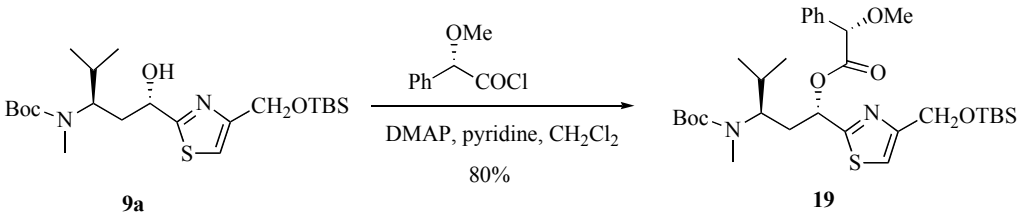
on both sides of the stereogenic carbon was calculated. The two substituents on the stereogenic carbon were then designated as L_1 ($\Delta\delta^{RS} > 0$) and L_2 ($\Delta\delta^{RS} < 0$) and fitted to the following model to determine the absolute configuration.[7]





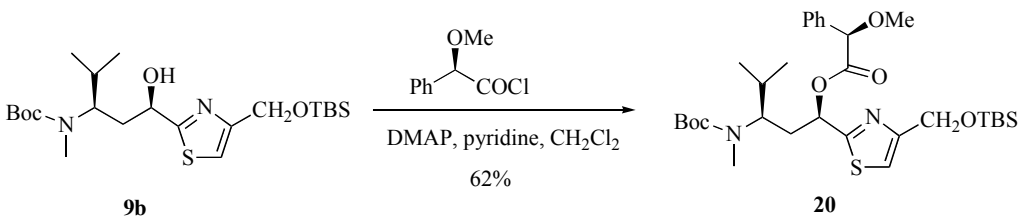
(*R*)-((1*S*,3*R*)-3-(*tert*-Butoxycarbonyl(methyl)amino)-1-(4-((*tert*-butyldimethylsilyl-oxy)methyl)thiazol-2-yl)-4-methylpentyl) 2-methoxy-2-phenylacetate (18). To a solution of (*R*)-(-)-α-phenylacetic acid (10 mg, 60 μmol) in anhydrous dichloromethane (0.05 mL) was added thionyl chloride (0.05 mL, 0.68 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent and excess thionyl chloride were removed by vacuum, and the residue was redissolved in anhydrous dichloromethane (0.2 mL) and added via syringe to a solution of **9a** (5 mg, 11 μmol), DMAP (1 mg, 9 μmol), and pyridine (46 mg, 0.58 mmol) in dichloromethane. The mixture was stirred at room temperature for 1 h, treated with saturated sodium bicarbonate (5 mL), extracted with ethyl acetate (30 mL), washed with brine (10 mL), dried (Na_2SO_4), concentrated, and purified by chromatography on SiO_2 (EtOAc/hexanes, 1:10) to give **18** (4.4 mg, 67%) as a colorless oil. ^{1}H NMR analysis at room temperature showed a 1.5:1 mixture of rotamers. Major rotamer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48-7.34 (m, 5 H), 7.21 (s, 1

H), 5.95 (quintet, 1 H, *J* = 4.6 Hz), 4.85 (s, 2 H), 4.77 (s, 1 H), 3.62 (bs, 1 H), 3.39 (s, 3 H), 2.62 (s, 3 H), 2.47-2.35 (m, 1 H), 1.97-1.60 (m, 2 H), 1.27 (s, 9 H), 0.96 (s, 9 H), 0.86 (d, 3 H, *J* = 6.5 Hz), 0.75 (d, 3 H, *J* = 6.5 Hz), 0.12 (s, 6 H); Characteristic signals of the minor rotamer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.16 (s, 1 H), 4.84 (s, 2 H), 4.81 (s, 1 H), 3.40 (s, 3 H), 2.52 (s, 3 H), 1.41 (s, 9 H), 0.95 (s, 9 H), 0.80 (d, 3 H, *J* = 7.0 Hz), 0.72 (d, 3 H, *J* = 7.0 Hz), 0.12 (s, 6 H); MS (ESI) *m*/*z* 629 ([M+Na]$^+$), 607 ([M+H]$^+$).



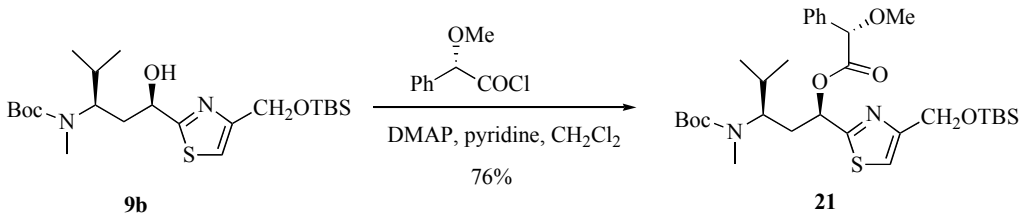
9a **19**

(*S*)-((1*S*,3*R*)-3-(*tert*-Butoxycarbonyl(methyl)amino)-1-(4-((*tert*-butyldimethylsilyl-oxy)methyl)thiazol-2-yl)-4-methylpentyl) 2-methoxy-2-phenylacetate (19). According to the protocol used for **18**, **9a** (7 mg, 15 μmol) provided **19** (7.4 mg, 80%) as a colorless oil. ^{1}H NMR analysis at room temperature showed a 1.6:1 mixture of rotamers. Major rotamer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43-7.32 (m, 5 H), 7.06 (s, 1 H), 6.00-5.98 (m, 1 H), 4.80 (s, 1 H), 4.78 (d, 2 H, *J* = 1.0 Hz), 3.78 (bs, 1 H), 3.40 (s, 3 H), 2.73 (s, 3 H), 2.52-2.43 (m, 1 H), 2.21-2.04 (m, 1 H), 1.75-1.65 (m, 1 H), 1.44 (s, 9 H), 0.95-0.93 (m, 12 H), 0.81 (d, 3 H, *J* = 7.0 Hz), 0.10 (s, 6 H); Characteristic signals of the minor rotamer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.02 (s, 1 H), 4.88 (s, 1 H), 4.77 (d, 2 H, *J* = 0.5 Hz), 3.43 (s, 3 H), 2.57 (s, 3 H), 1.34 (s, 9 H), 0.80 (d, 3 H, *J* = 7.0 Hz), 0.09 (s, 6 H); MS (ESI) *m*/*z* 629 (M+Na]$^+$), 607 ([M+H]$^+$).



9b **20**

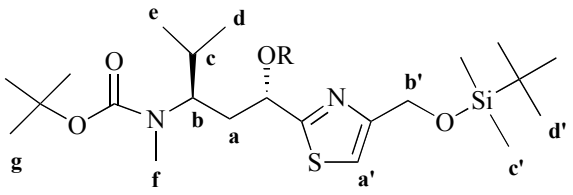
(*R*)-((1*R*,3*R*)-3-(*tert*-Butoxycarbonyl(methyl)amino)-1-(4-((*tert*-butyldimethylsilyl-oxy)methyl)thiazol-2-yl)-4-methylpentyl) 2-methoxy-2-phenylacetate (20). According to the protocol used for **18**, **9b** (5 mg, 11 μmol) was converted into colorless, oily **20** (4.1 mg, 62%). ^{1}H NMR analysis at room temperature showed a 2.6:1 mixture of rotamers. Major rotamer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45-7.32 (m, 5 H), 6.93 (t, 1 H, J = 1.2 Hz), 5.88 (dd, 1 H, J = 11.2, 2.8 Hz), 4.97 (s, 1 H), 4.74 (s, 2 H), 4.08-4.04 (m, 1 H), 3.48 (s, 3 H), 2.70 (s, 3 H), 2.25-2.15 (m, 1 H), 2.09-2.03 (m, 1 H), 1.72-1.67 (m, 1 H), 1.47 (s, 9 H), 0.96 (d, 3 H, J = 6.5 Hz), 0.92 (s, 9 H), 0.88 (d, 3 H, J = 6.5 Hz), 0.07 (s, 6 H); Characteristic signals of the minor rotamer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.98 (s, 1 H), 6.00 (t, 1 H, J = 6.2 Hz), 4.84 (s, 1 H), 3.39 (s, 3 H), 2.65 (s, 3 H), 1.43 (s, 9 H), 0.92 (s, 9 H), 0.84 (d, 6 H, J = 6.5 Hz), 0.09 (s, 6 H); MS (ESI) *m*/*z* 629 ($[M+Na]^+$), 607 ($[M+H]^+$).



9b **21**

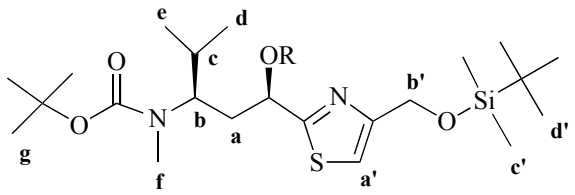
(*S*)-((1*R*,3*R*)-3-(*tert*-Butoxycarbonyl(methyl)amino)-1-(4-((*tert*-butyldimethylsilyl-oxy)methyl)thiazol-2-yl)-4-methylpentyl) 2-methoxy-2-phenylacetate (21). According to the protocol used for **18**, **9b** (5.4 mg, 12 μmol) was converted into colorless, oily **21** (5.4 mg, 76%). ^{1}H NMR analysis at room temperature showed a 1.1:1 mixture of

rotamers. Major rotamer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51-7.32 (m, 5 H), 7.09 (s, 1 H), 5.92 (t, 1 H, *J* = 6.8 Hz), 4.87 (s, 1 H), 4.82 (d, 2 H, *J* = 1.0 Hz), 3.43 (s, 3 H), 2.71-2.62 (m, 1 H), 2.51 (s, 3 H), 2.28-2.15 (m, 2 H), 1.78-1.63 (m, 1 H), 1.42 (s, 9 H), 0.95 (s, 9 H), 0.87 (d, 3 H, *J* = 6.5 Hz), 0.79 (d, 3 H, *J* = 6.5 Hz), 0.12 (s, 6 H); Characteristic signals of the minor rotamer: 7.13 (s, 1 H), 5.96-5.95 (m, 1 H), 4.85 (s, 1 H), 4.83 (d, 2 H, *J* = 1.0 Hz), 3.51 (s, 3 H), 1.37 (s, 9 H), 0.81 (d, 3 H, *J* = 6.5 Hz), 0.74 (d, 3 H, *J* = 6.0 Hz), 0.11 (s, 6 H); MS (ESI) *m*/*z* 629 ([M+Na]$^+$).



^{1}H	b	d	e	f	g	a’	b’	c’	d’
δ^R (**18**)	3.62 (-)	0.86 (0.80)	0.75 (0.72)	2.62 (2.52)	1.27 (1.41)	7.21 (7.16)	4.85 (4.84)	0.12 (0.12)	0.96 (0.95)
δ^S (**19**)	3.78 (-)	0.94 (0.93)	0.81 (0.80)	2.73 (2.57)	1.44 (1.34)	7.06 (7.02)	4.78 (4.77)	0.10 (0.09)	0.94 (-)
$\Delta\delta^{RS}$ (δ^R - δ^S)	-0.16 (-)	-0.08 (-0.13)	-0.06 (-0.08)	-0.11 (-0.05)	-0.17 (0.07)	0.15 (0.14)	0.07 (0.07)	0.02 (0.03)	0.02 (-)

Table 1. Proton chemical shifts differences between **18** and **19**. The values in parentheses are characteristic signals of the minor rotamers.



^{1}H	d	e	f	g	a'	b'	c'	d'
δ^R (**20**)	0.96 (-)	0.88 (0.84)	2.70 (2.65)	1.47 (1.43)	6.93 (6.98)	4.74 (-)	0.07 (0.09)	0.92 (0.92)
δ^S (**21**)	0.87 (0.81)	0.79 (0.74)	2.51 (-)	1.42 (1.37)	7.09 (7.13)	4.82 (4.83)	0.12 (0.11)	0.95 (-)
$\Delta\delta^{RS}$	0.09 (-)	0.09 (0.10)	0.19 (-)	0.05 (0.06)	-0.16 (-0.15)	-0.08 (-)	-0.05 (-0.02)	-0.03 (-)

Table 2. Proton chemical shifts differences between **20** and **21**. The values in parentheses are characteristic signals of the minor rotamers.

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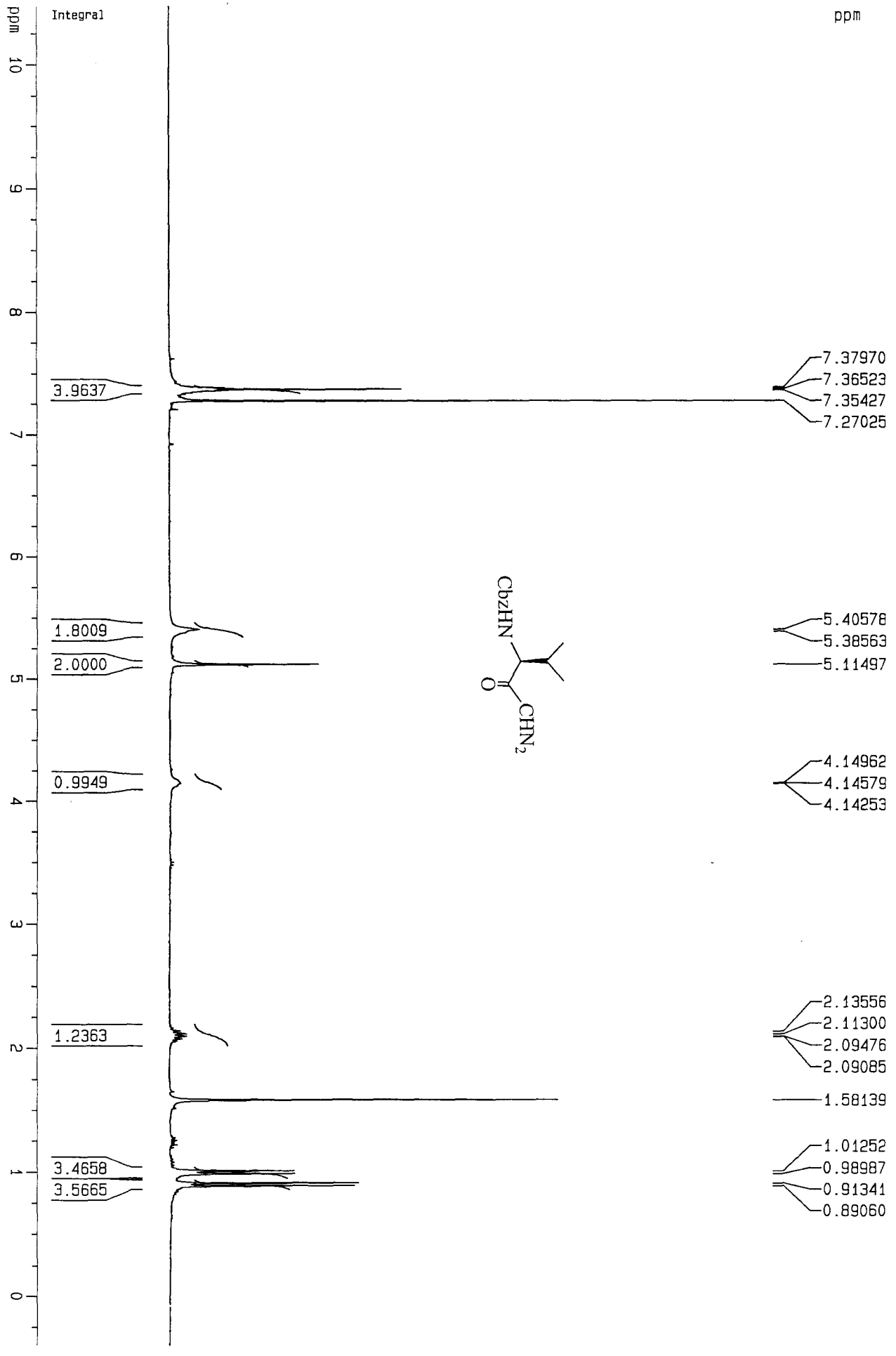

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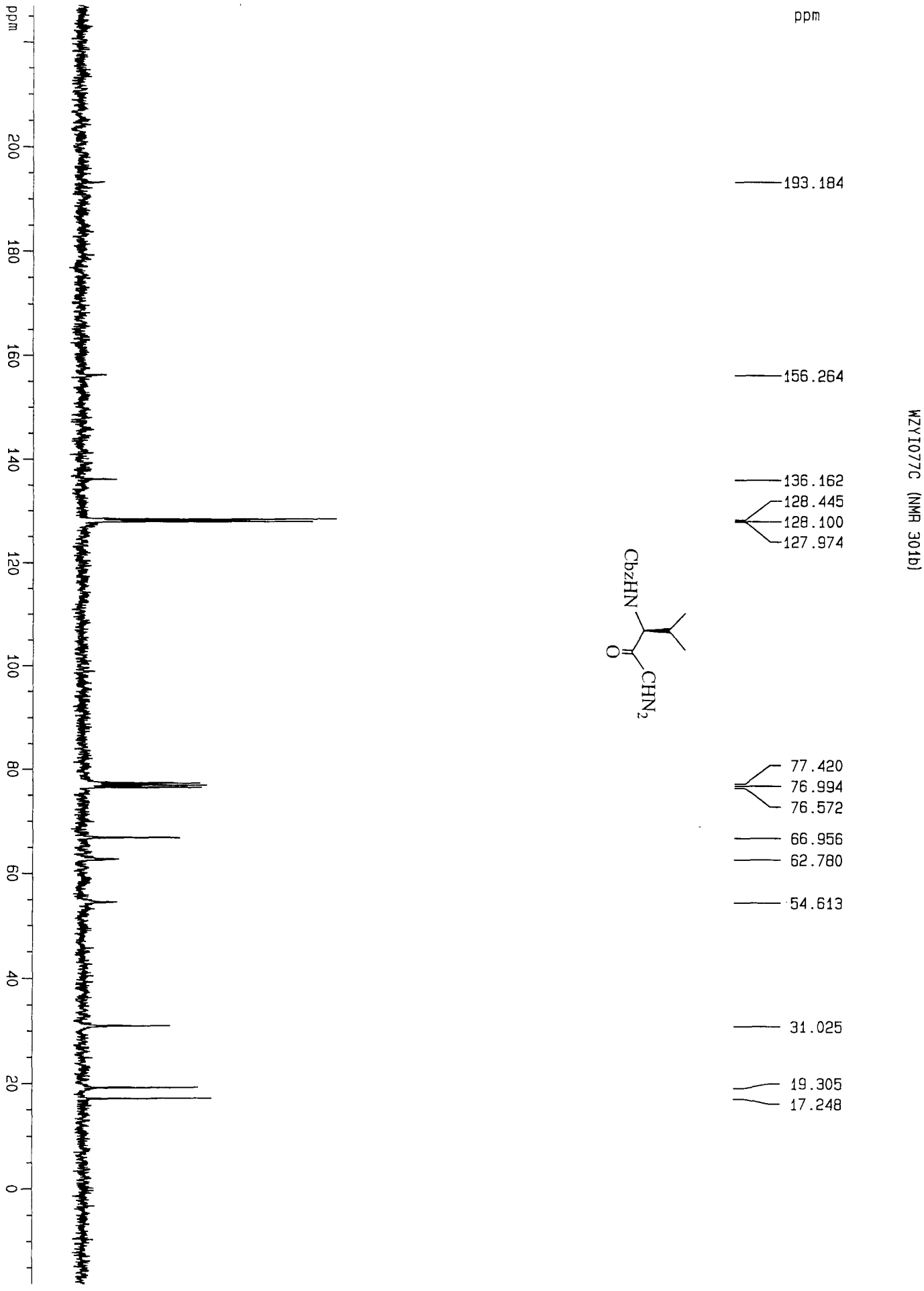
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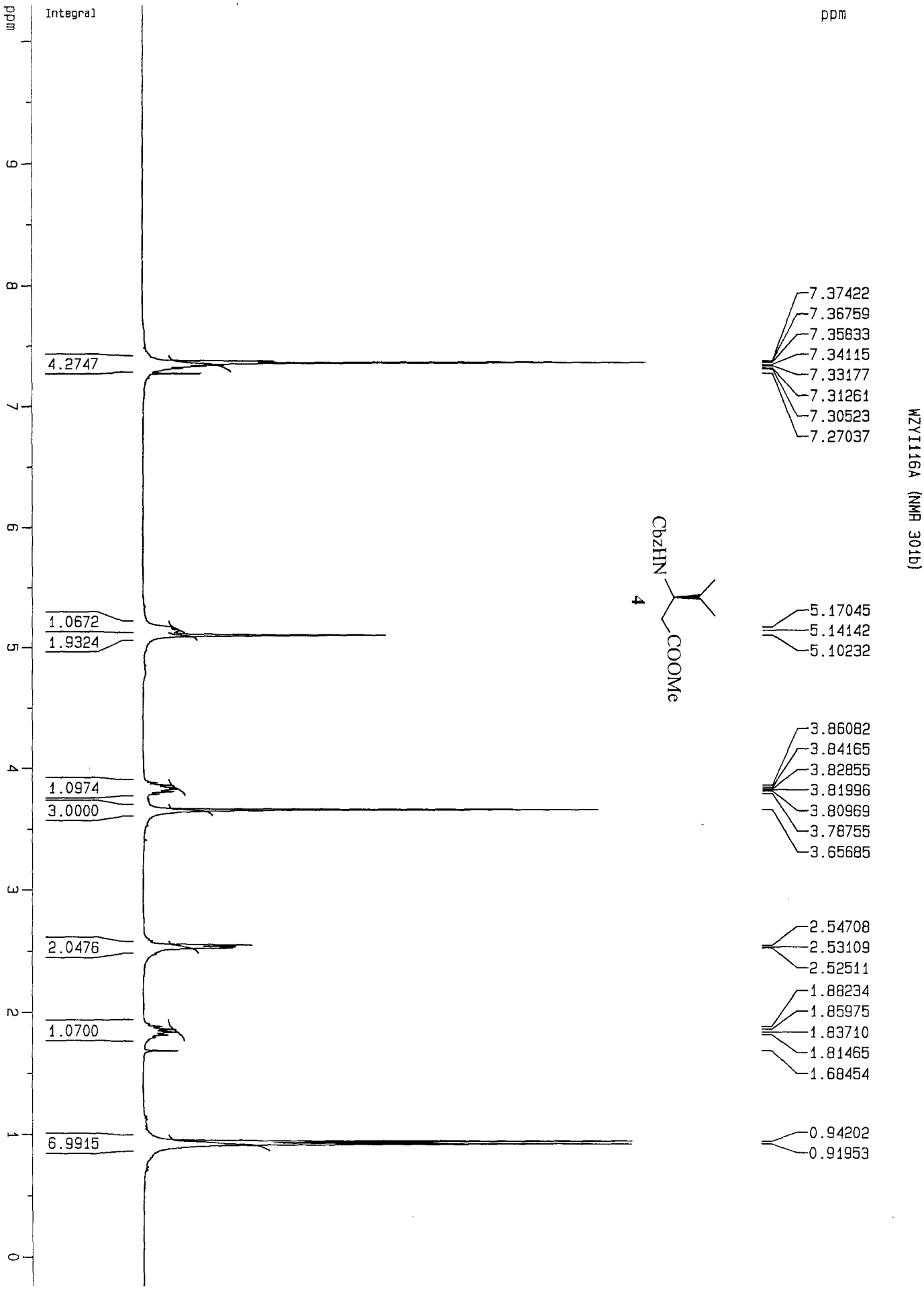
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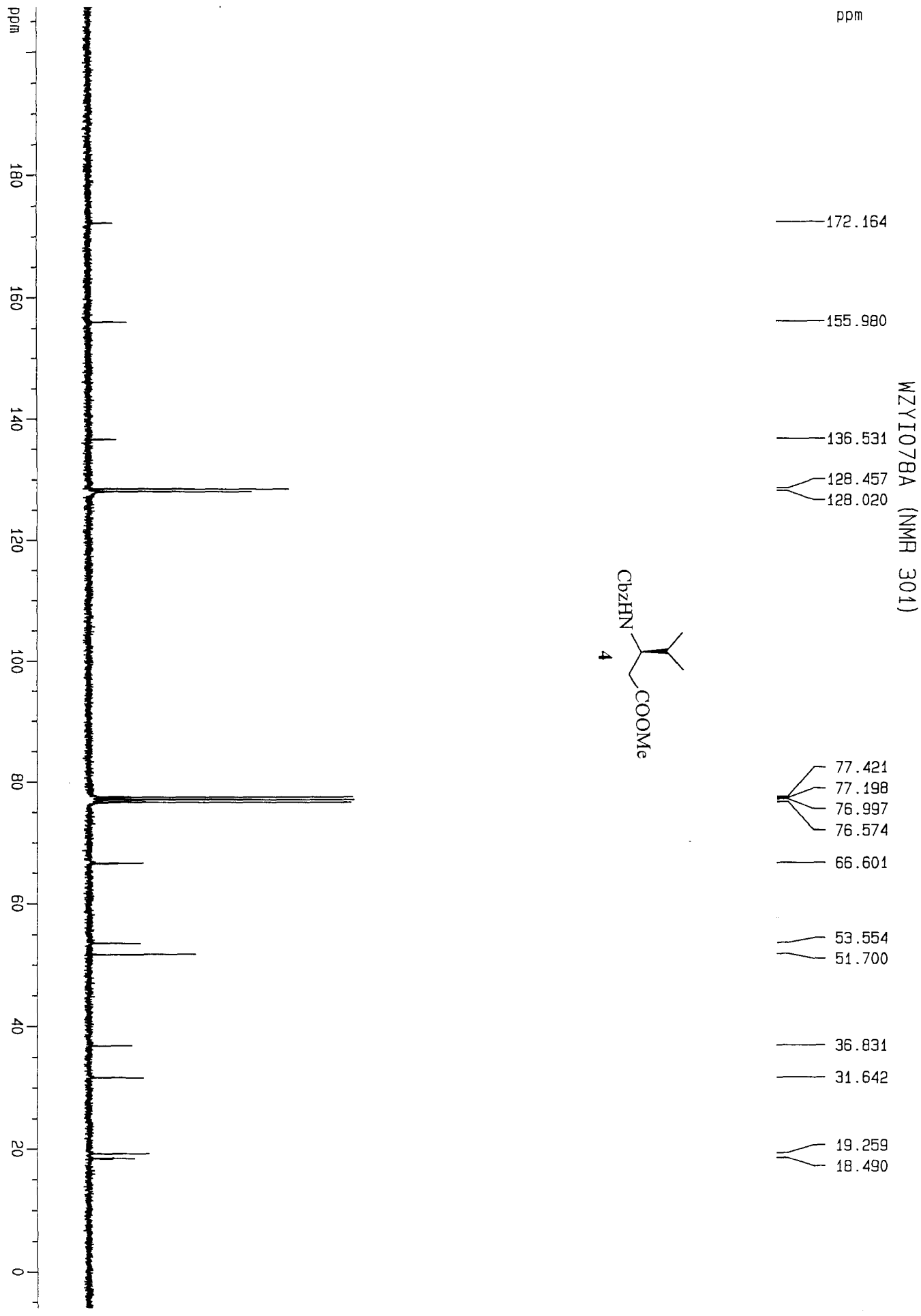
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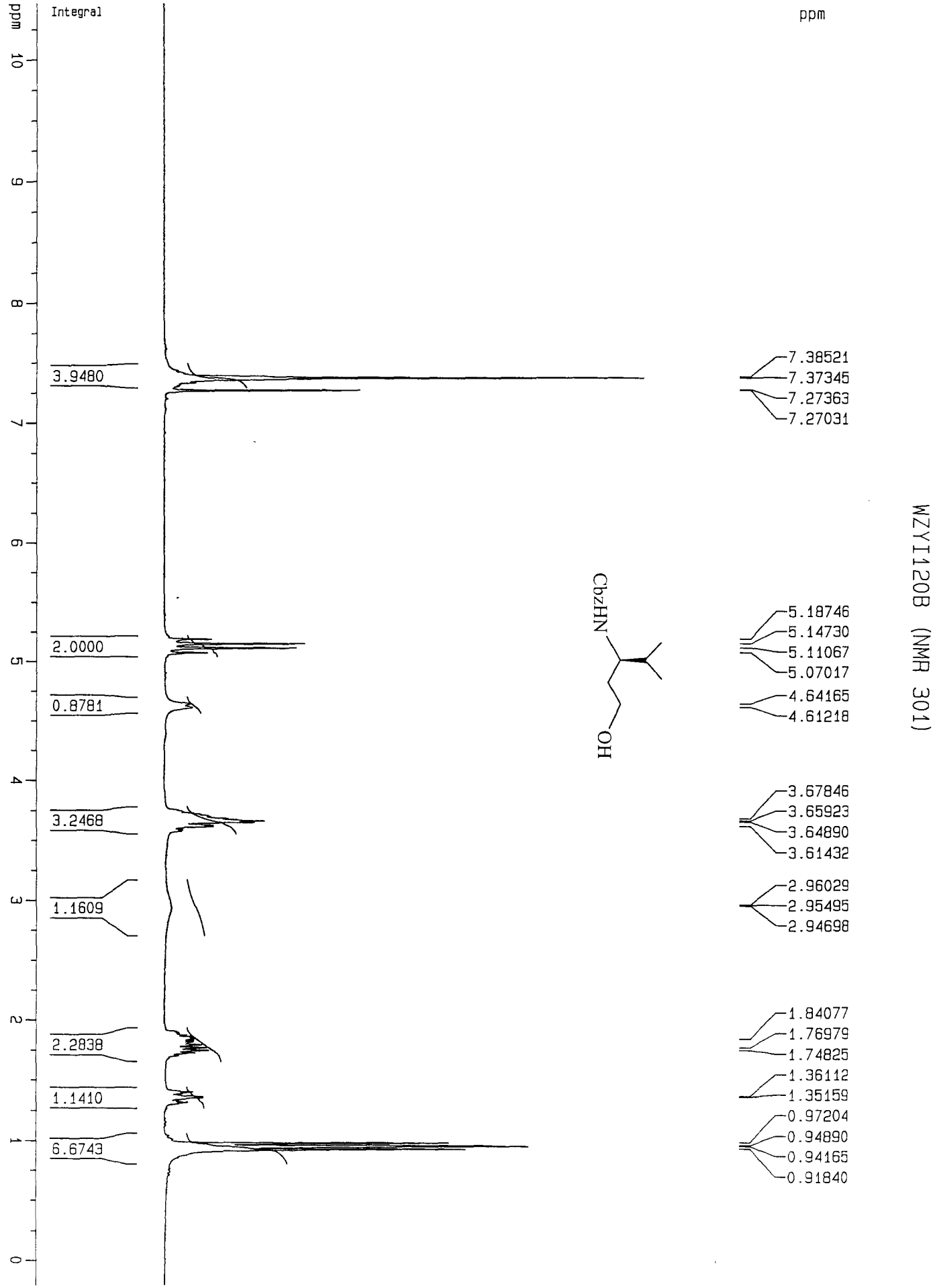
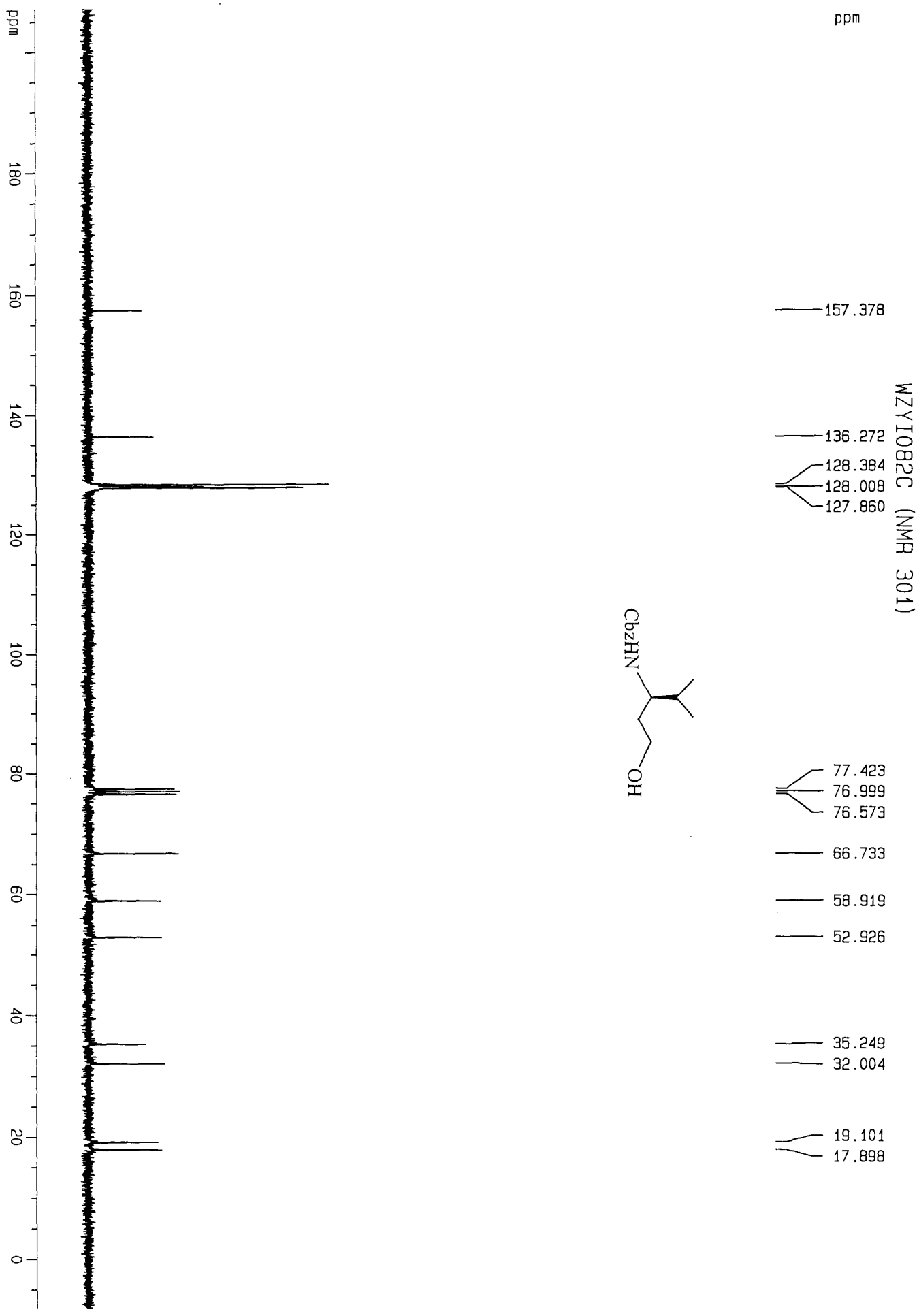


WZYI120B (NMR 301)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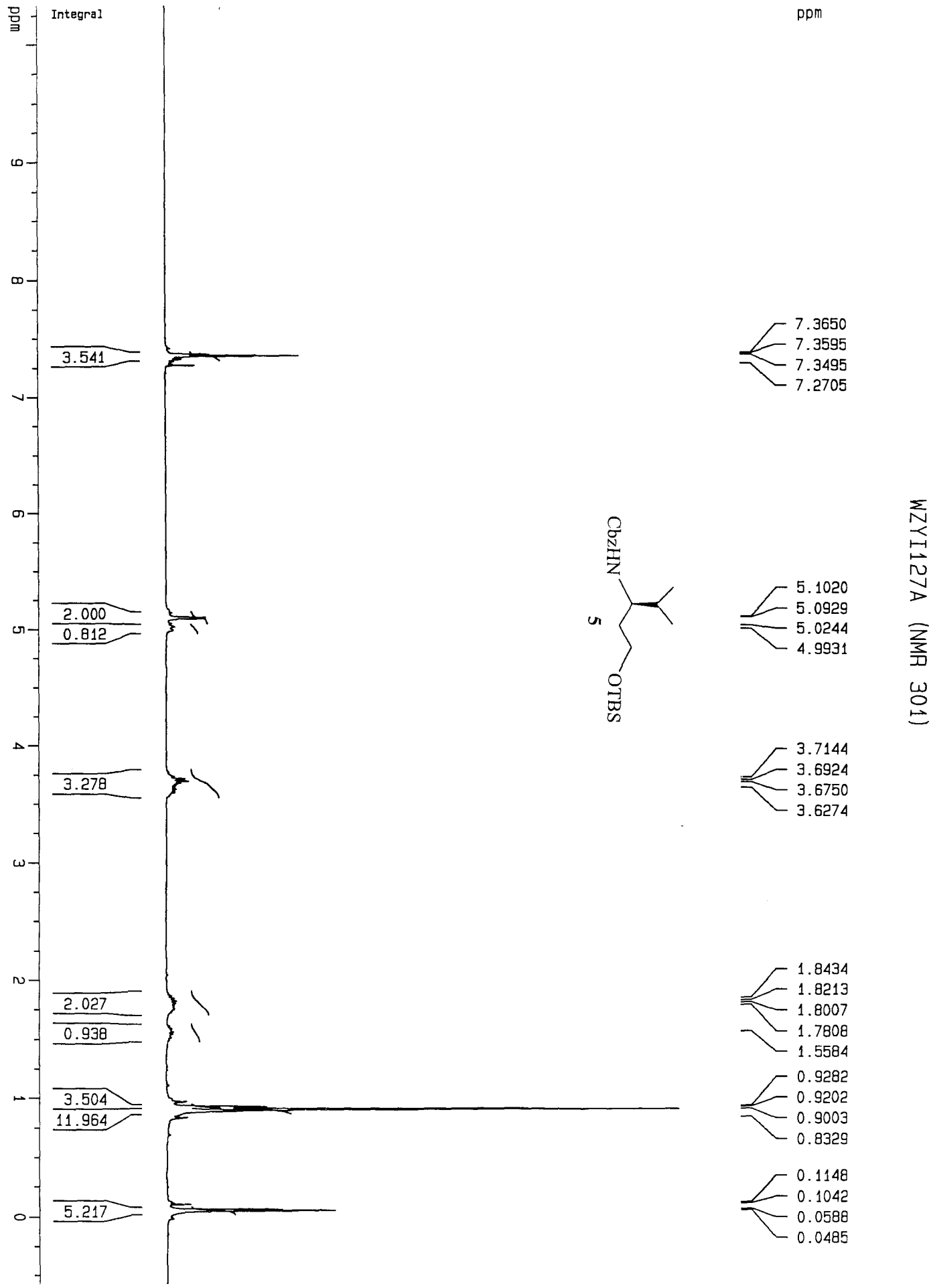
180
160
140
120
100
80
60
40
20
0
ppm
157.378
136.272
128.384
128.008
127.860
77.423
76.999
76.573
66.733
58.919
52.926
35.249
32.004
19.101
17.898
CbzHN
HO
WZYI082C (NMR 301)


Integral
ppm
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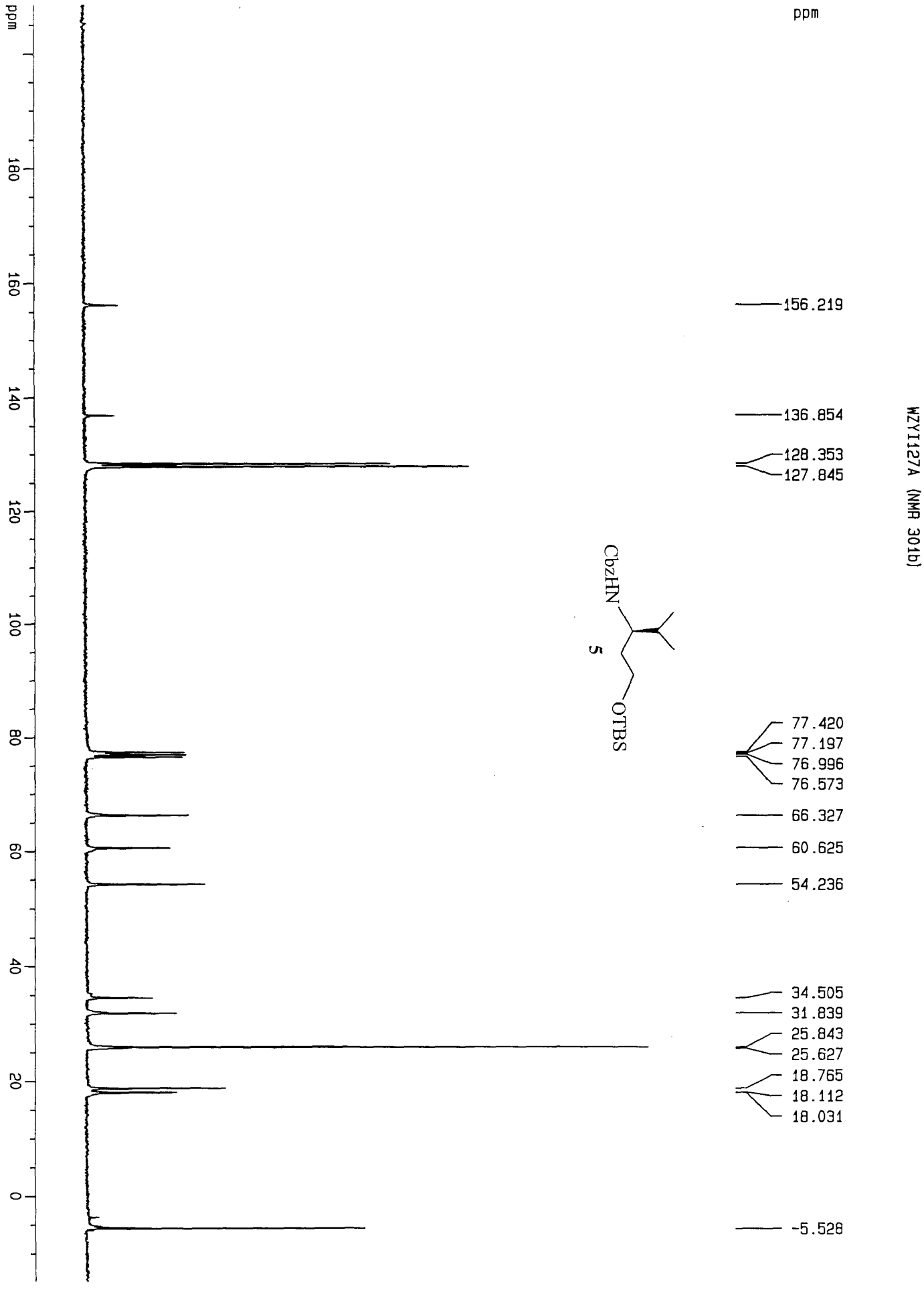
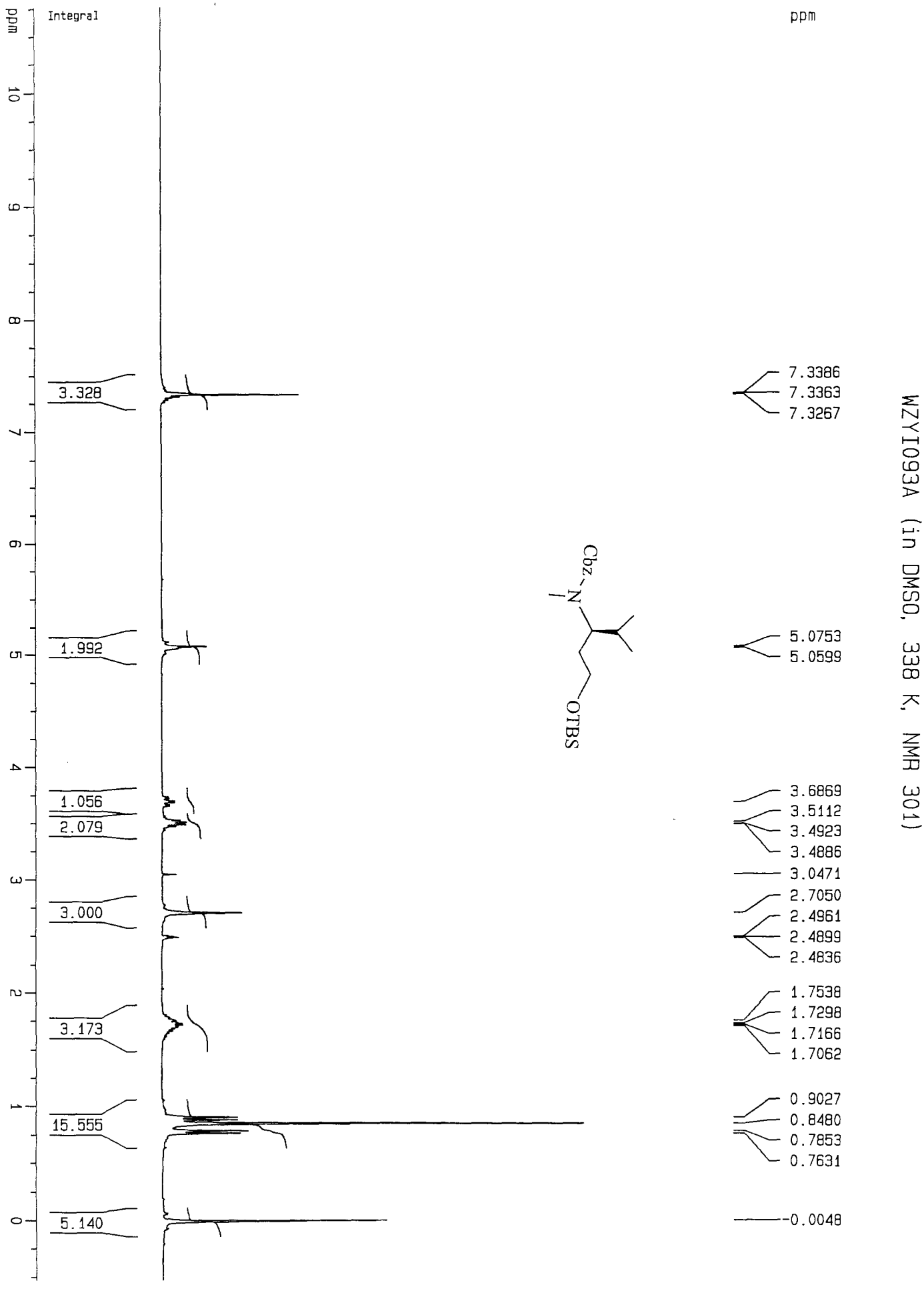
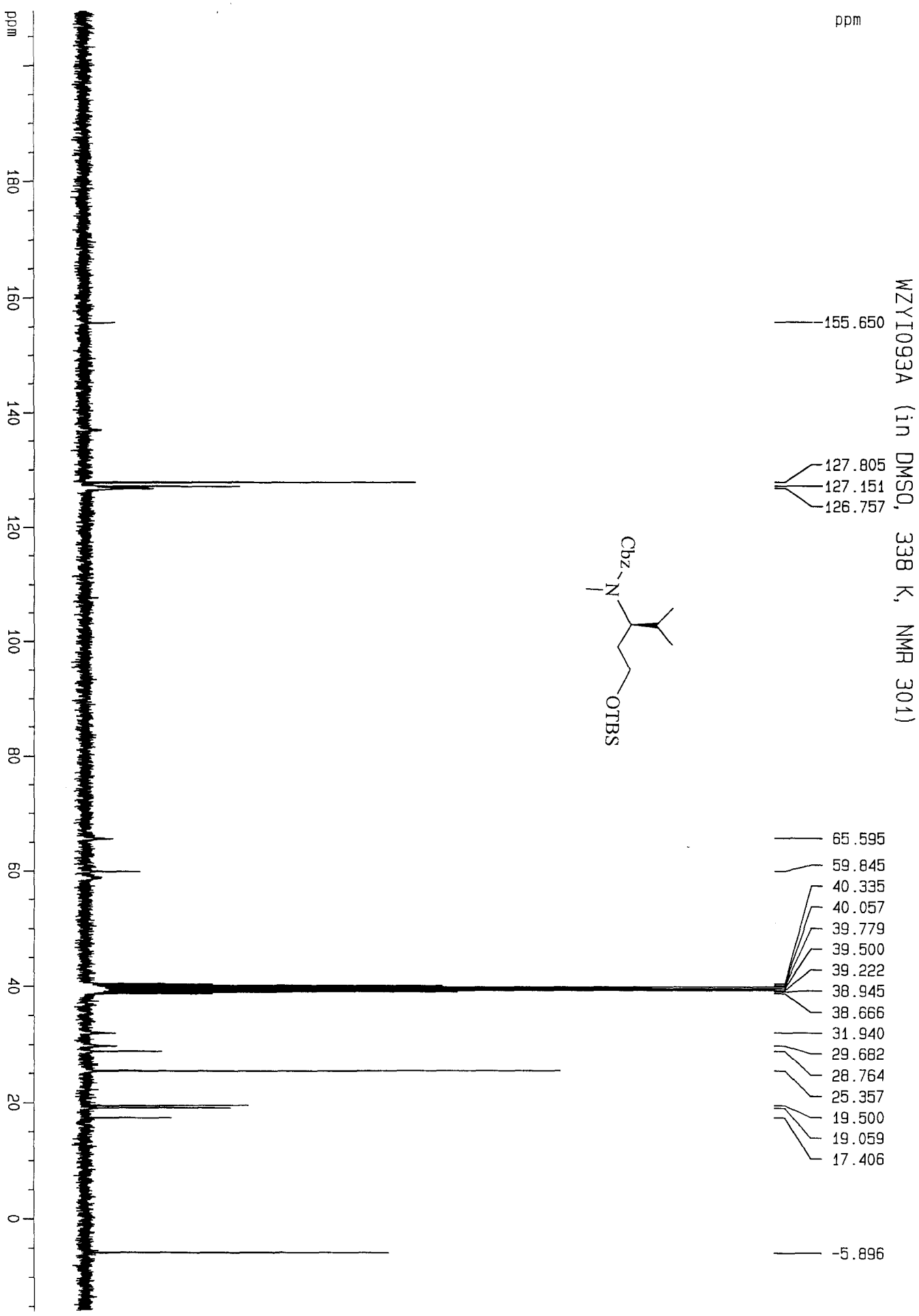
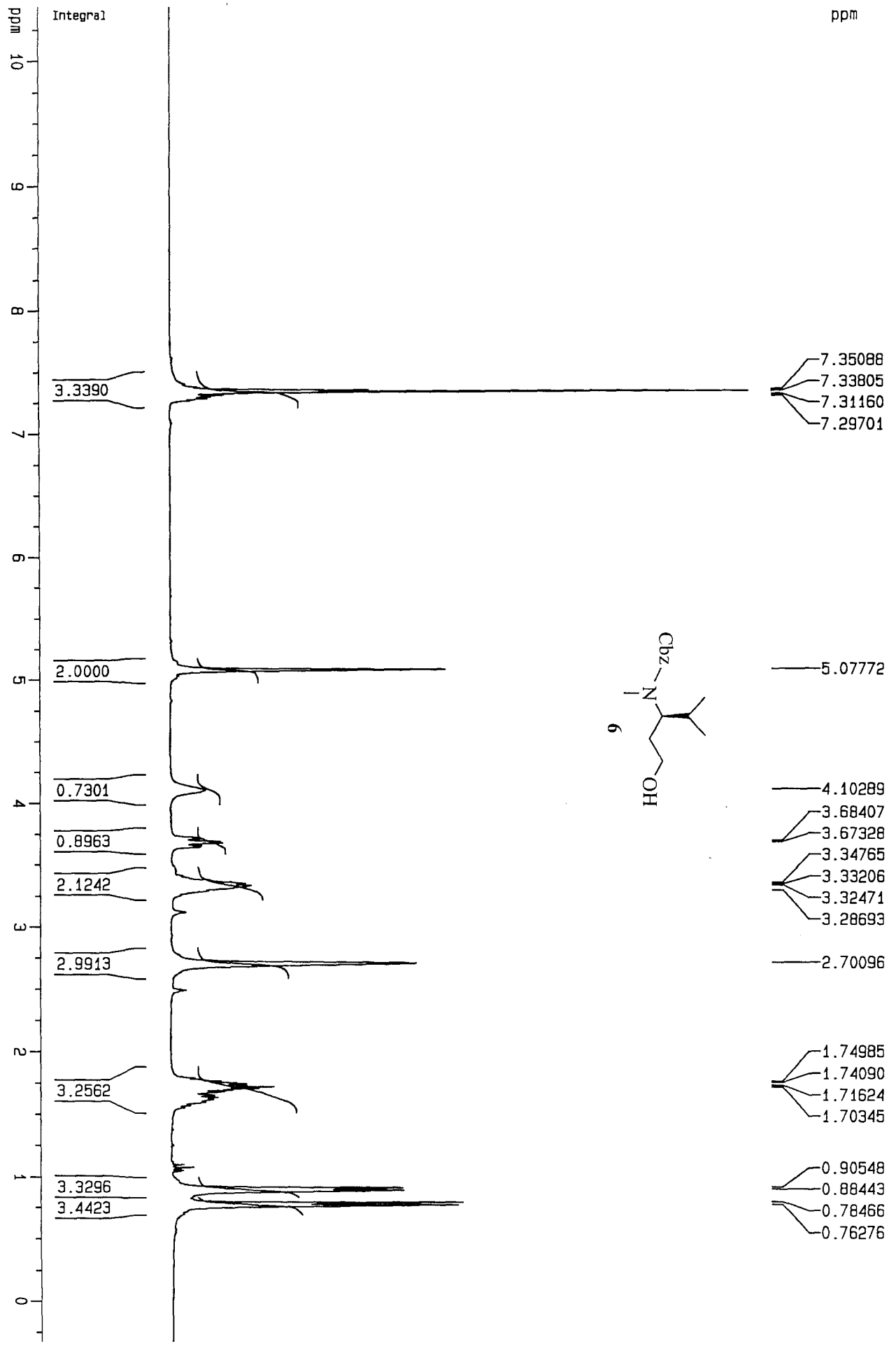
2.000
0.812
3.278
2.027
0.938
3.504
11.964
5.217
7.3650
7.3595
7.3495
7.2705
5.1020
5.0929
5.0244
4.9931
3.7144
3.6924
3.6750
3.6274
1.8434
1.8213
1.8007
1.7808
1.5584
0.9282
0.9202
0.9003
0.8329
0.1148
0.1042
0.0588
0.0485
CbzHN
5
OTBS
WZYI127A (NMR 301)


ppm
180
160
140
120
100
80
60
40
20
0
ppm
156.219
136.854
128.353
127.845
77.420
77.197
76.996
76.573
66.327
60.625
54.236
34.505
31.839
25.843
25.627
18.765
18.112
18.031
-5.528
CbzHN
OTBS
5
WZY1127A (NMR 301b)

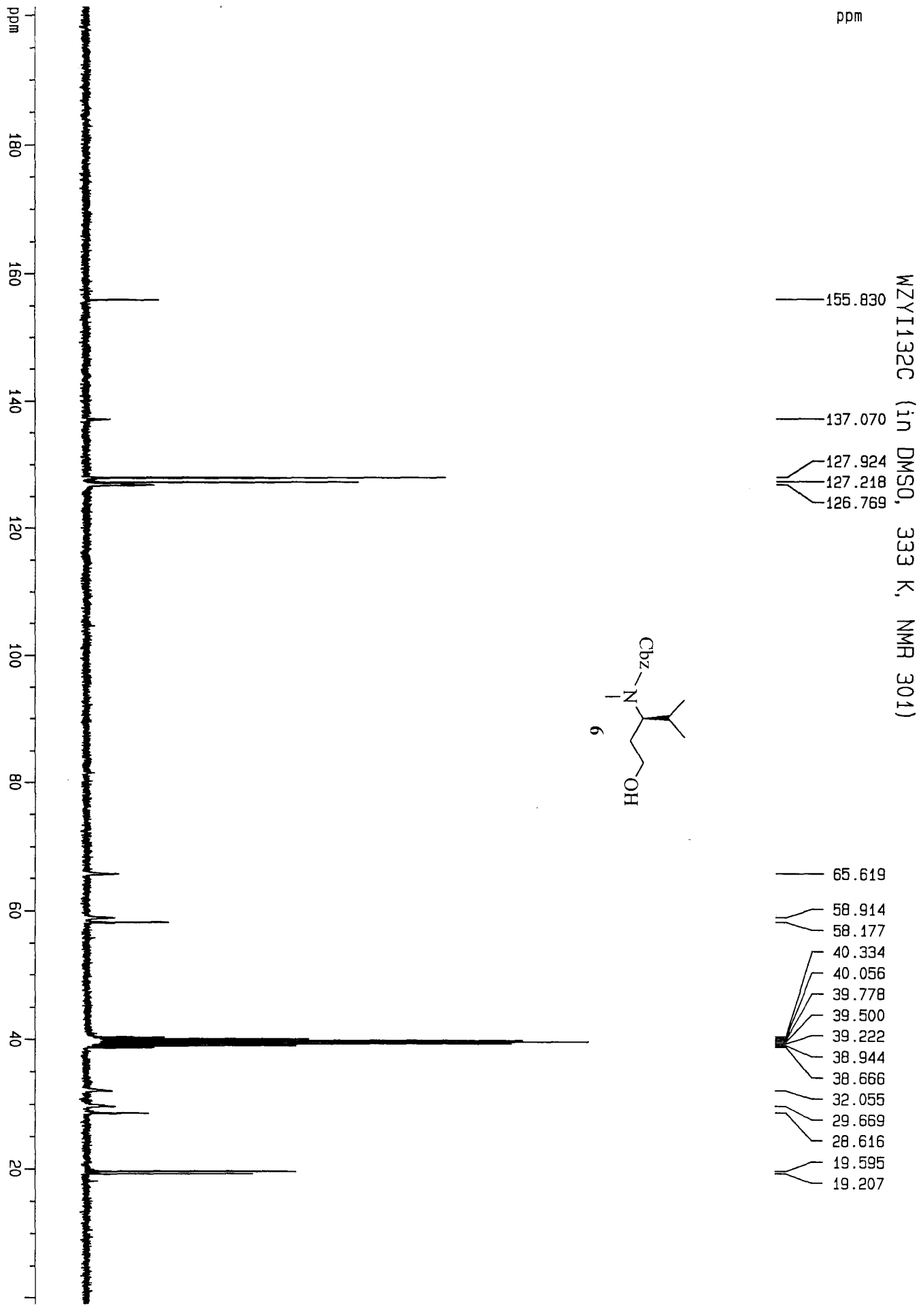


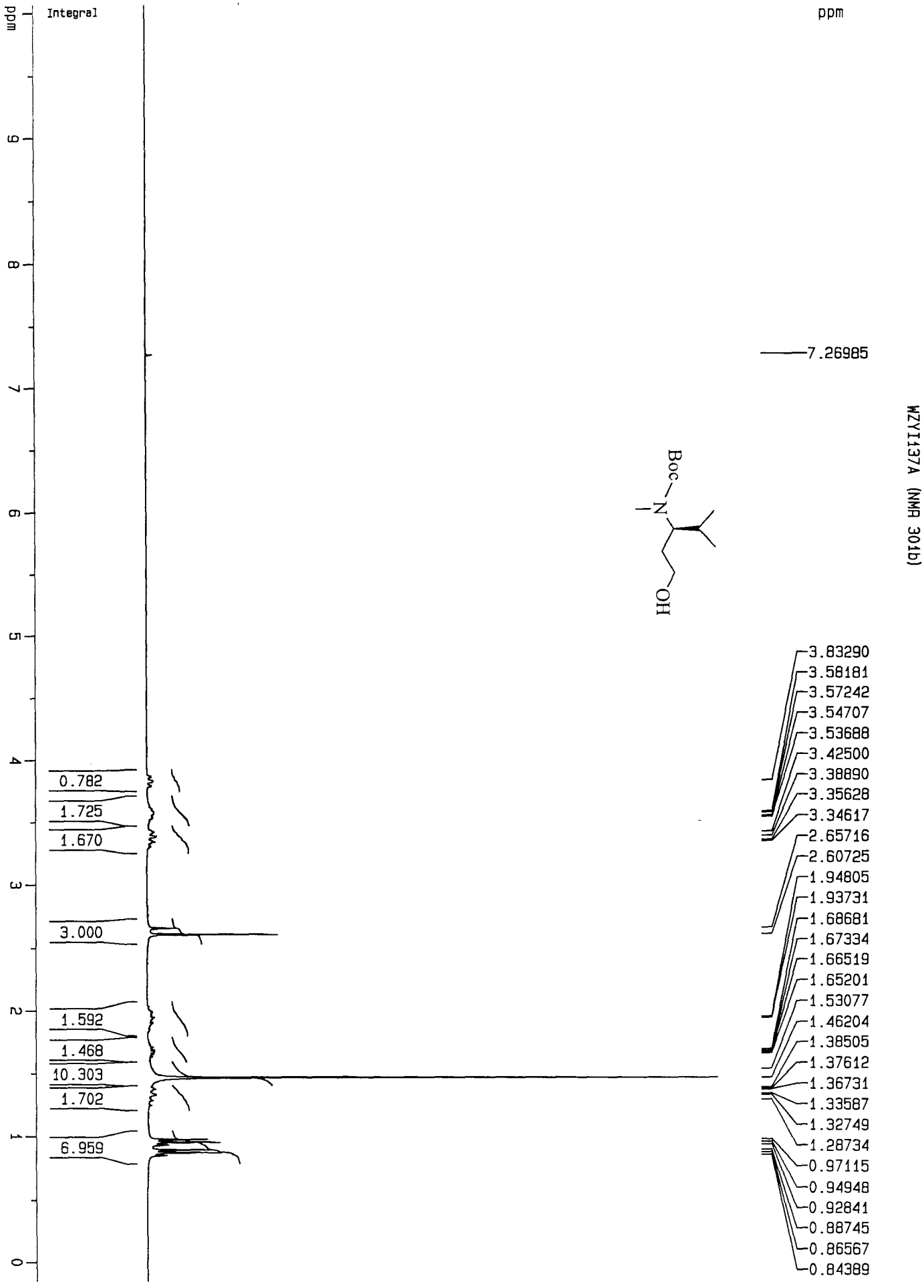
WZYI093A (in DMSO, 338 K, NMR 301)


ppm
180
160
140
120
100
80
60
40
20
0
WZYI093A (in DMSO, 338 K, NMR 301)
155.650
127.805
127.151
126.757
65.595
59.845
40.335
40.057
39.779
39.500
39.222
38.945
38.666
31.940
29.682
28.764
25.357
19.500
19.059
17.406
-5.896
Cbz
N
OTBS



WZYI132C (in DMSO, 333 K, NMR 301)


ppm
180
160
140
120
100
80
60
40
20
WZYI132C (in DMSO, 333 K, NMR 301)
155.830
137.070
127.924
127.218
126.769
65.619
58.914
58.177
40.334
40.056
39.778
39.500
39.222
38.944
38.666
32.055
29.669
28.616
19.595
19.207
Cbz
N
HO
6


ppm
Integral
ppm
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MZY1137A (NMR 301Q)
Boc
N
OH
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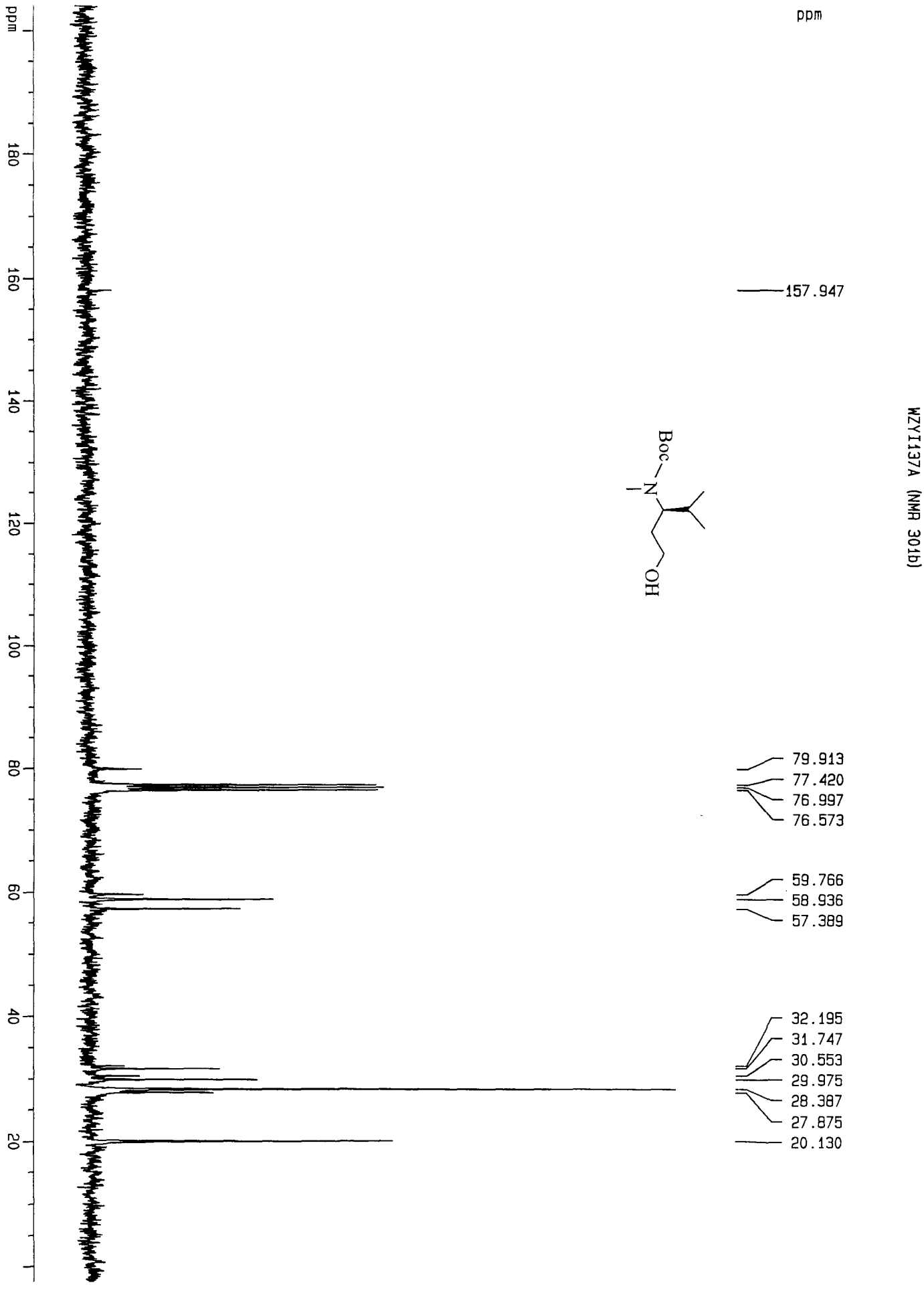
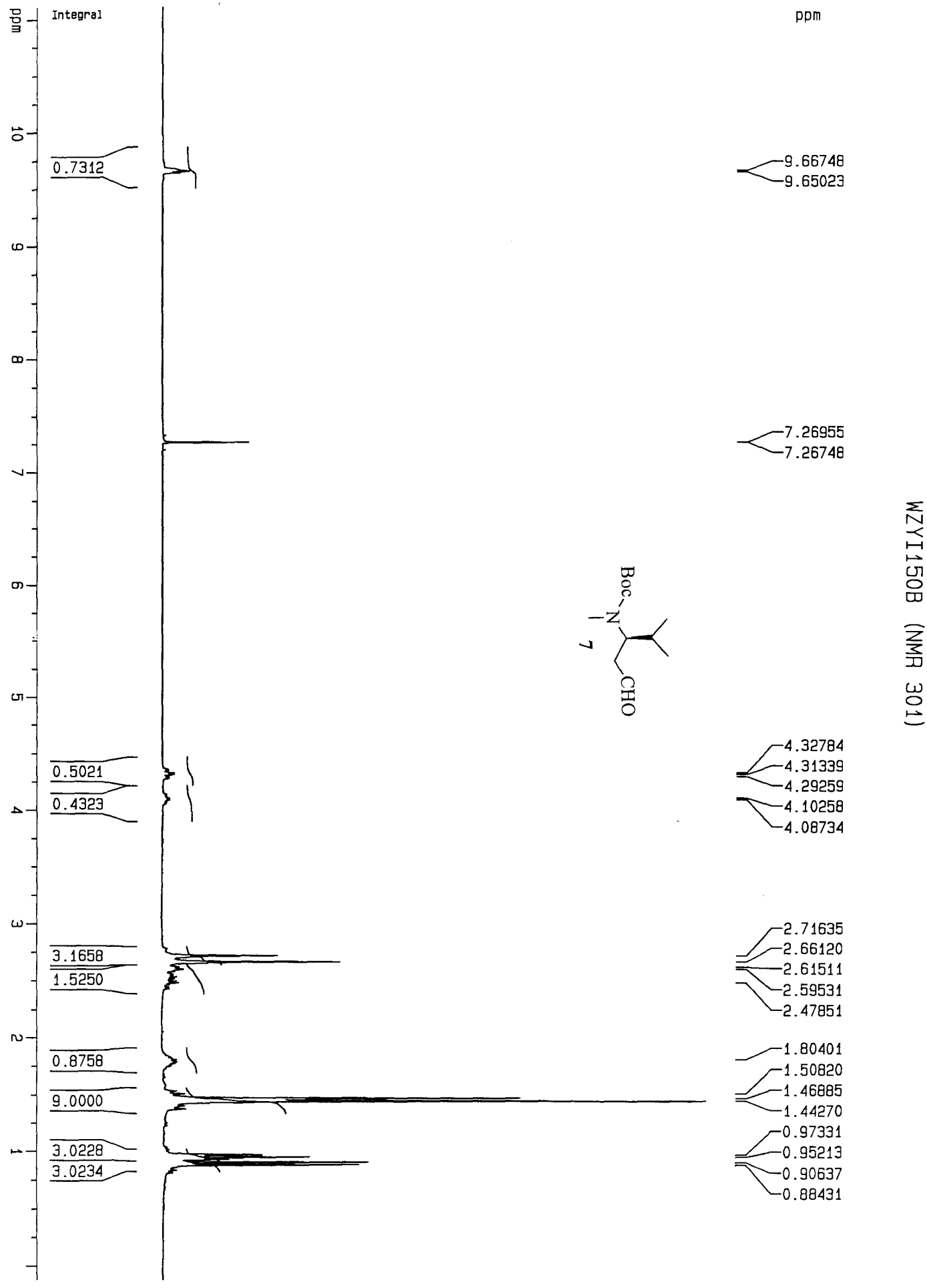
3.58181
3.57242
3.54707
3.53688
3.42500
3.38890
3.35628
3.34617
2.65716
2.60725
1.94805
1.93731
1.68681
1.67334
1.66519
1.65201
1.53077
1.46204
1.38505
1.37612
1.36731
1.33587
1.32749
1.28734
0.97115
0.94948
0.92841
0.88745
0.86567
0.84389
0.782
1.725
1.670
3.000
1.592
1.468
10.303
1.702
6.959


ppm
180
160
140
120
100
80
60
40
20
ppm
157.947
79.913
77.420
76.997
76.573
59.766
58.936
57.389
32.195
31.747
30.553
29.975
28.387
27.875
20.130
Boc
N
OH
WZY1137A (NMR 301b)


Integral
ppm
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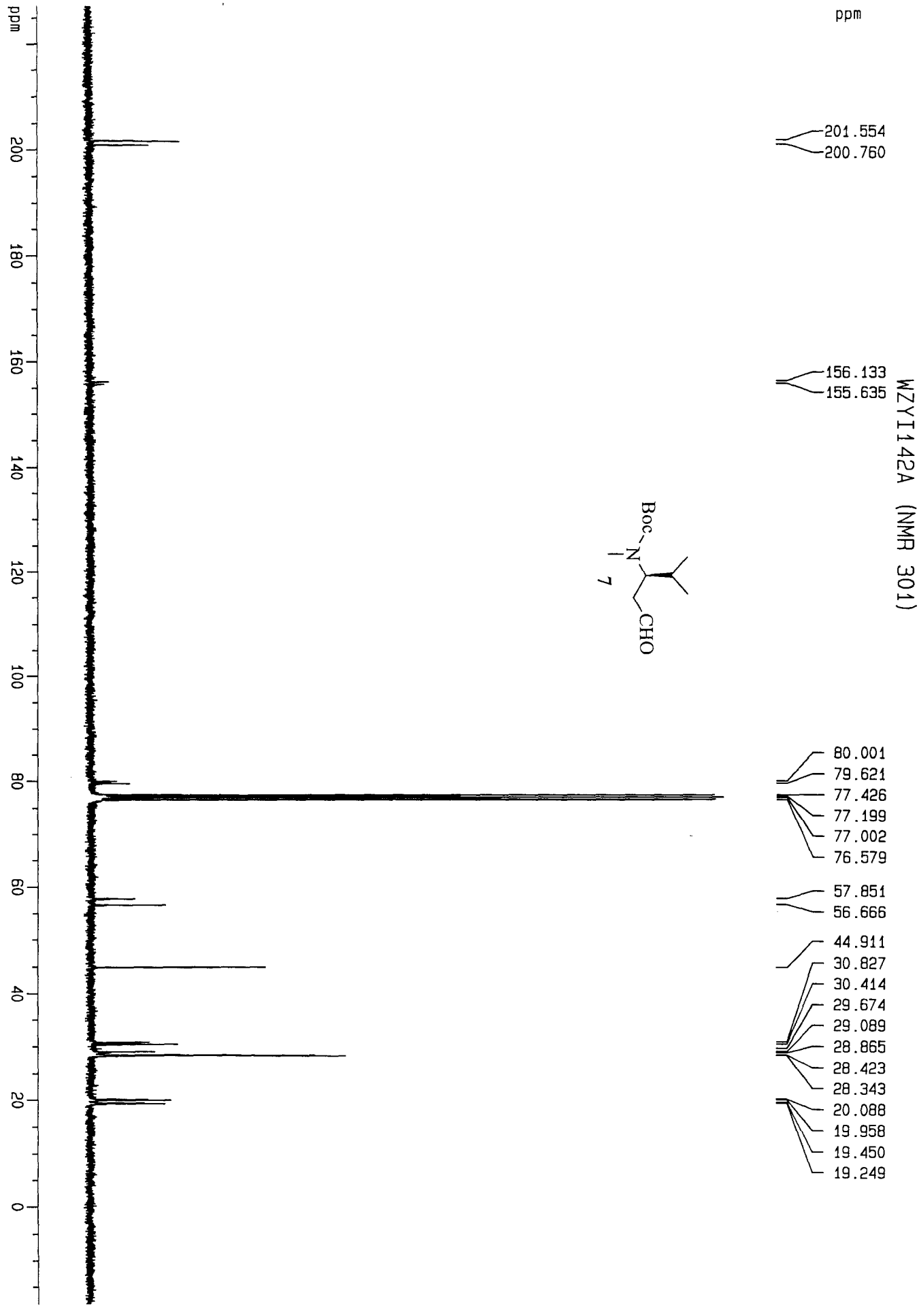
0.4323
3.1658
1.5250
0.8758
9.0000
3.0228
3.0234
9.66748
9.65023
7.26955
7.26748
4.32784
4.31339
4.29259
4.10258
4.08734
2.71635
2.66120
2.61511
2.59531
2.47851
1.80401
1.50820
1.46885
1.44270
0.97331
0.95213
0.90637
0.88431
Boc
N
7
CHO
WZYI150B (NMR 301)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156.133
155.635
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77.426
77.199
77.002
76.579
57.851
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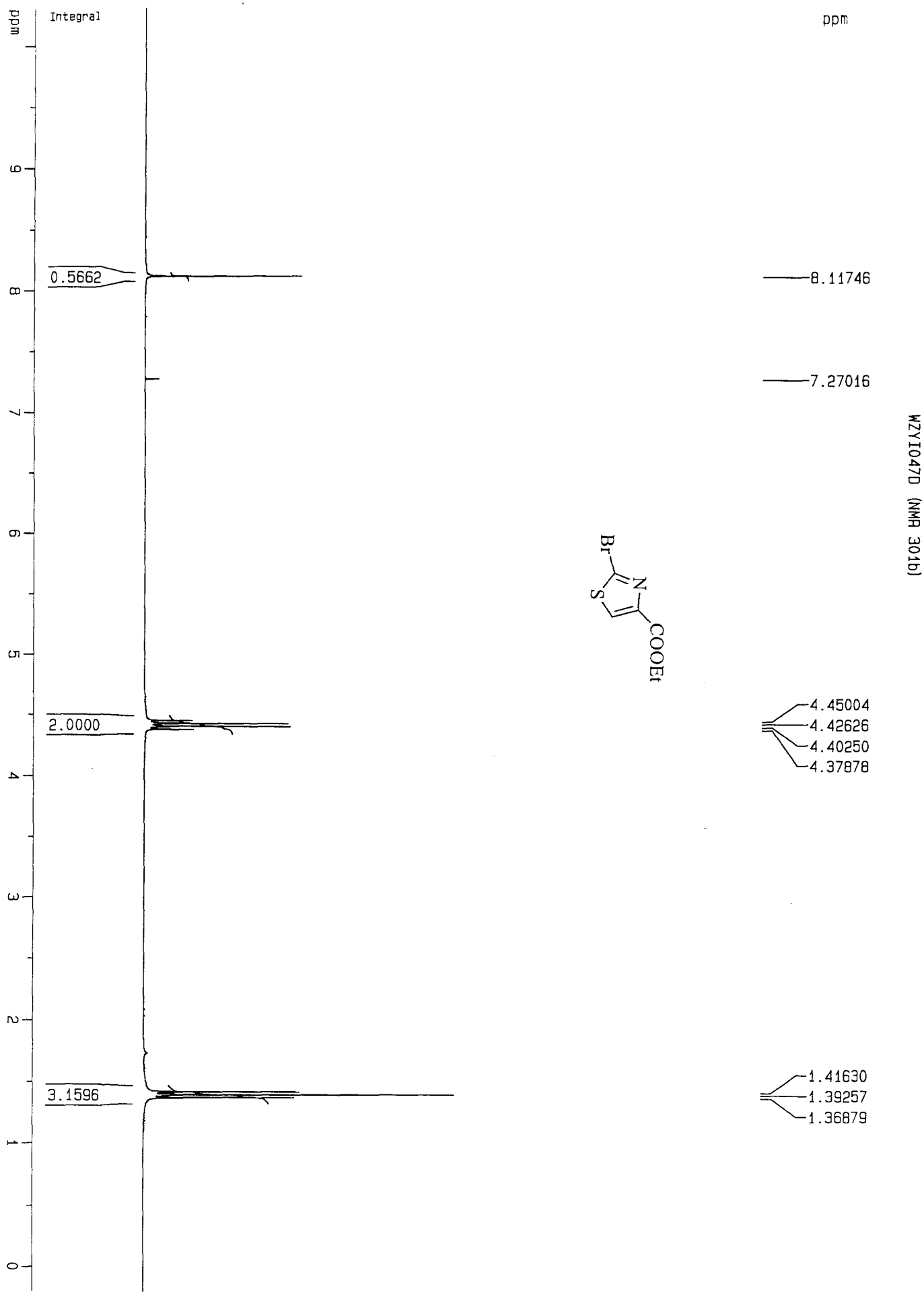
44.911
30.827
30.414
29.674
29.089
28.865
28.423
28.343
20.088
19.958
19.450
19.249
Boc
N
7
CHO
WZYI142A (NMR 301)


ppm
Integral
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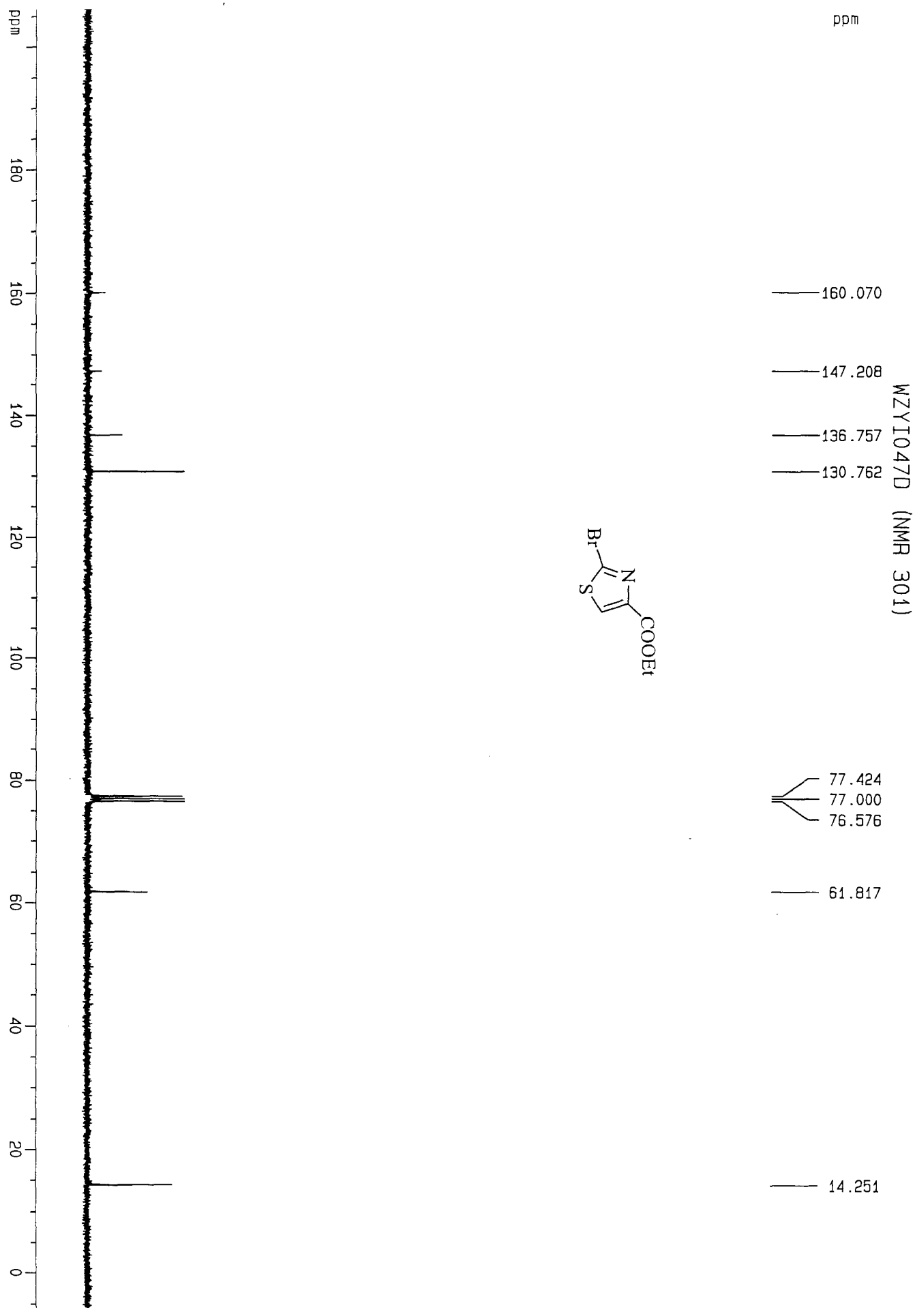
8.11746
7.27016
4.45004
4.42626
4.40250
4.37878
1.41630
1.39257
1.36879
Br
N
S
COOEt
WZYI047D (NMR 301b)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180
160
140
120
100
80
60
40
20
0
ppm
160.070
147.208
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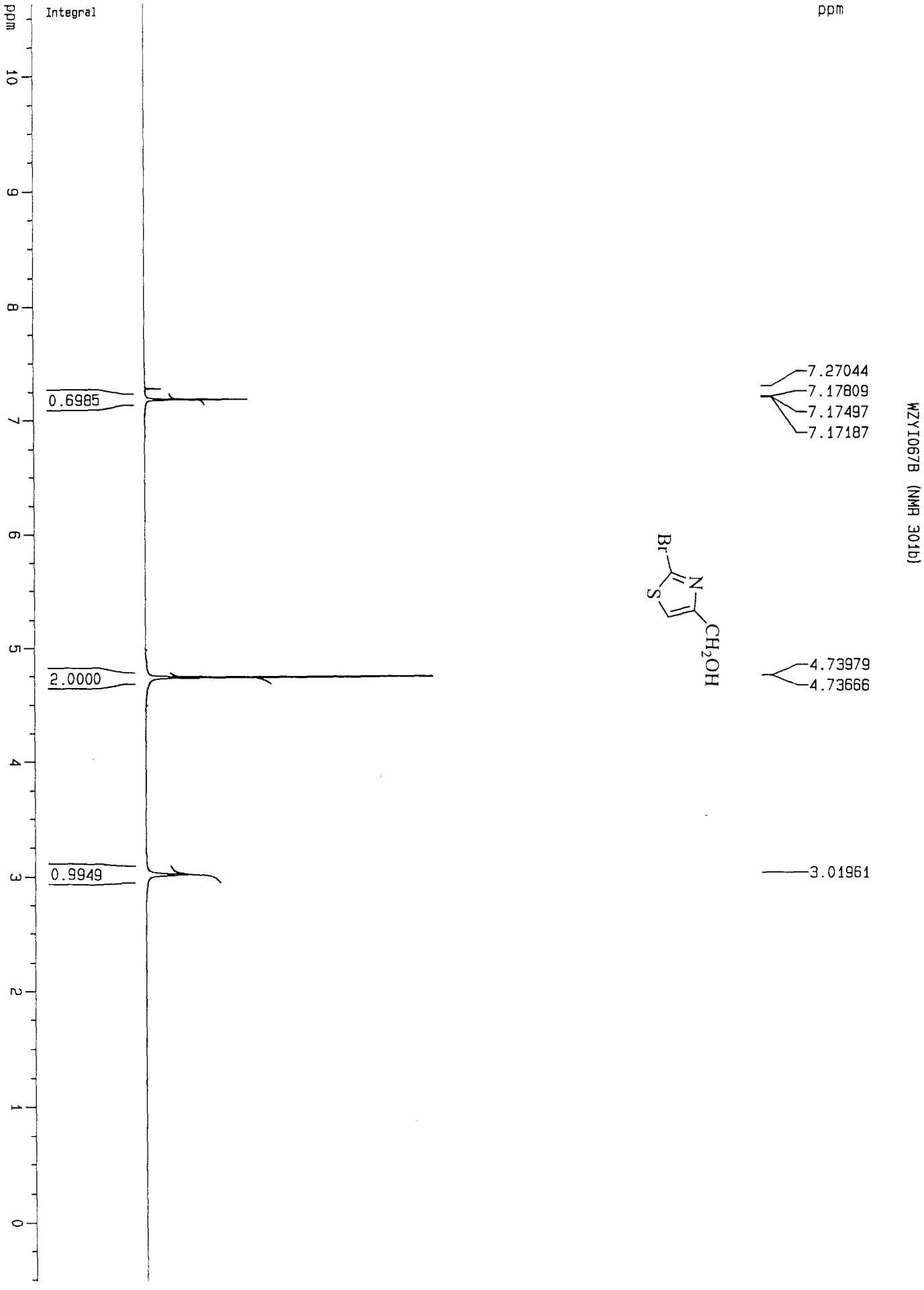
130.762
77.424
77.000
76.576
61.817
14.251
WZYI047D (NMR 301)
Br
N
S
COOEt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2.0000
0.9949
ppm
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7.17809
7.17497
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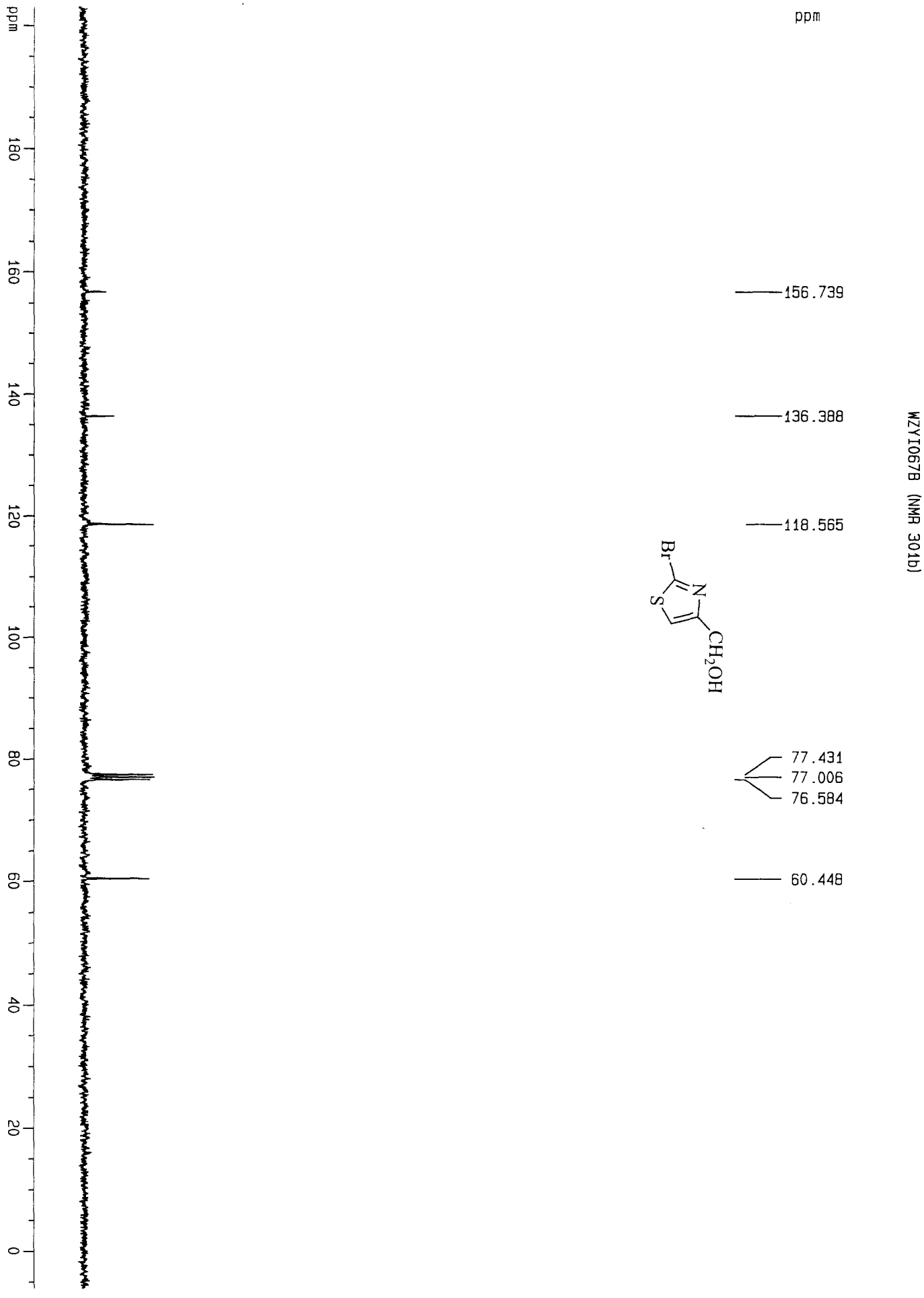
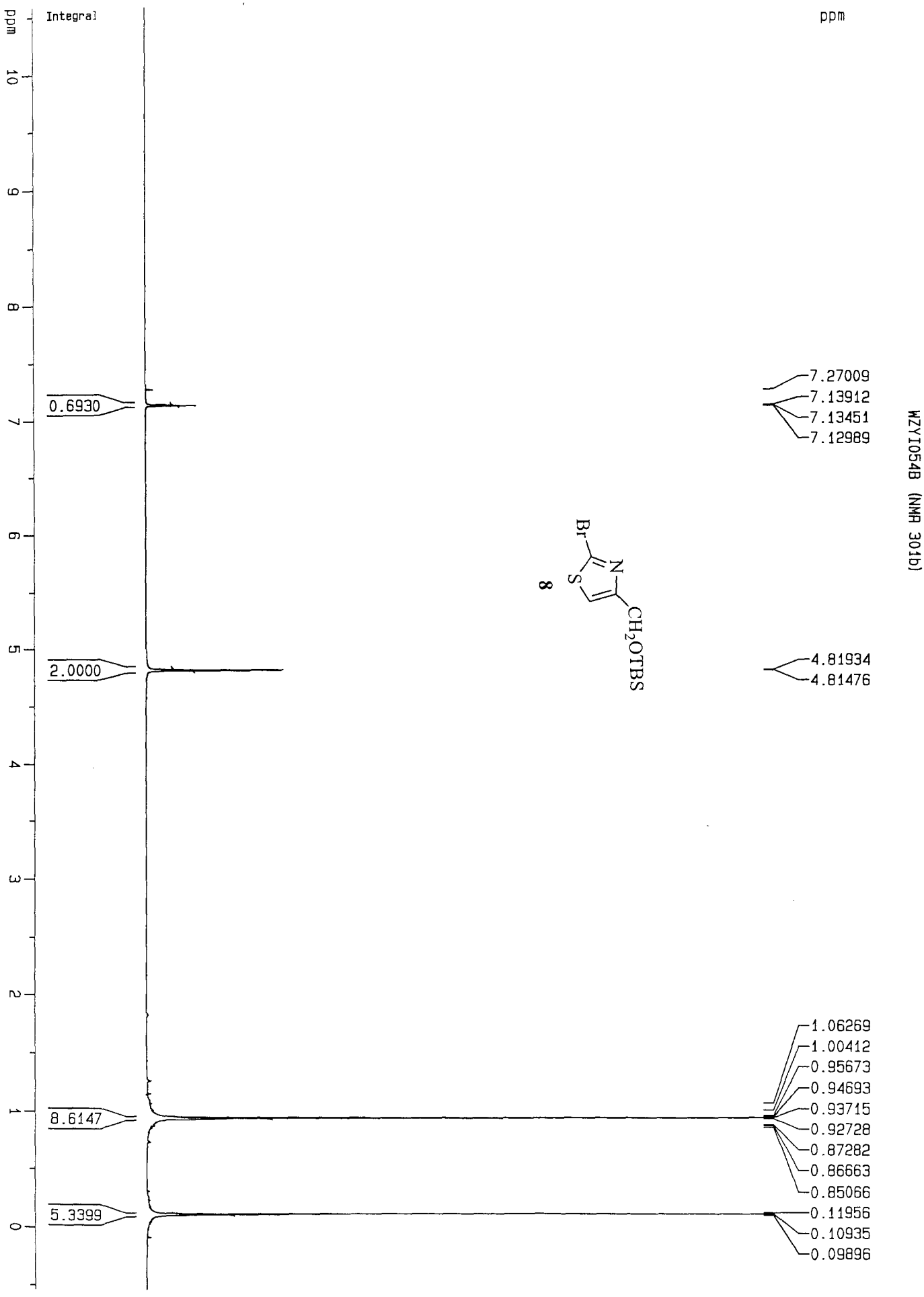
4.73979
4.73666
3.01961
Br
N
S
CH2OH
WZYI067B (NMR 301b)


ppm
180
160
140
120
100
80
60
40
20
0
ppm
156.739
136.388
118.565
77.431
77.006
76.584
60.448
Br
N
S
CH2OH
WZYI067B (NMR 301b)


Integral
ppm
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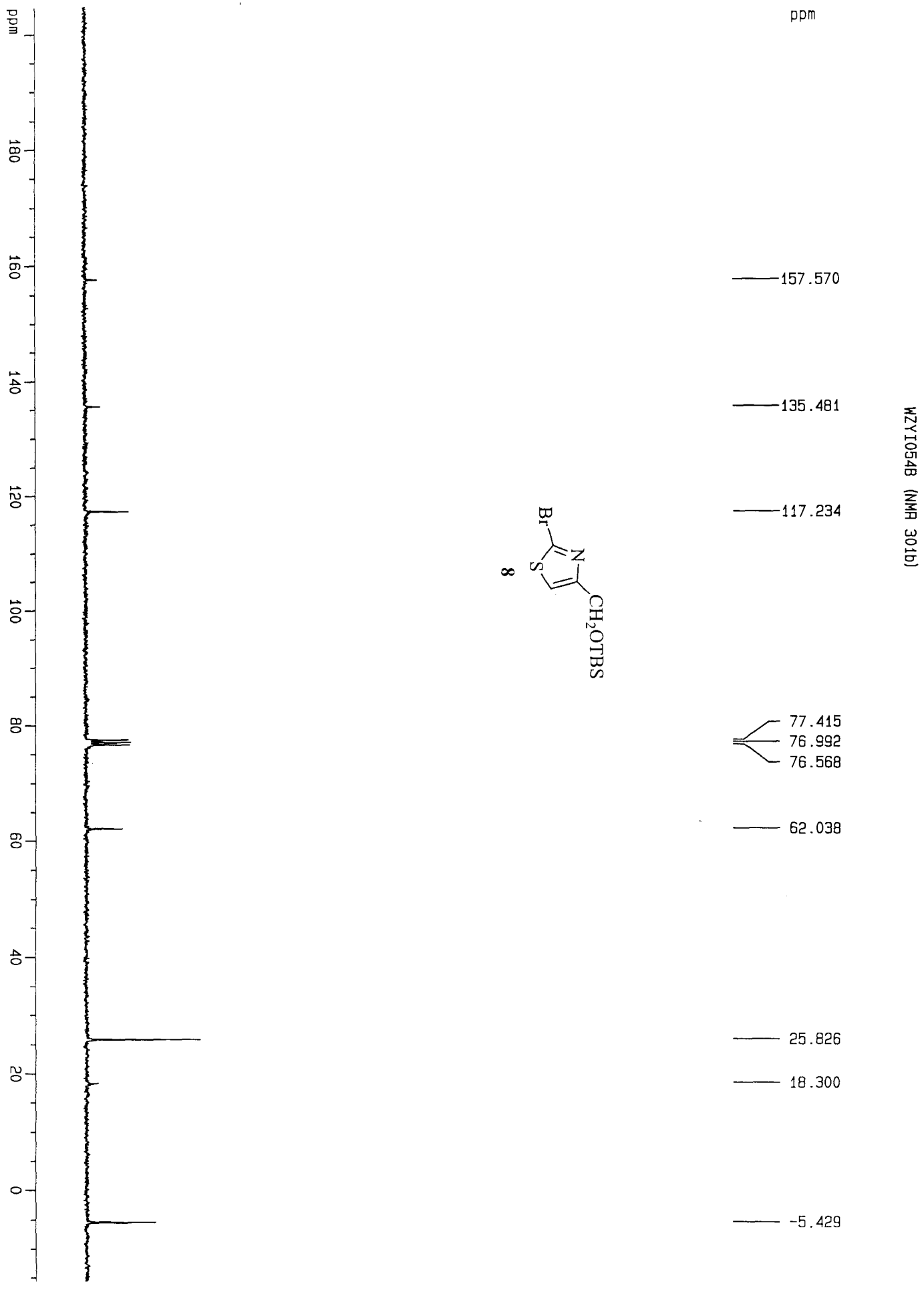
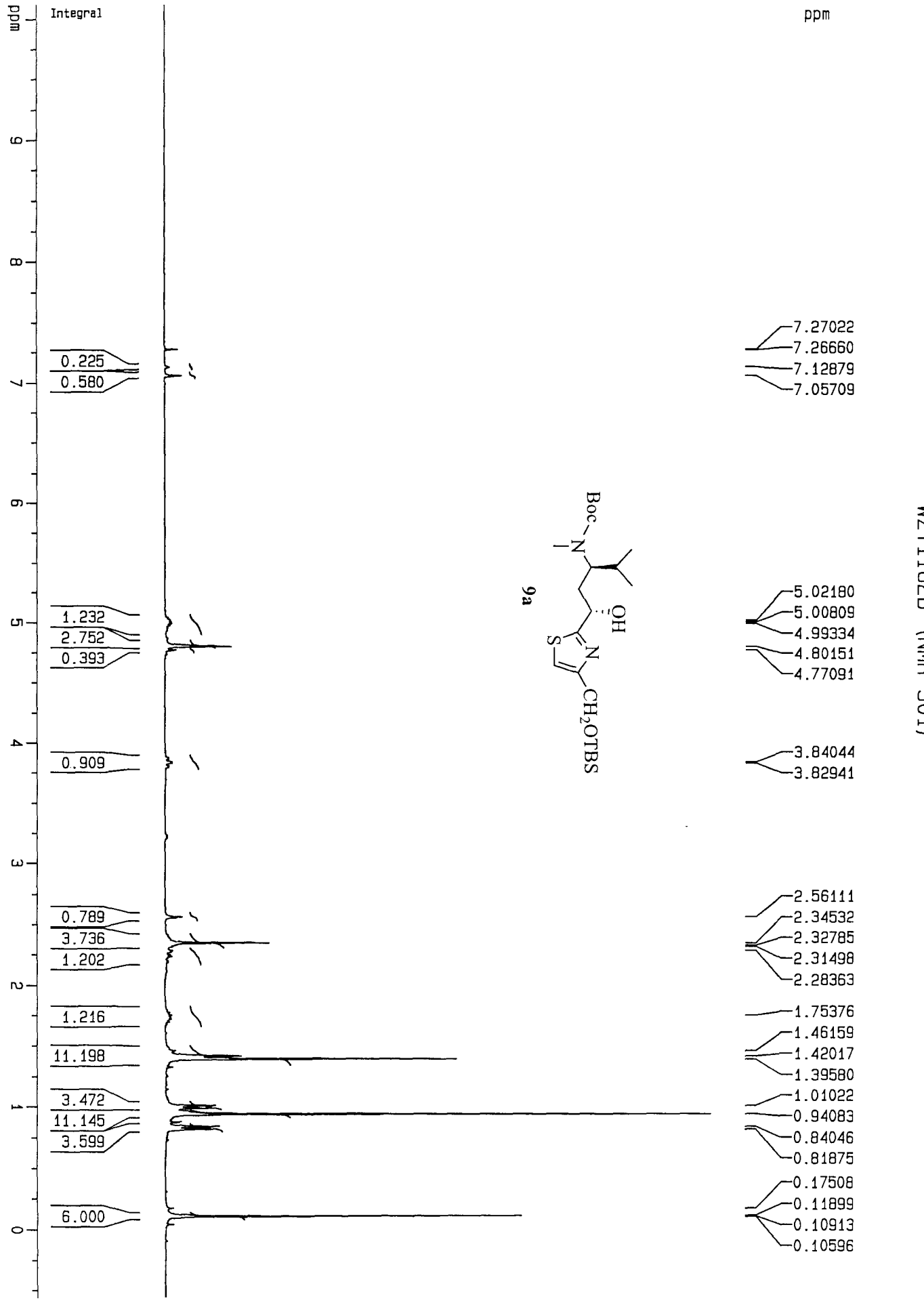
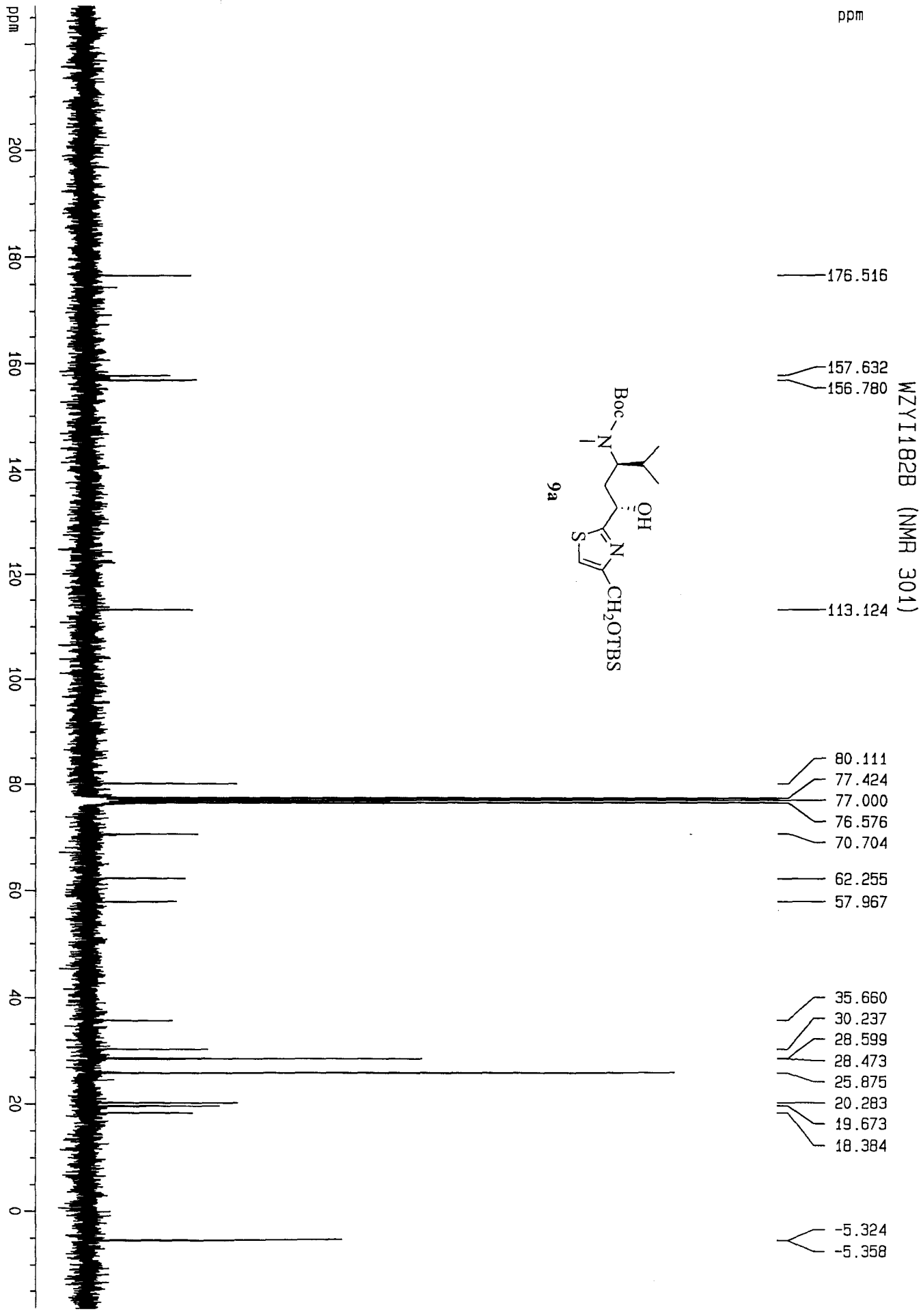
9
8
7
6
5
4
3
2
1
0
0.6930
2.0000
8.6147
5.3399
7.27009
7.13912
7.13451
7.12989
4.81934
4.81476
1.06269
1.00412
0.95673
0.94693
0.93715
0.92728
0.87282
0.86663
0.85066
0.11956
0.10935
0.09896
Br
N
S
CH2OTBS
8
WZYI054B (NMR 301b)


ppm
180
160
140
120
100
80
60
40
20
0
ppm
157.570
135.481
117.234
77.415
76.992
76.568
62.038
25.826
18.300
-5.429
Br
N
S
CH2OTBS
8
WZYI054B (NMR 301b)



WZYI182B (NMR 301)


ppm
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180
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140
120
100
80
60
40
20
0
ppm
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156.780
113.124
80.111
77.424
77.000
76.576
70.704
62.255
57.967
35.660
30.237
28.599
28.473
25.875
20.283
19.673
18.384
-5.324
-5.358
WZYI182B (NMR 301)
Boc
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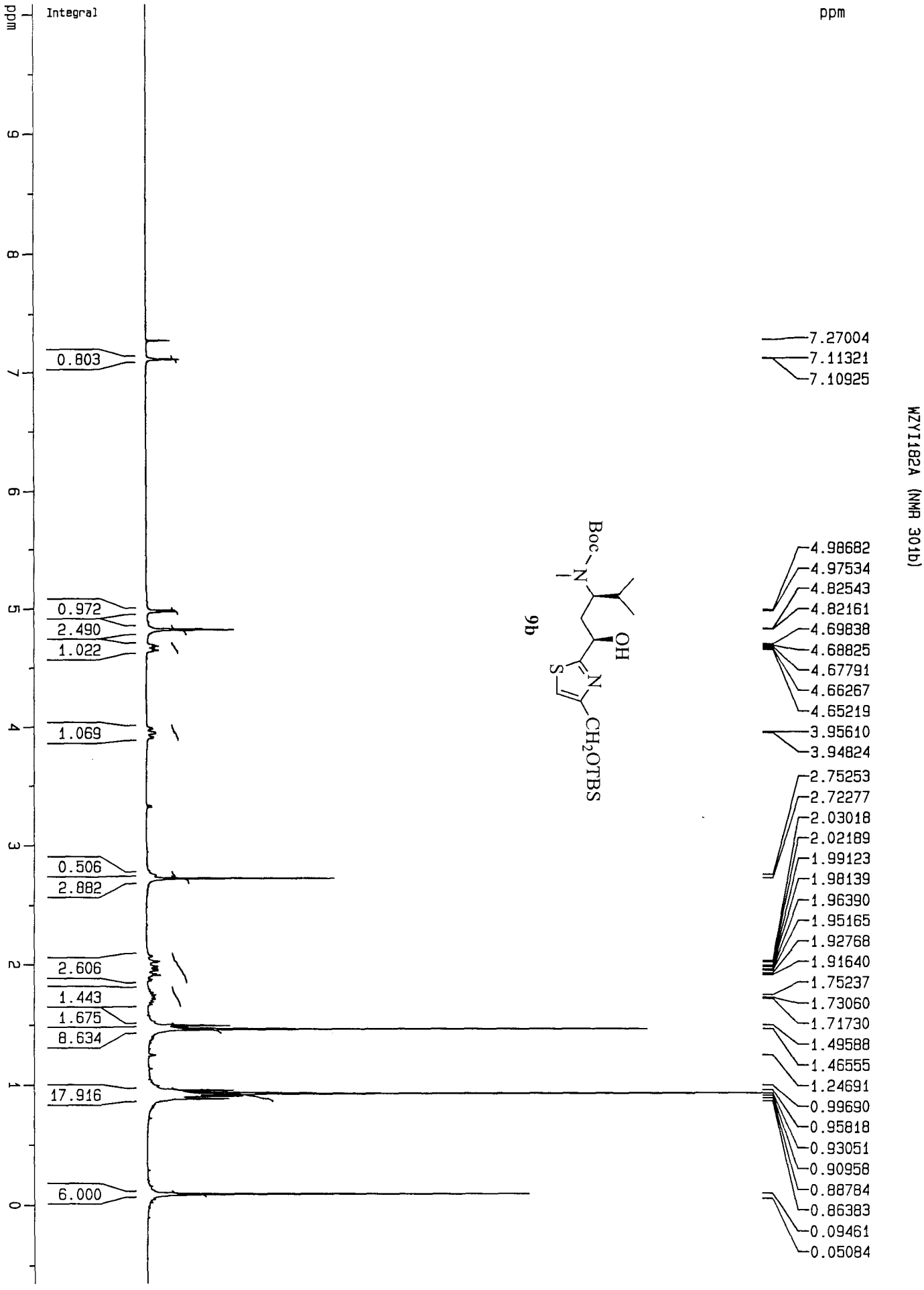
OH
S
N
CH2OTBS
9a


ppm
Integral
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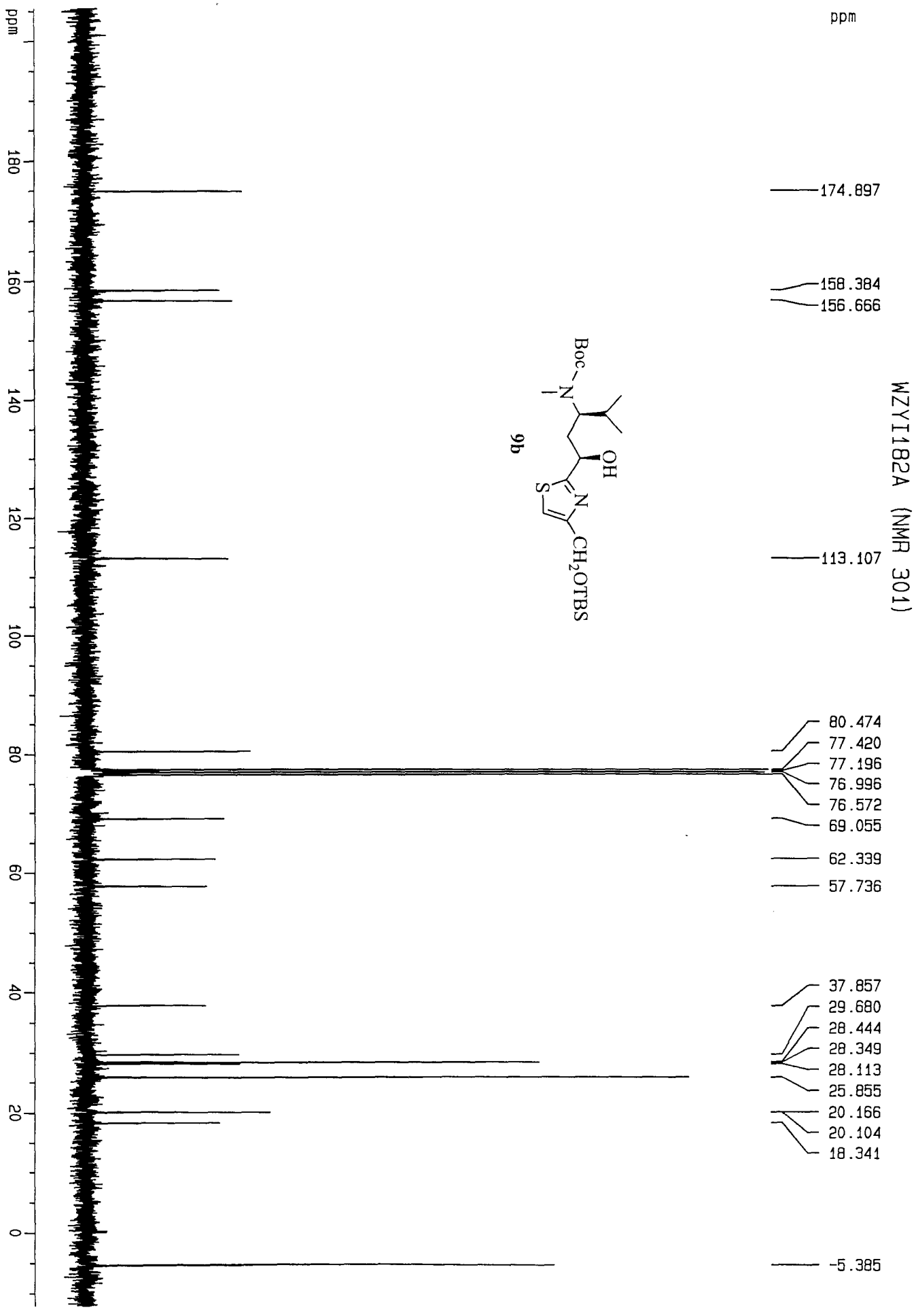
2.490
1.022
1.069
0.506
2.882
2.606
1.443
1.675
8.634
17.916
6.000
Boc
N
OH
S
N
CH2OTBS
9b
7.27004
7.11321
7.10925
4.98682
4.97534
4.82543
4.82161
4.69838
4.68825
4.67791
4.66267
4.65219
3.95610
3.94824
2.75253
2.72277
2.03018
2.02189
1.99123
1.98139
1.96390
1.95165
1.92768
1.91640
1.75237
1.73060
1.71730
1.49588
1.46555
1.24691
0.99690
0.95818
0.93051
0.90958
0.88784
0.86383
0.09461
0.05084
WZYI182A (NMR 301b)


ppm
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120
100
80
60
40
20
0
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156.666
113.107
80.474
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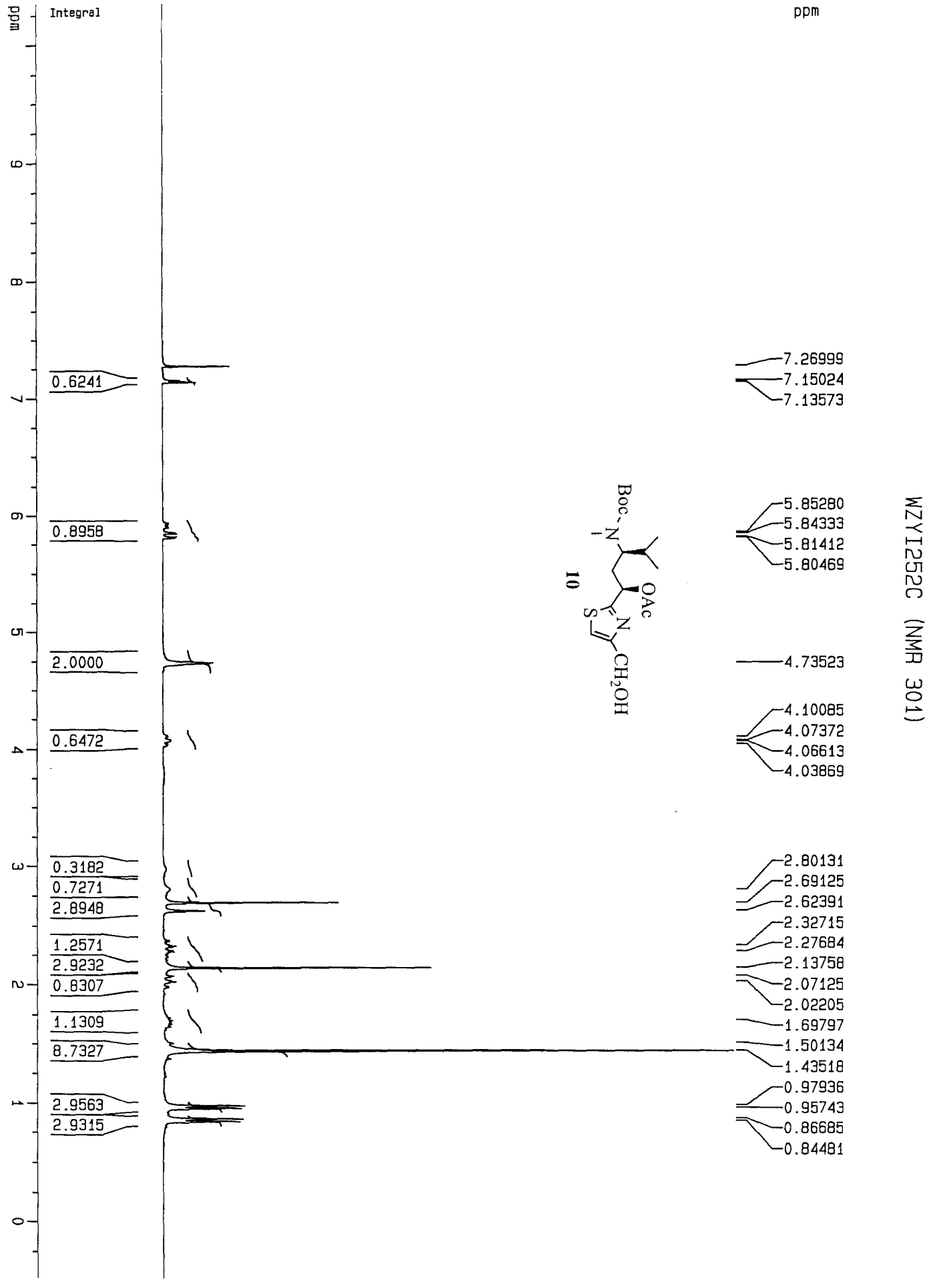
76.996
76.572
69.055
62.339
57.736
37.857
29.680
28.444
28.349
28.113
25.855
20.166
20.104
18.341
-5.385
Boc
N
OH
S
N
CH2OTBS
9b
WZYI182A (NMR 301)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1.2571
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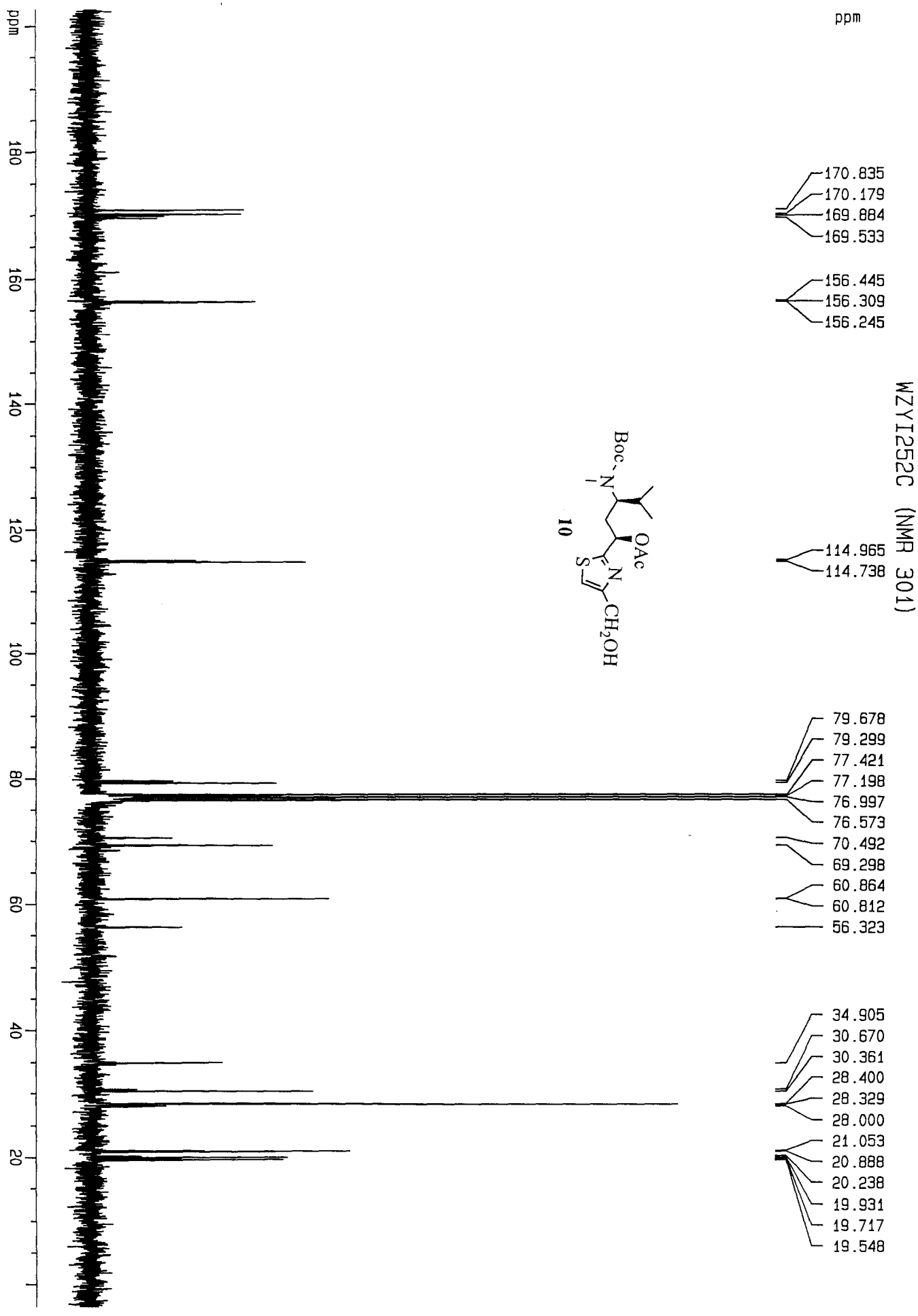
0.8307
1.1309
8.7327
2.9563
2.9315
7.26999
7.15024
7.13573
5.85280
5.84333
5.81412
5.80469
4.73523
4.10085
4.07372
4.06613
4.03869
2.80131
2.69125
2.62391
2.32715
2.27684
2.13758
2.07125
2.02205
1.69797
1.50134
1.43518
0.97936
0.95743
0.86685
0.84481
Boc
N
OAc
S
N
CH2OH
10
WZY1252C (NMR 301)


ppm
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160
140
120
100
80
60
40
20
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170.179
169.884
169.533
156.445
156.309
156.245
114.965
114.738
79.678
79.299
77.421
77.198
76.997
76.573
70.492
69.298
60.864
60.812
56.323
34.905
30.670
30.361
28.400
28.329
28.000
21.053
20.888
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19.717
19.548
Boc
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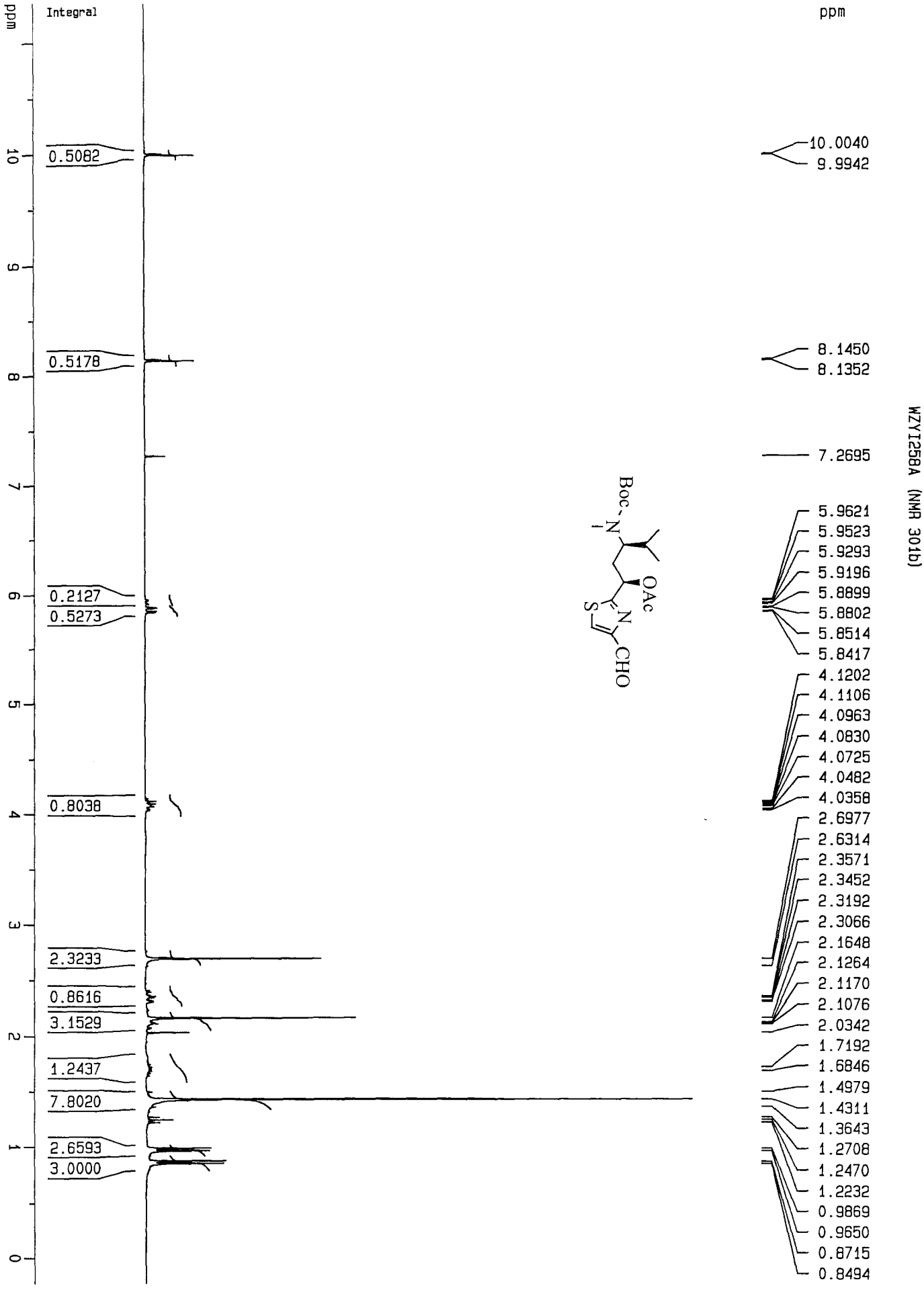
OAc
S
N
CH2OH
10
WZYI252C (NMR 301)


Integral
ppm
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0.2127
0.5273
0.8038
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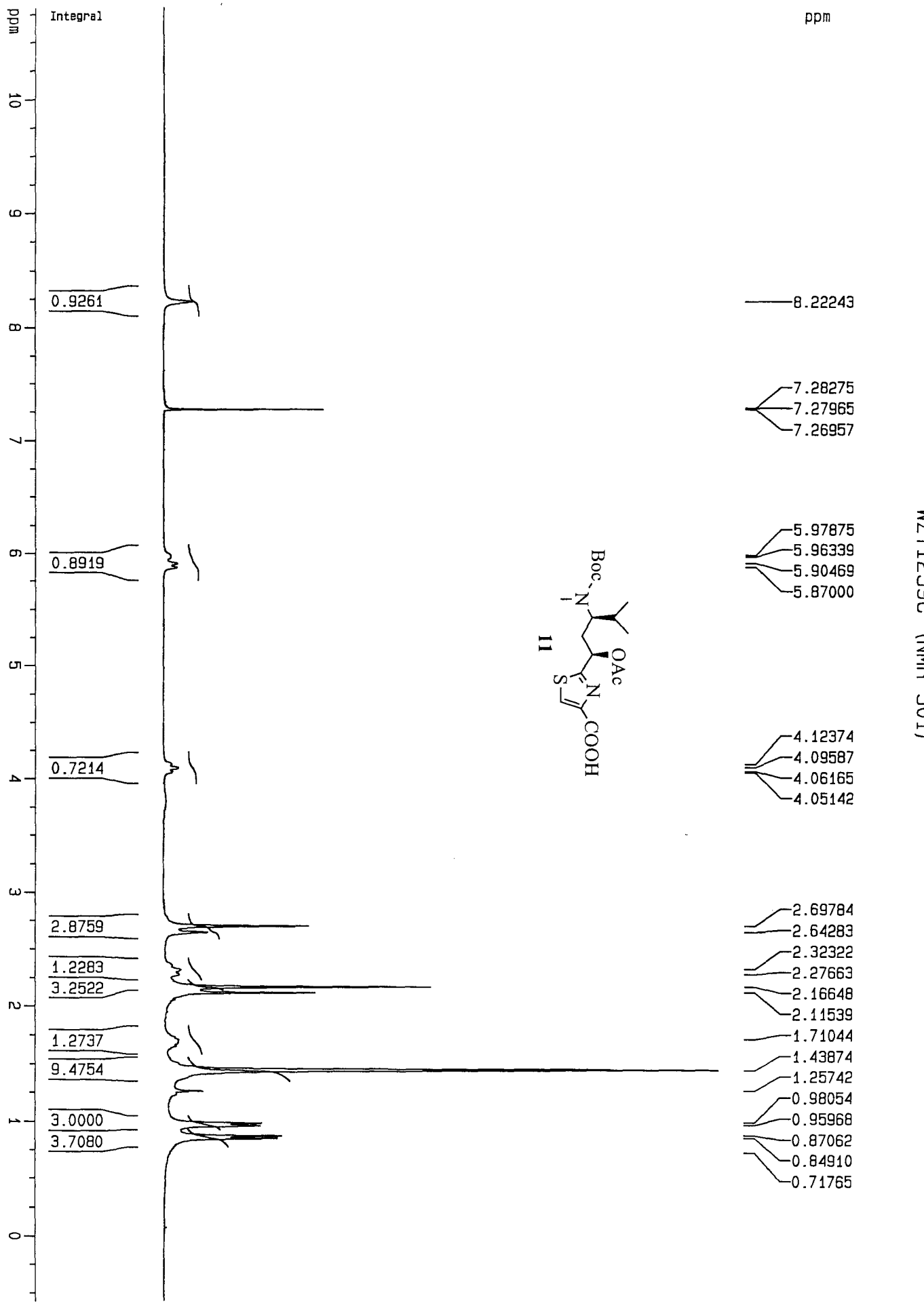
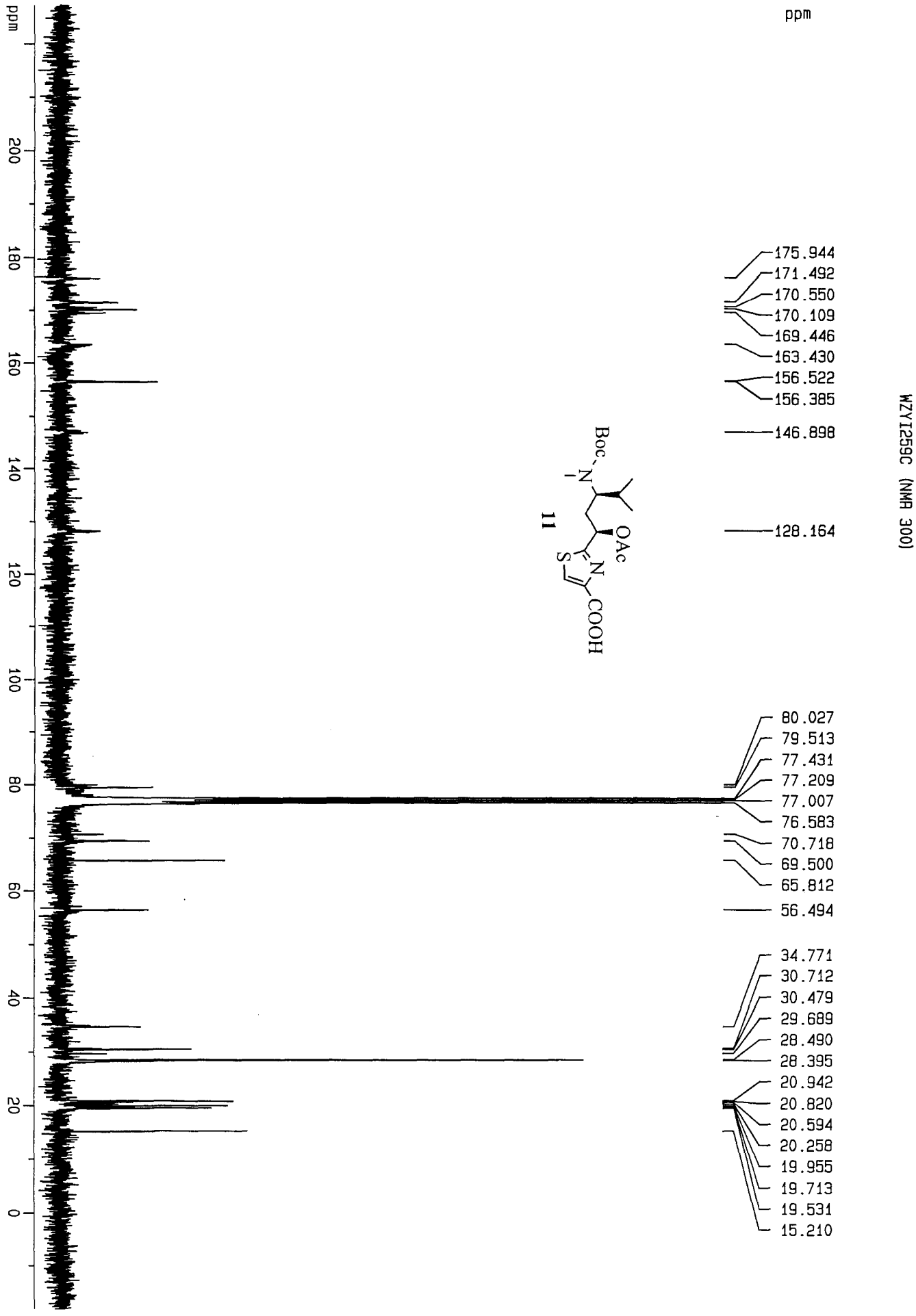
0.8616
3.1529
1.2437
7.8020
2.6593
3.0000
Boc
N
OAc
S
N
CHO
10.0040
9.9942
8.1450
8.1352
7.2695
5.9621
5.9523
5.9293
5.9196
5.8899
5.8802
5.8514
5.8417
4.1202
4.1106
4.0963
4.0830
4.0725
4.0482
4.0358
2.6977
2.6314
2.3571
2.3452
2.3192
2.3066
2.1648
2.1264
2.1170
2.1076
2.0342
1.7192
1.6846
1.4979
1.4311
1.3643
1.2708
1.2470
1.2232
0.9869
0.9650
0.8715
0.8494
WZYI258A (NMR 301b)



WZYI259C (NMR 301)


ppm
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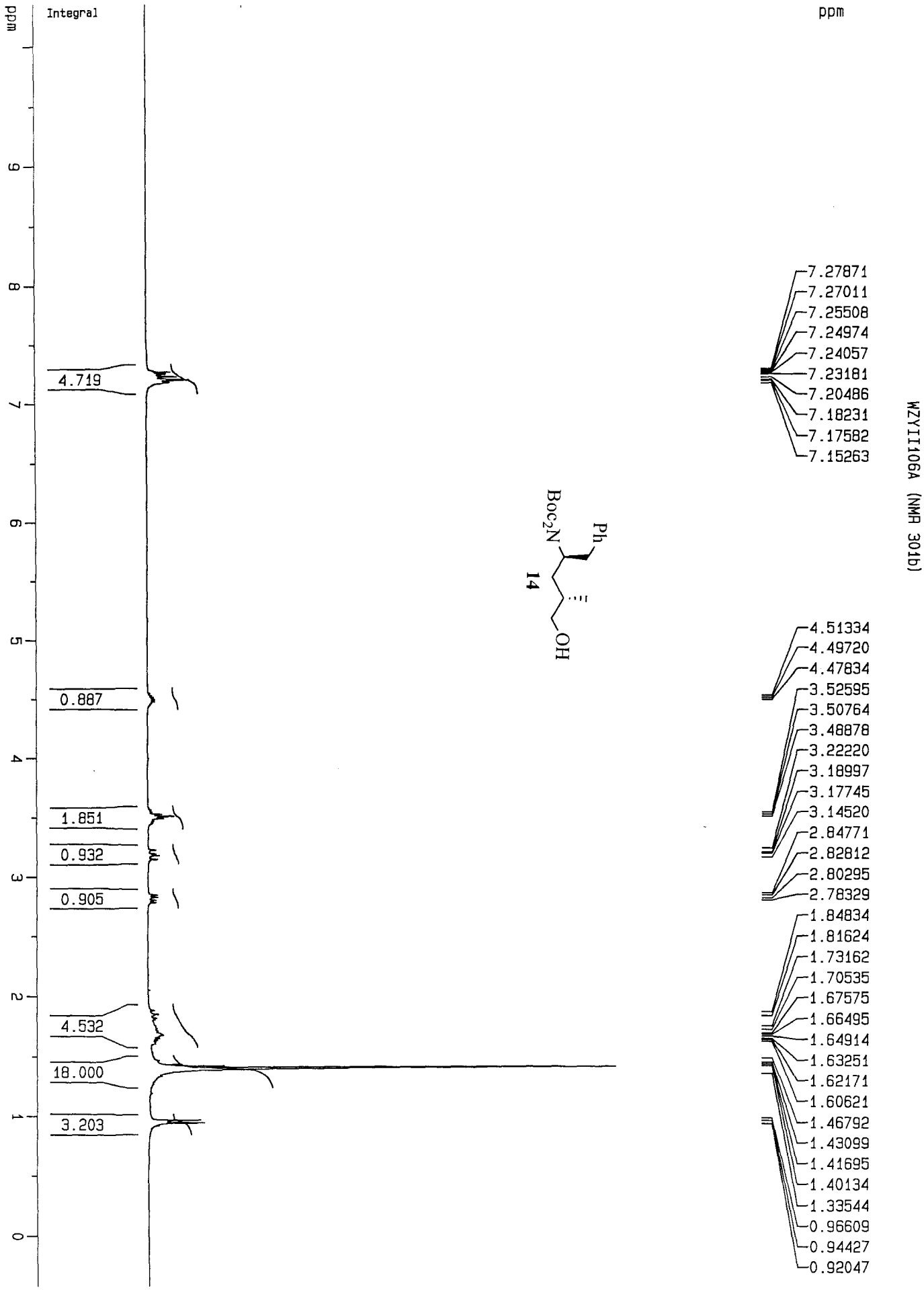
171.492
170.550
170.109
169.446
163.430
156.522
156.385
146.898
128.164
80.027
79.513
77.431
77.209
77.007
76.583
70.718
69.500
65.812
56.494
34.771
30.712
30.479
29.689
28.490
28.395
20.942
20.820
20.594
20.258
19.955
19.713
19.531
15.210
Boc
N
OAc
S
N
COOH
11
WZY1259C (NMR 300)


ppm
Integral
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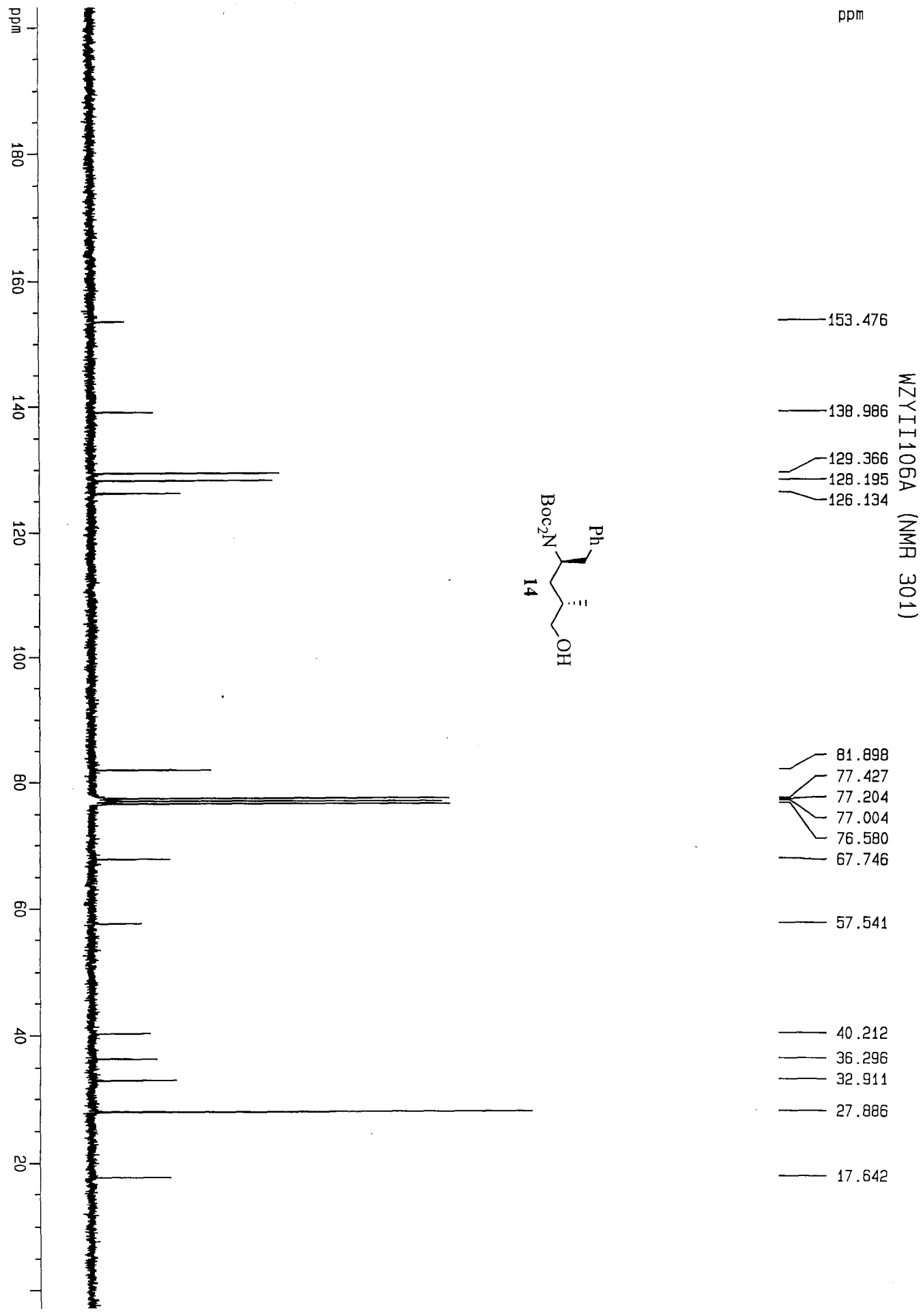
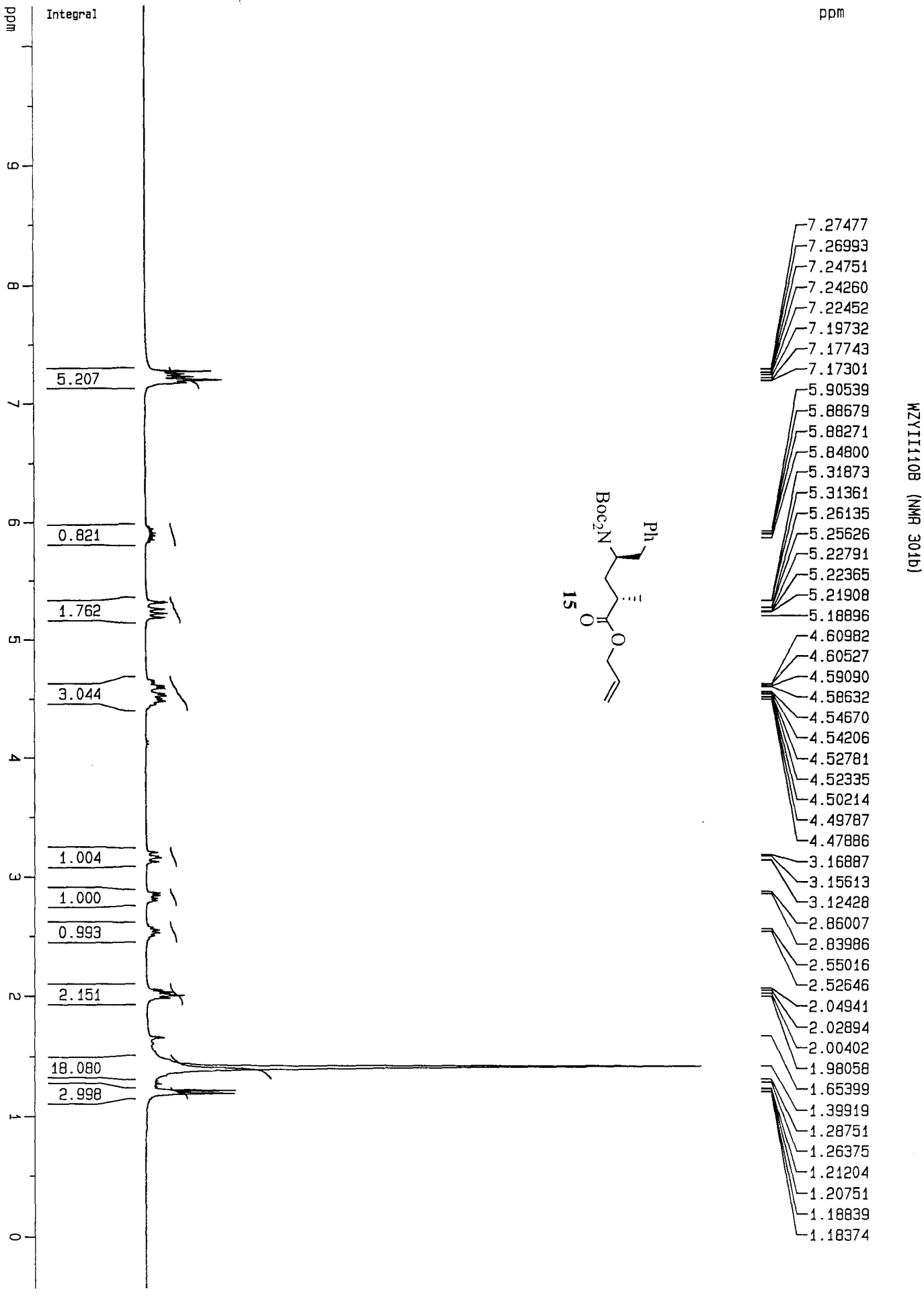
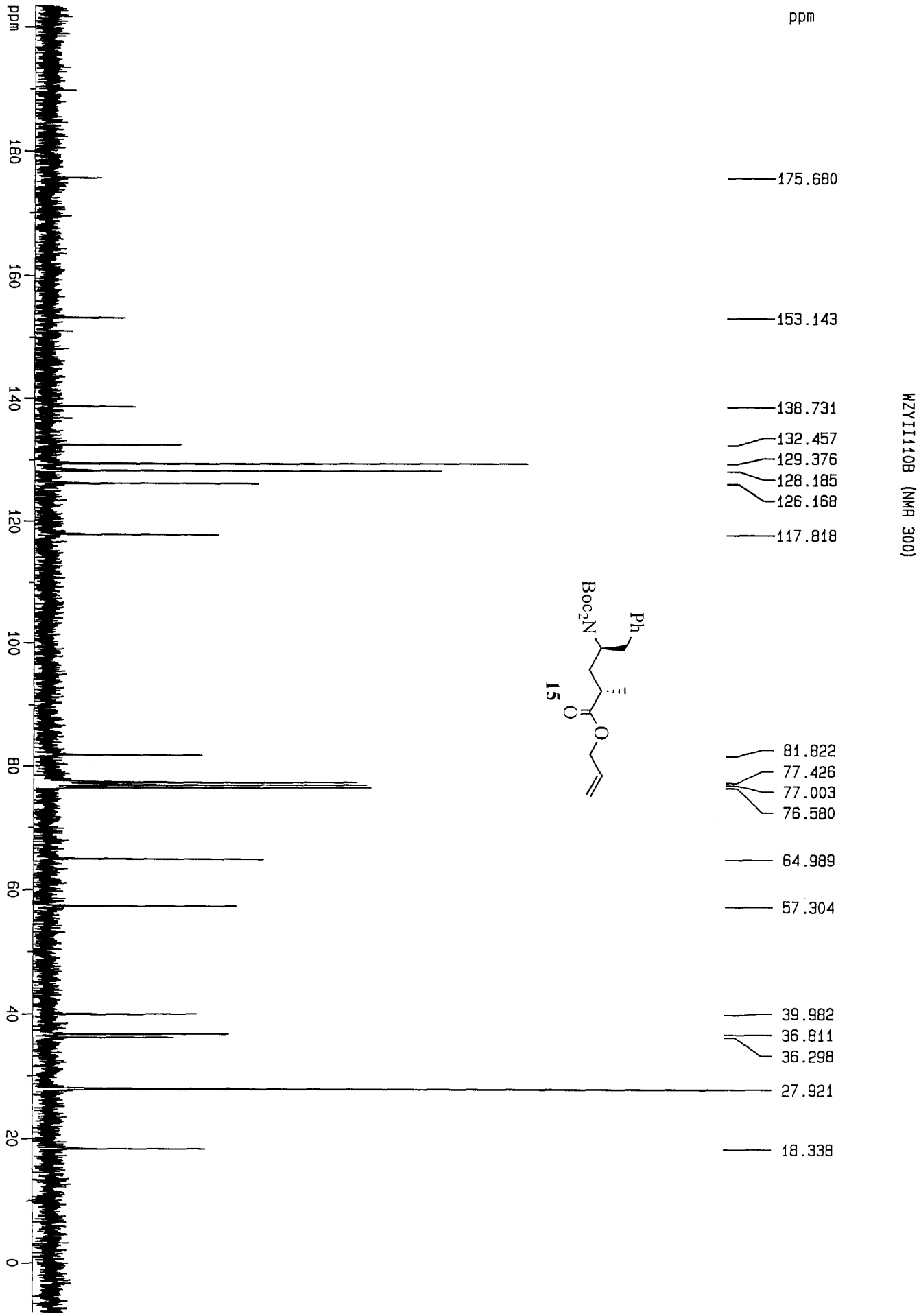
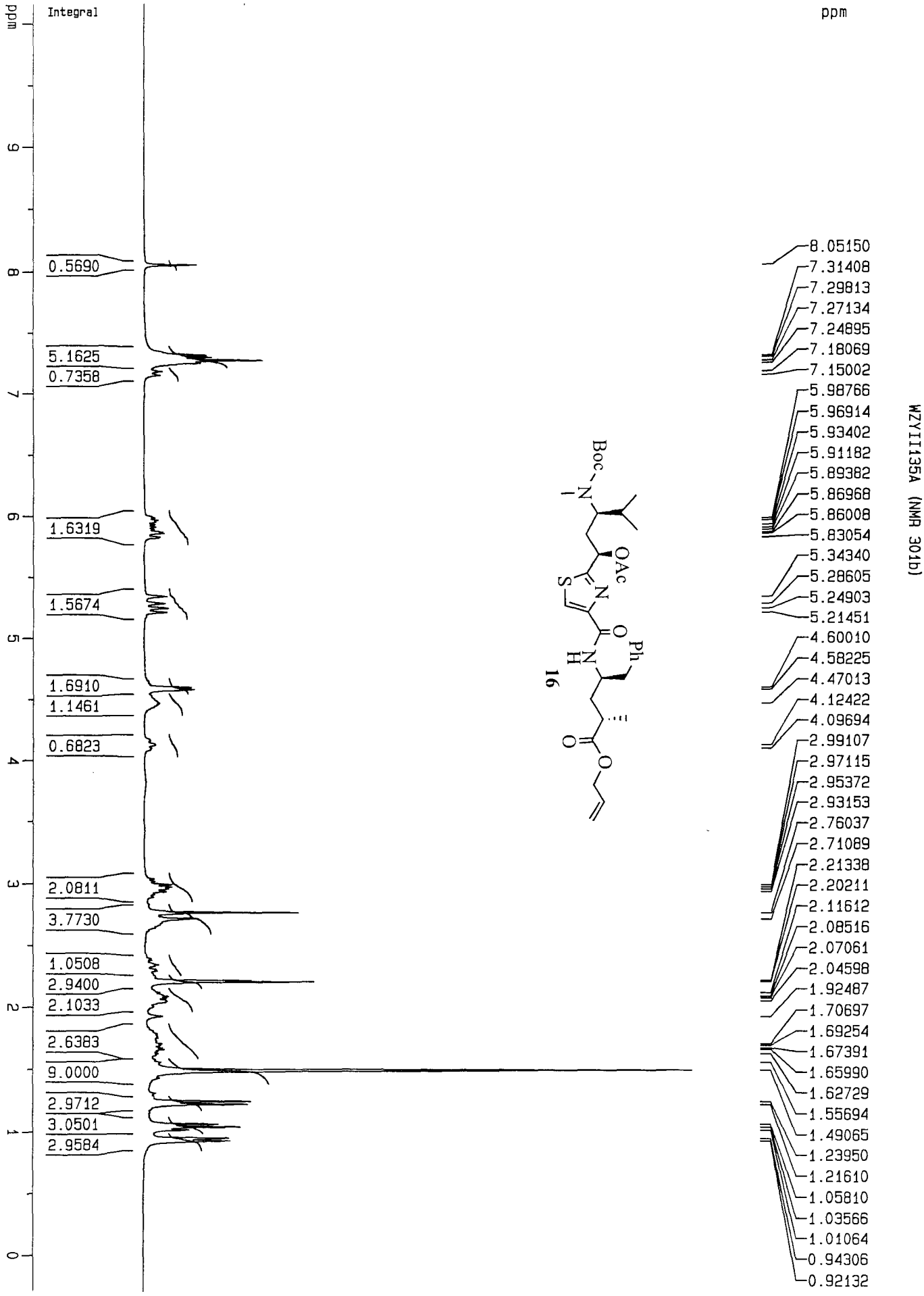
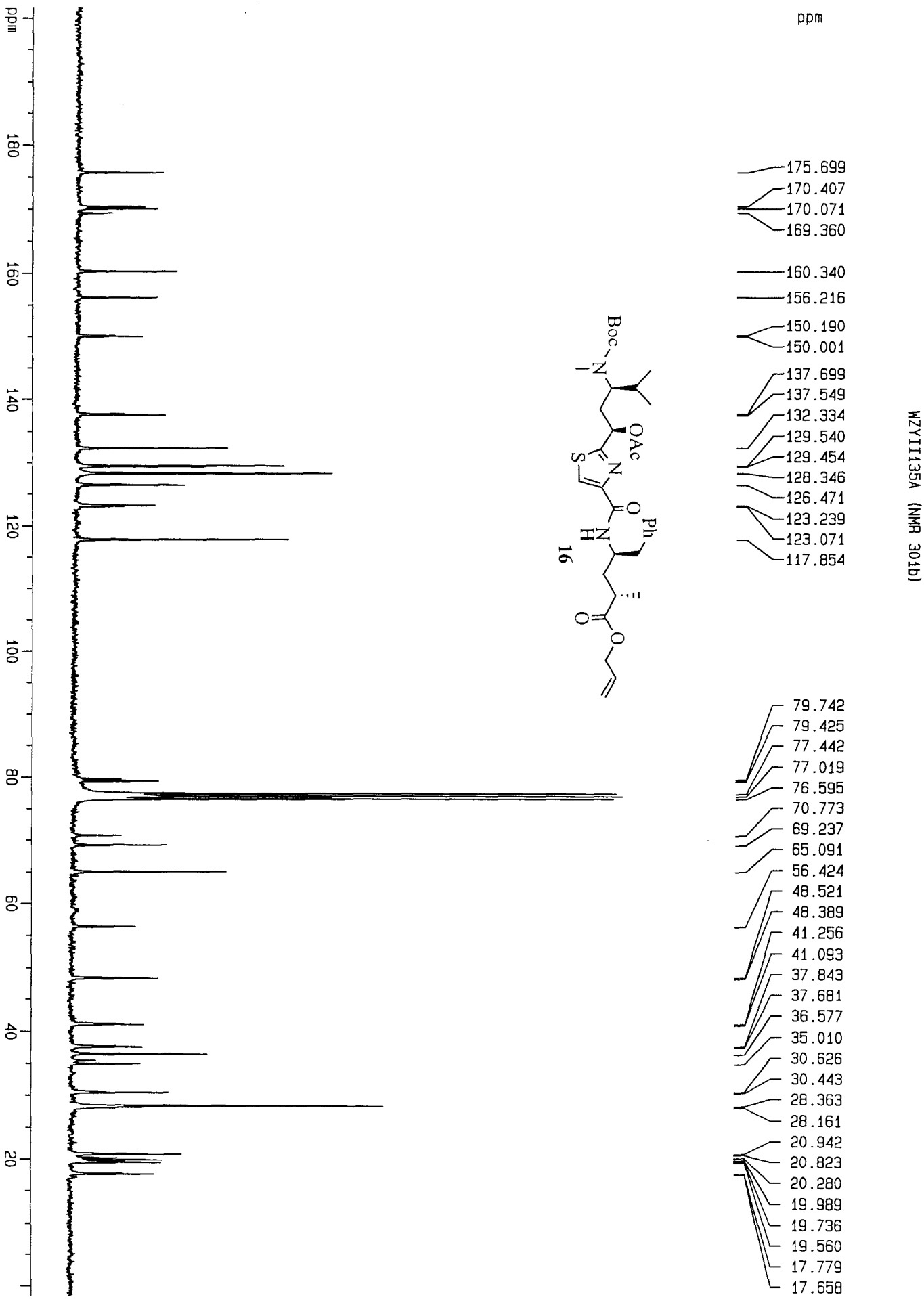
0.887
1.851
0.932
0.905
4.532
18.000
3.203
Boc2N
Ph
OH
14
ppm
7.27871
7.27011
7.25508
7.24974
7.24057
7.23181
7.20486
7.18231
7.17582
7.15263
4.51334
4.49720
4.47834
3.52595
3.50764
3.48878
3.22220
3.18997
3.17745
3.14520
2.84771
2.82812
2.80295
2.78329
1.84834
1.81624
1.73162
1.70535
1.67575
1.66495
1.64914
1.63251
1.62171
1.60621
1.46792
1.43099
1.41695
1.40134
1.33544
0.96609
0.94427
0.92047
WZYII106A (NMR 301b)

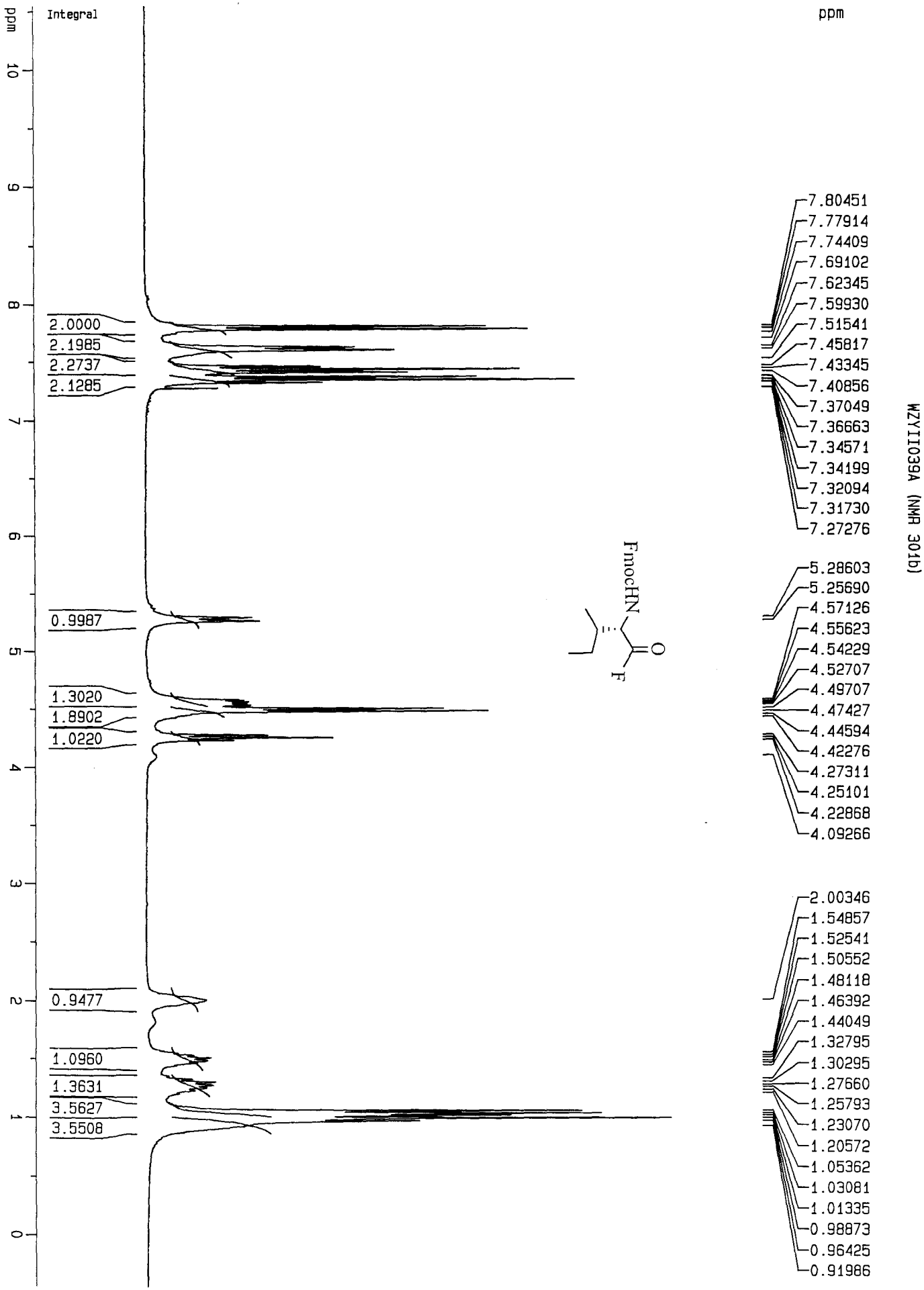

ppm
180
160
140
120
100
80
60
40
20
Boc2N
Ph
OH
14
WZYII106A (NMR 301)
ppm
153.476
138.986
129.366
128.195
126.134
81.898
77.427
77.204
77.004
76.580
67.746
57.541
40.212
36.296
32.911
27.886
17.642

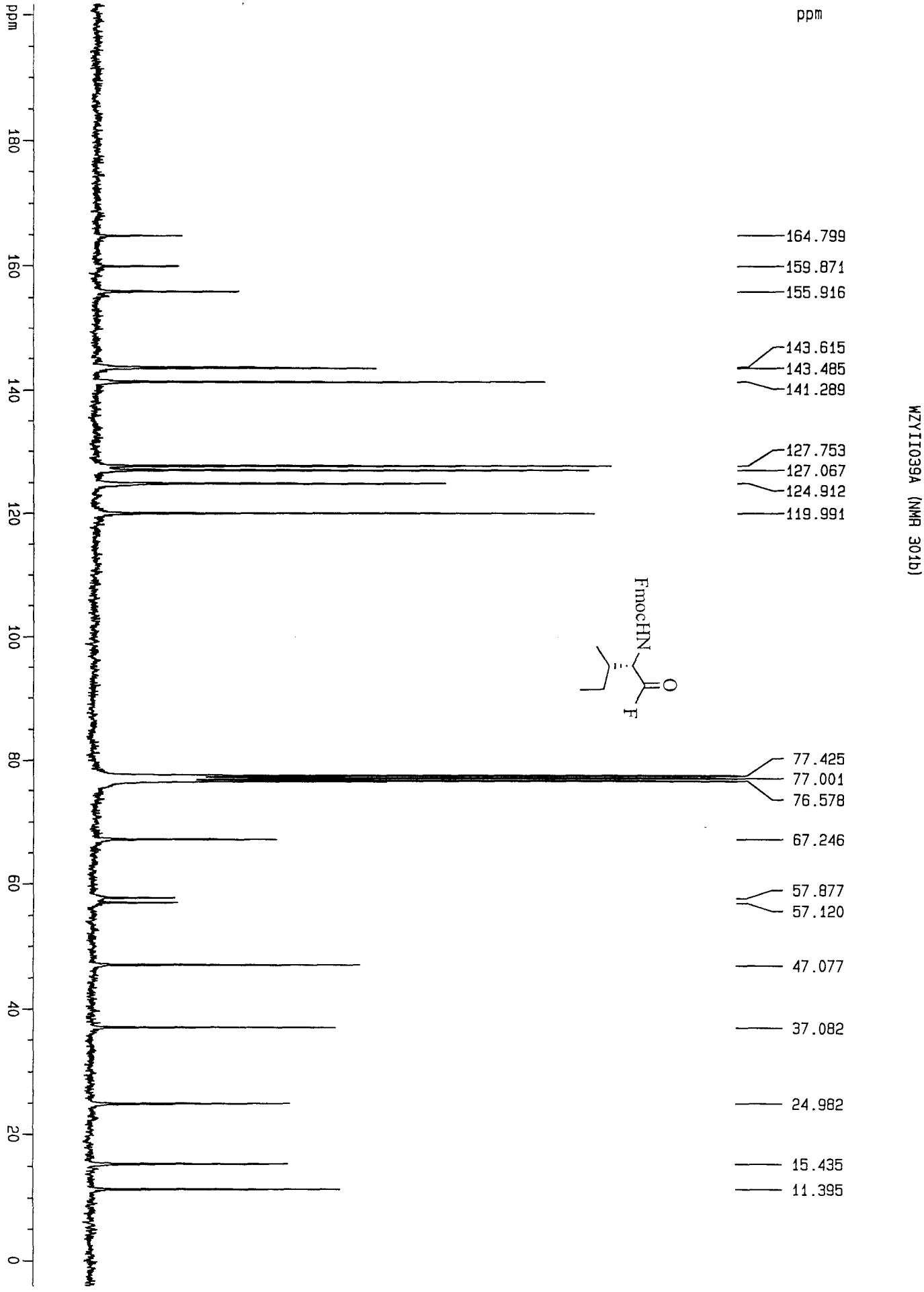

ppm
Integral
5.207
0.821
1.762
3.044
1.004
1.000
0.993
2.151
18.080
2.998
Boc2N
Ph
15
O
O
ppm
7.27477
7.26993
7.24751
7.24260
7.22452
7.19732
7.17743
7.17301
5.90539
5.88679
5.88271
5.84800
5.31873
5.31361
5.26135
5.25626
5.22791
5.22365
5.21908
5.18896
4.60982
4.60527
4.59090
4.58632
4.54670
4.54206
4.52781
4.52335
4.50214
4.49787
4.47886
3.16887
3.15613
3.12428
2.86007
2.83986
2.55016
2.52646
2.04941
2.02894
2.00402
1.98058
1.65399
1.39919
1.28751
1.26375
1.21204
1.20751
1.18839
1.18374
WZYII1410B (NMR 301b)


ppm
180
160
140
120
100
80
60
40
20
0
ppm
175.680
153.143
138.731
132.457
129.376
128.185
126.168
117.818
81.822
77.426
77.003
76.580
64.989
57.304
39.982
36.811
36.298
27.921
18.338
WZYII110B (NMR 300)
Boc2N
Ph
O
O
15

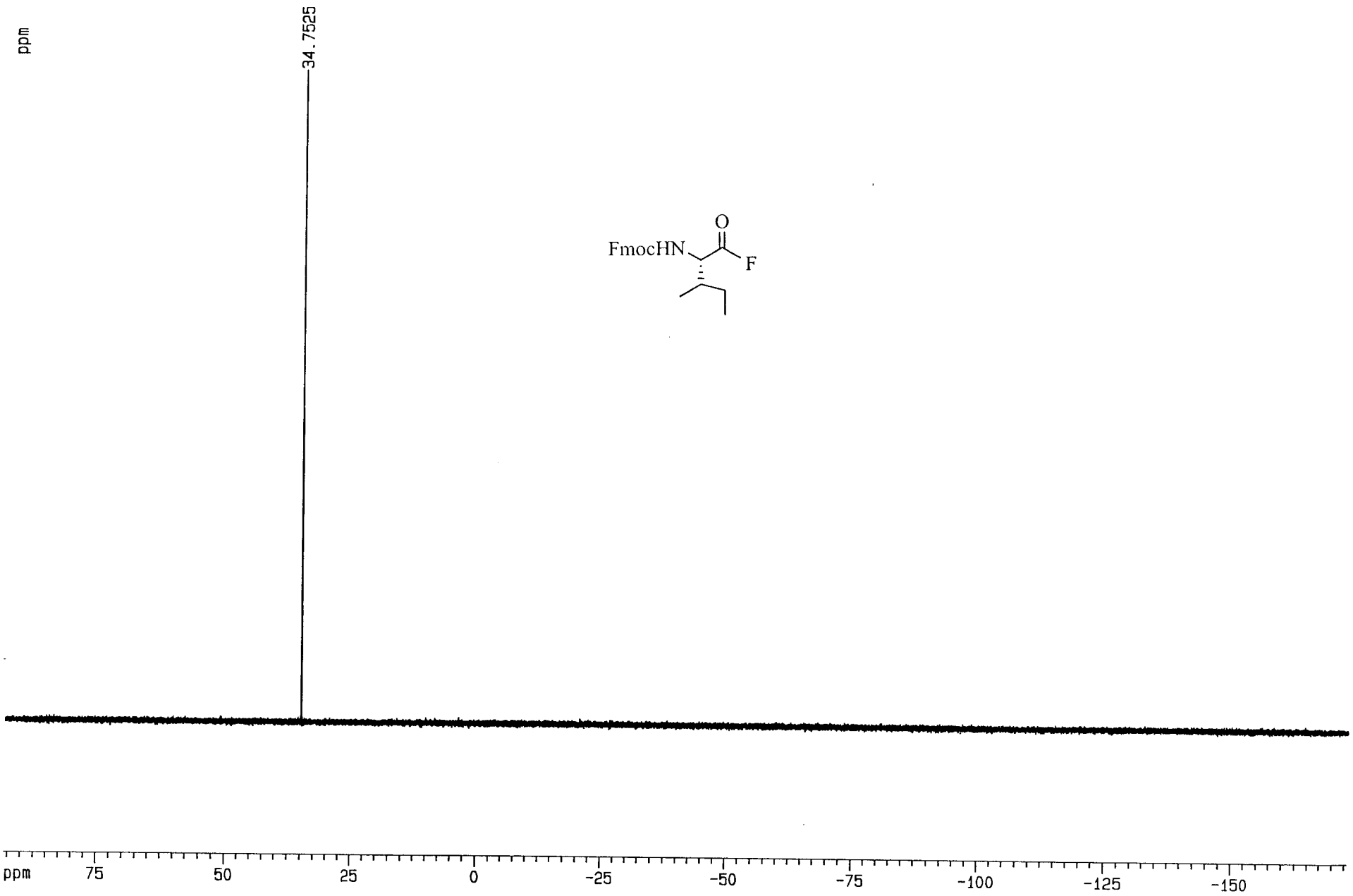

Integral
ppm
0.5690
5.1625
0.7358
1.6319
1.5674
1.6910
1.1461
0.6823
2.0811
3.7730
1.0508
2.9400
2.1033
2.6383
9.0000
2.9712
3.0501
2.9584
Boc
OAc
Ph
16
ppm
8.05150
7.31408
7.29813
7.27134
7.24895
7.18069
7.15002
5.98766
5.96914
5.93402
5.91182
5.89382
5.86968
5.86008
5.83054
5.34340
5.28605
5.24903
5.21451
4.60010
4.58225
4.47013
4.12422
4.09694
2.99107
2.97115
2.95372
2.93153
2.76037
2.71089
2.21338
2.20211
2.11612
2.08516
2.07061
2.04598
1.92487
1.70697
1.69254
1.67391
1.65990
1.62729
1.55694
1.49065
1.23950
1.21610
1.05810
1.03566
1.01064
0.94306
0.92132
WZYII135A (NMR 301b)

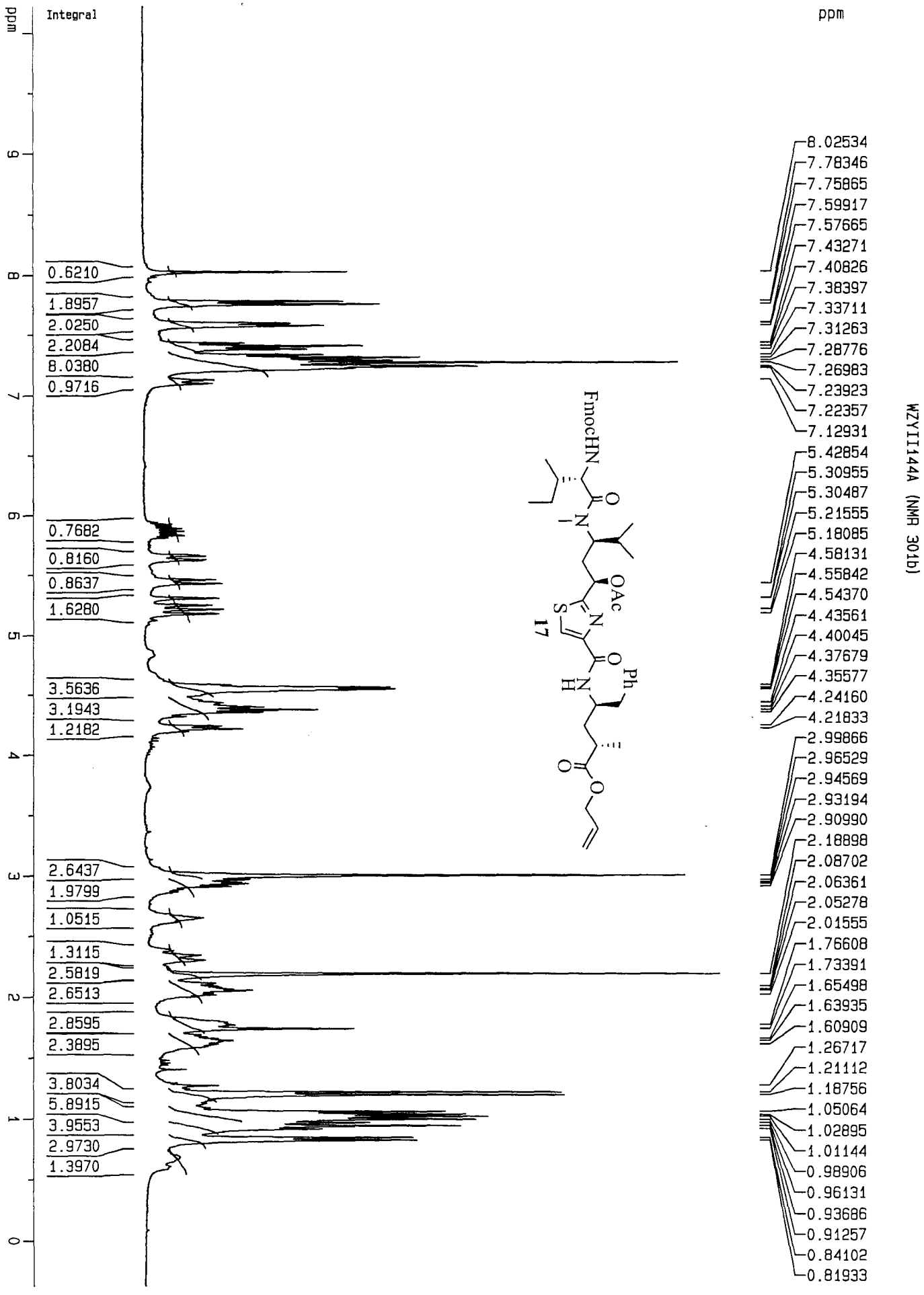

ppm
180
160
140
120
100
80
60
40
20
Boc
N
OAc
S
N
O
Ph
N
H
O
O
O
16
ppm
175.699
170.407
170.071
169.360
160.340
156.216
150.190
150.001
137.699
137.549
132.334
129.540
129.454
128.346
126.471
123.239
123.071
117.854
79.742
79.425
77.442
77.019
76.595
70.773
69.237
65.091
56.424
48.521
48.389
41.256
41.093
37.843
37.681
36.577
35.010
30.626
30.443
28.363
28.161
20.942
20.823
20.280
19.989
19.736
19.560
17.779
17.658
WZYII135A (NMR 301b)


Integral
ppm
2.0000
2.1985
2.2737
2.1285
0.9987
1.3020
1.8902
1.0220
0.9477
1.0960
1.3631
3.5627
3.5508
FmocHN
O
F
ppm
7.80451
7.77914
7.74409
7.69102
7.62345
7.59930
7.51541
7.45817
7.43345
7.40856
7.37049
7.36663
7.34571
7.34199
7.32094
7.31730
7.27276
5.28603
5.25690
4.57126
4.55623
4.54229
4.52707
4.49707
4.47427
4.44594
4.42276
4.27311
4.25101
4.22868
4.09266
2.00346
1.54857
1.52541
1.50552
1.48118
1.46392
1.44049
1.32795
1.30295
1.27660
1.25793
1.23070
1.20572
1.05362
1.03081
1.01335
0.98873
0.96425
0.91986
WZYII039A (NMR 304b)


ppm
180
160
140
120
100
80
60
40
20
0
ppm
164.799
159.871
155.916
143.615
143.485
141.289
127.753
127.067
124.912
119.991
77.425
77.001
76.578
67.246
57.877
57.120
47.077
37.082
24.982
15.435
11.395
FmocHN
O
F
WZYII039A (NMR 301b)

WZYII039A (NMR 301)

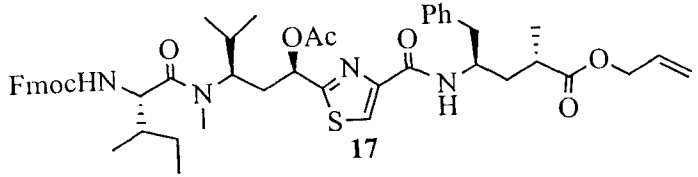



Integral
ppm
0.6210
1.8957
2.0250
2.2084
8.0380
0.9716
0.7682
0.8160
0.8637
1.6280
3.5636
3.1943
1.2182
2.6437
1.9799
1.0515
1.3115
2.5819
2.6513
2.8595
2.3895
3.8034
5.8915
3.9553
2.9730
1.3970
FmocHN
OAc
Ph
17
8.02534
7.78346
7.75865
7.59917
7.57665
7.43271
7.40826
7.38397
7.33711
7.31263
7.28776
7.26983
7.23923
7.22357
7.12931
5.42854
5.30955
5.30487
5.21555
5.18085
4.58131
4.55842
4.54370
4.43561
4.40045
4.37679
4.35577
4.24160
4.21833
2.99866
2.96529
2.94569
2.93194
2.90990
2.18898
2.08702
2.06361
2.05278
2.01555
1.76608
1.73391
1.65498
1.63935
1.60909
1.26717
1.21112
1.18756
1.05064
1.02895
1.01144
0.98906
0.96131
0.93686
0.91257
0.84102
0.81933
WZYII144A (NMR 301b)

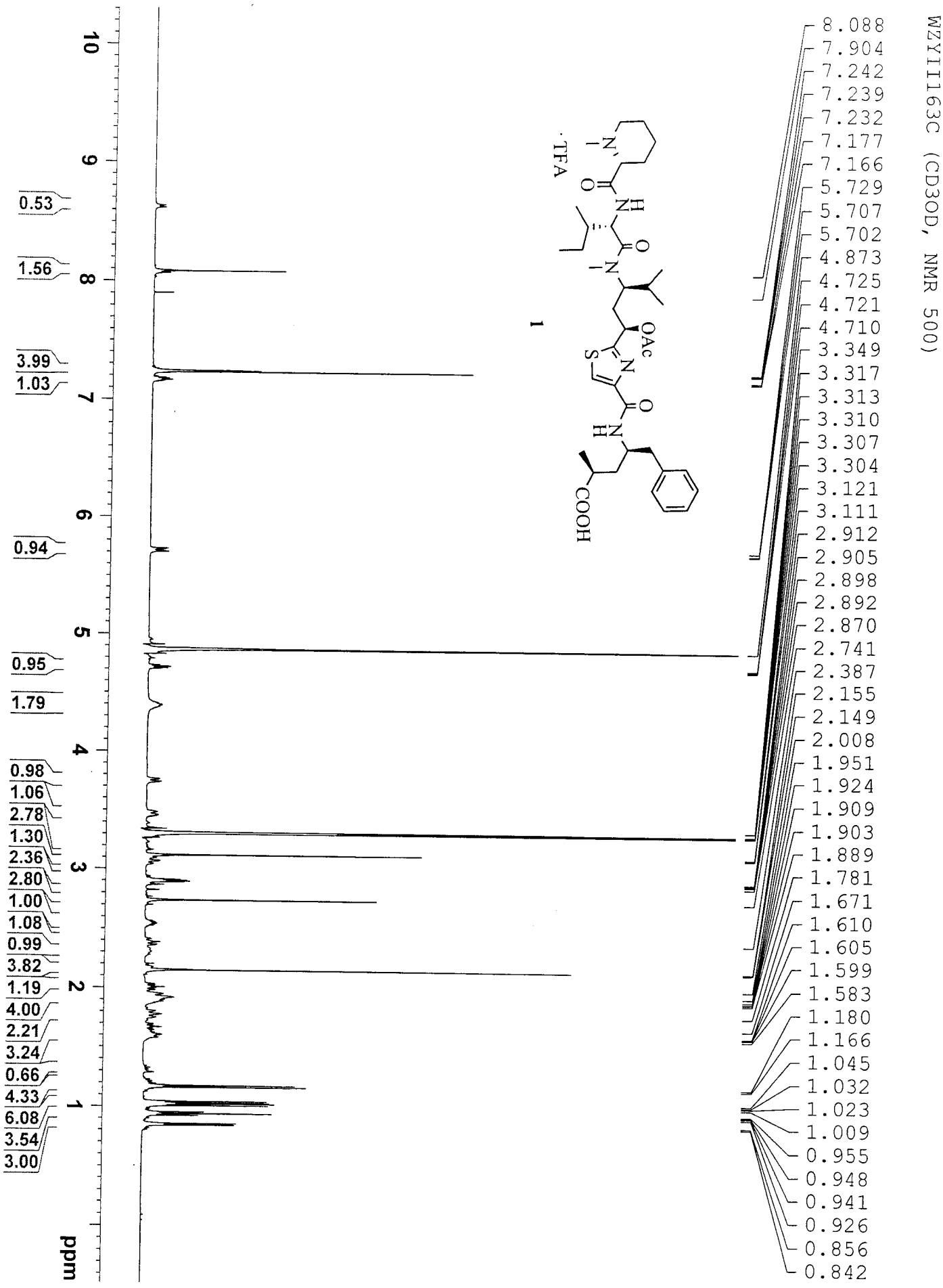
WZYII144A (NMR 301A)

175.72
173.57
170.00
169.89
160.25
156.34
150.00
143.89
143.73
141.27
141.25
137.49
132.24
129.55
128.35
127.65
127.02
126.49
125.09
125.06
123.40
119.93
117.93

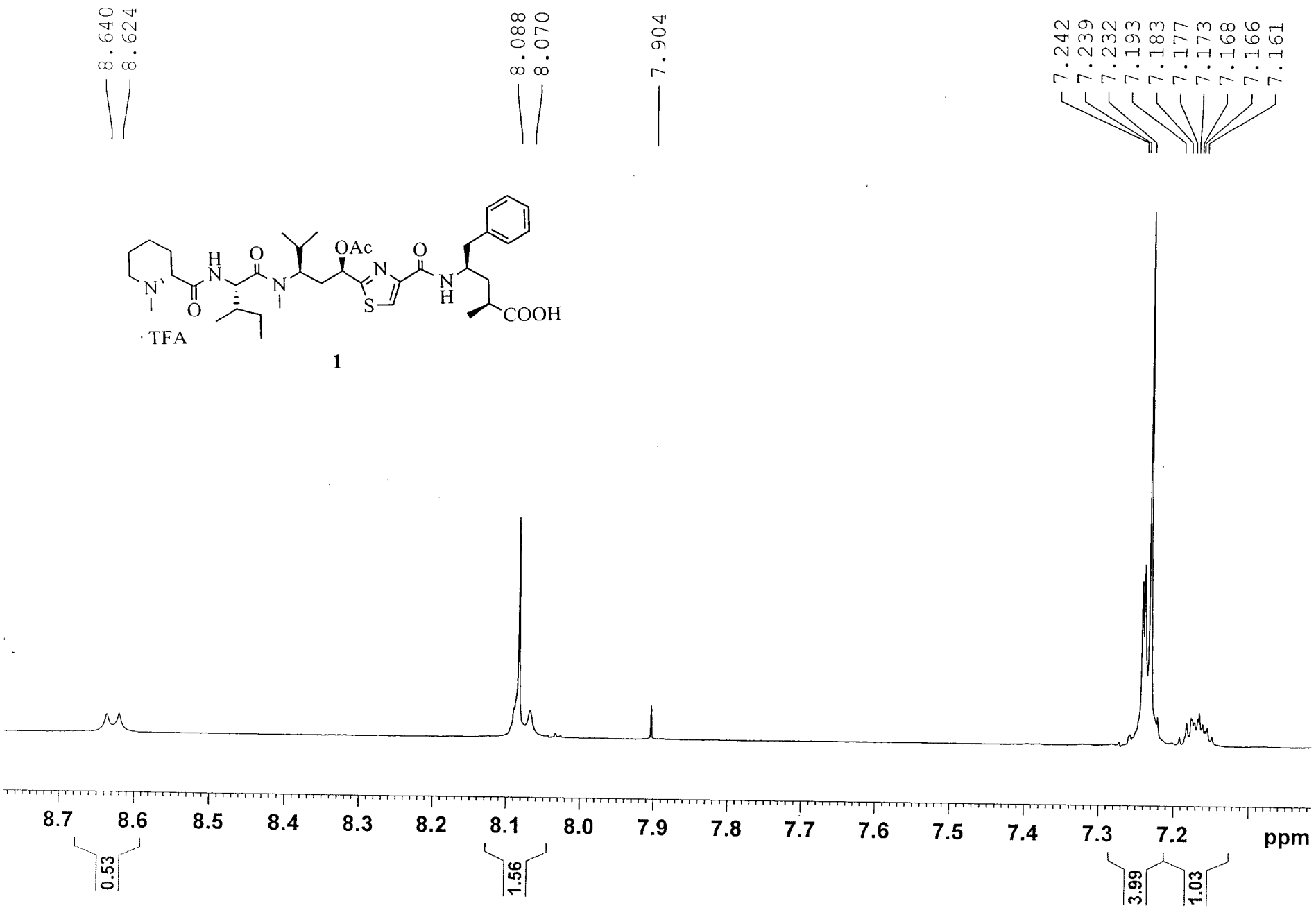
77.42
77.20
77.00
76.56
69.46
66.97
65.10
55.75
48.33
47.18
40.95
37.59
37.29
36.58
34.57
29.94
29.62
23.83
20.76
20.06
19.53
17.65
16.01



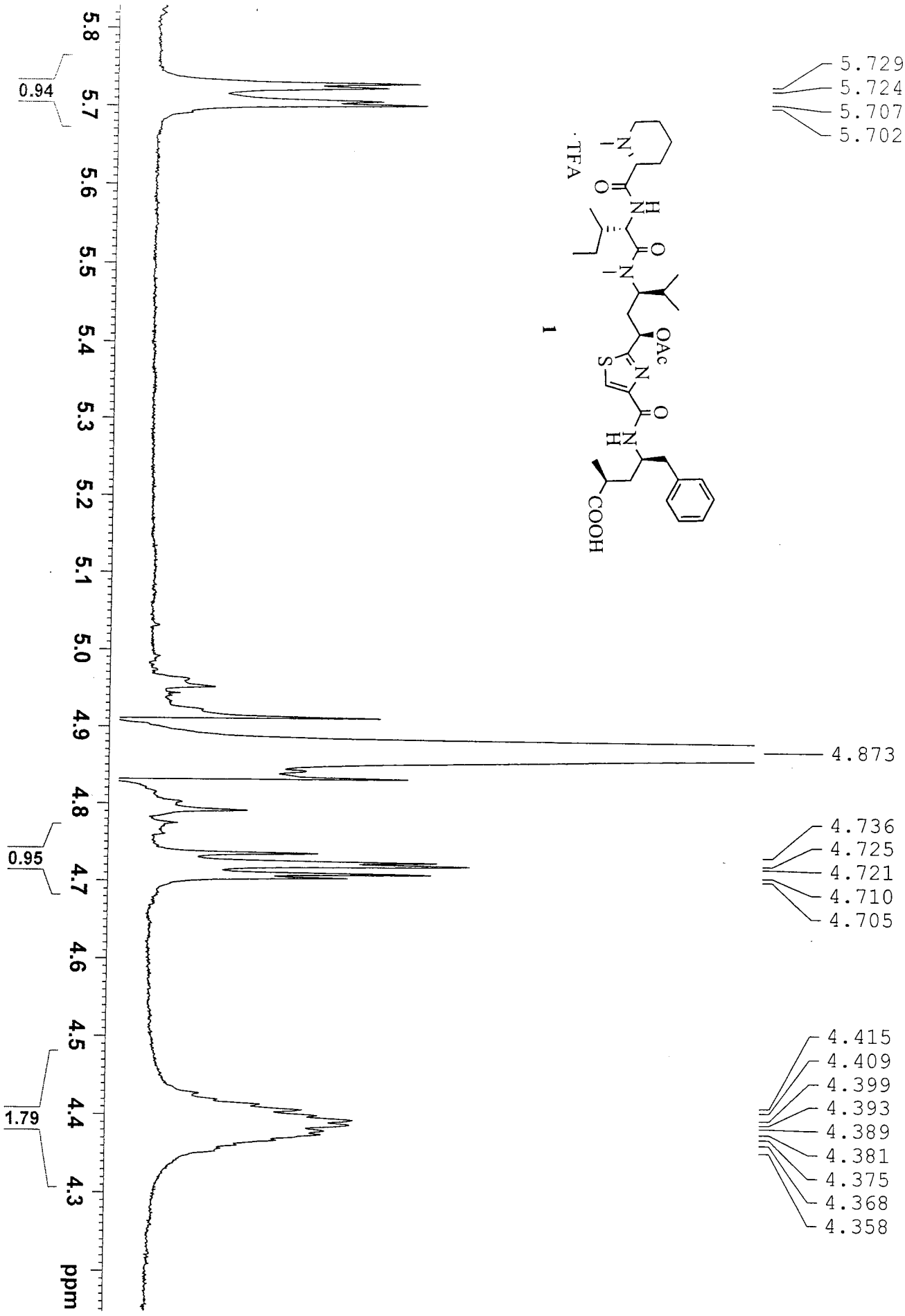
17


WZYII163C (CD3OD, NMR 500)
8.088
7.904
7.242
7.239
7.232
7.177
7.166
5.729
5.707
5.702
4.873
4.725
4.721
4.710
3.349
3.317
3.313
3.310
3.307
3.304
3.121
3.111
2.912
2.905
2.898
2.892
2.870
2.741
2.387
2.155
2.149
2.008
1.951
1.924
1.909
1.903
1.889
1.781
1.671
1.610
1.605
1.599
1.583
1.180
1.166
1.045
1.032
1.023
1.009
0.955
0.948
0.941
0.926
0.856
0.842
0.53
1.56
3.99
1.03
0.94
0.95
1.79
0.98
1.06
2.78
1.30
2.36
2.80
1.00
1.08
0.99
3.82
1.19
4.00
2.21
3.24
0.66
4.33
6.08
3.54
3.00
ppm
10
9
8
7
6
5
4
3
2
1
·TFA
OAc
COOH
1

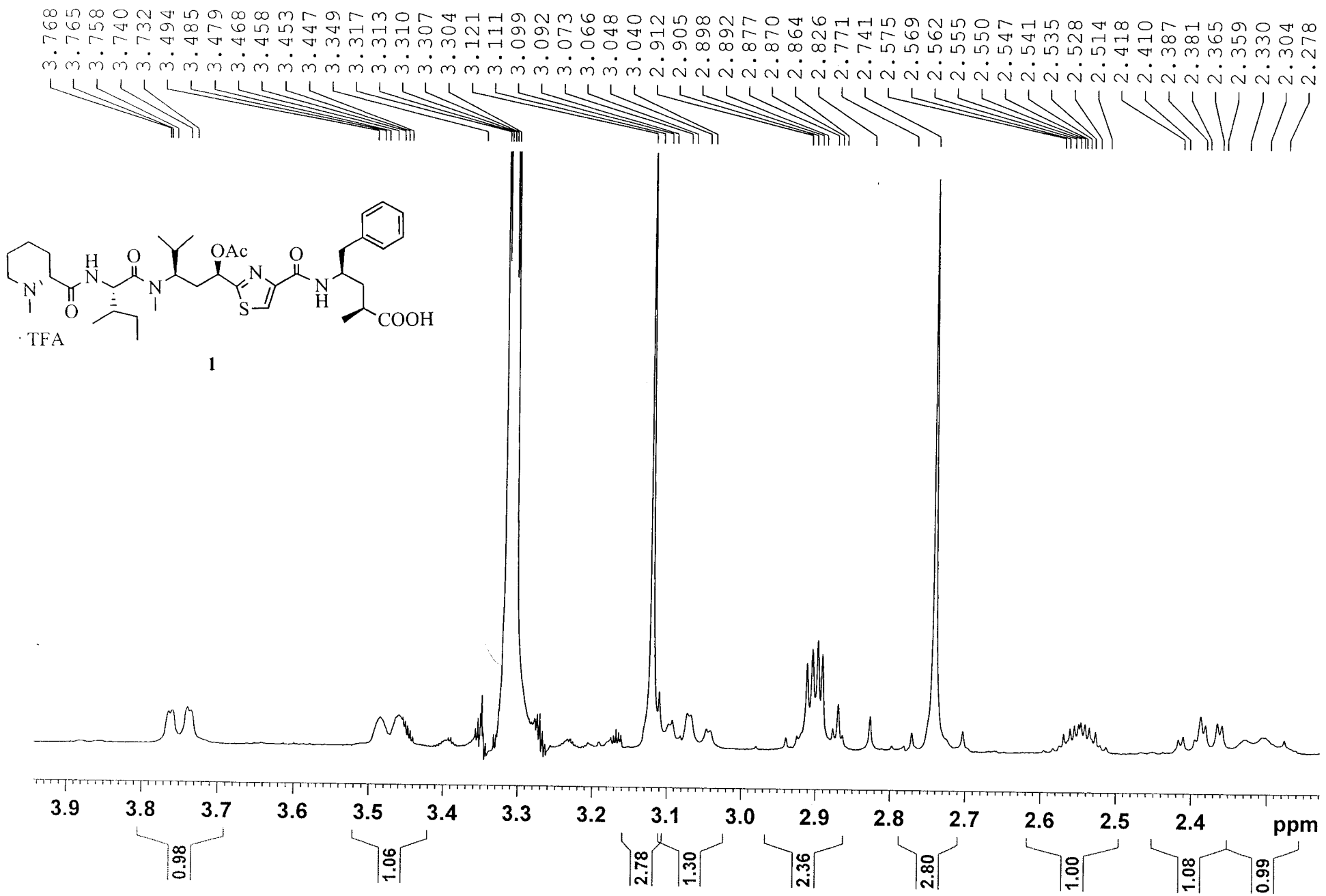
WZYII163C (CD3OD, NMR 500)



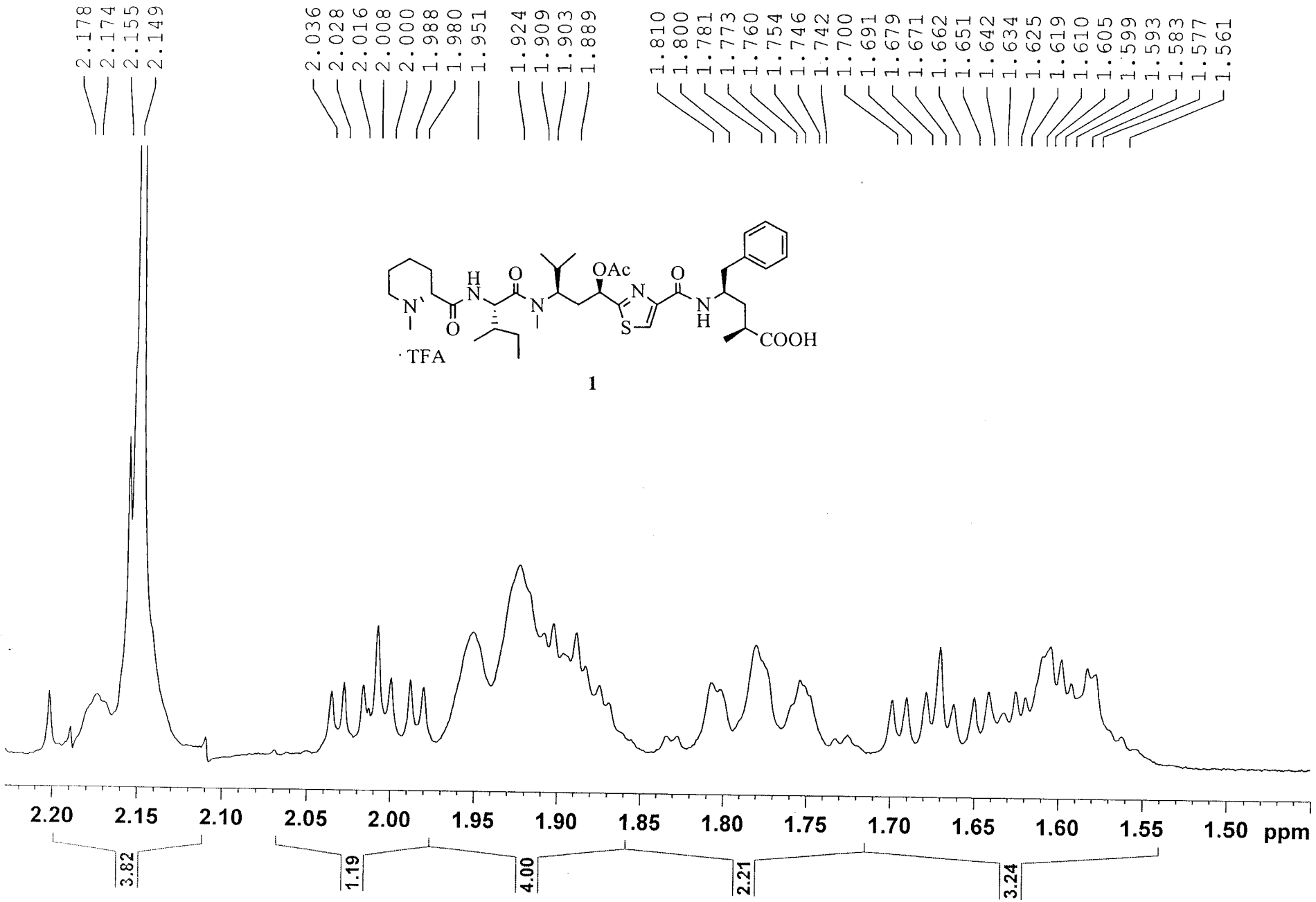
1


WZYII163C (CD3OD, NMR 500)
5.729
5.724
5.707
5.702
4.873
4.736
4.725
4.721
4.710
4.705
4.415
4.409
4.399
4.393
4.389
4.381
4.375
4.368
4.358
0.94
0.95
1.79
5.8
5.7
5.6
5.5
5.4
5.3
5.2
5.1
5.0
4.9
4.8
4.7
4.6
4.5
4.4
4.3
ppm
·TFA
OAc
COOH
1

WZYII163C (CD3OD, NMR 500)

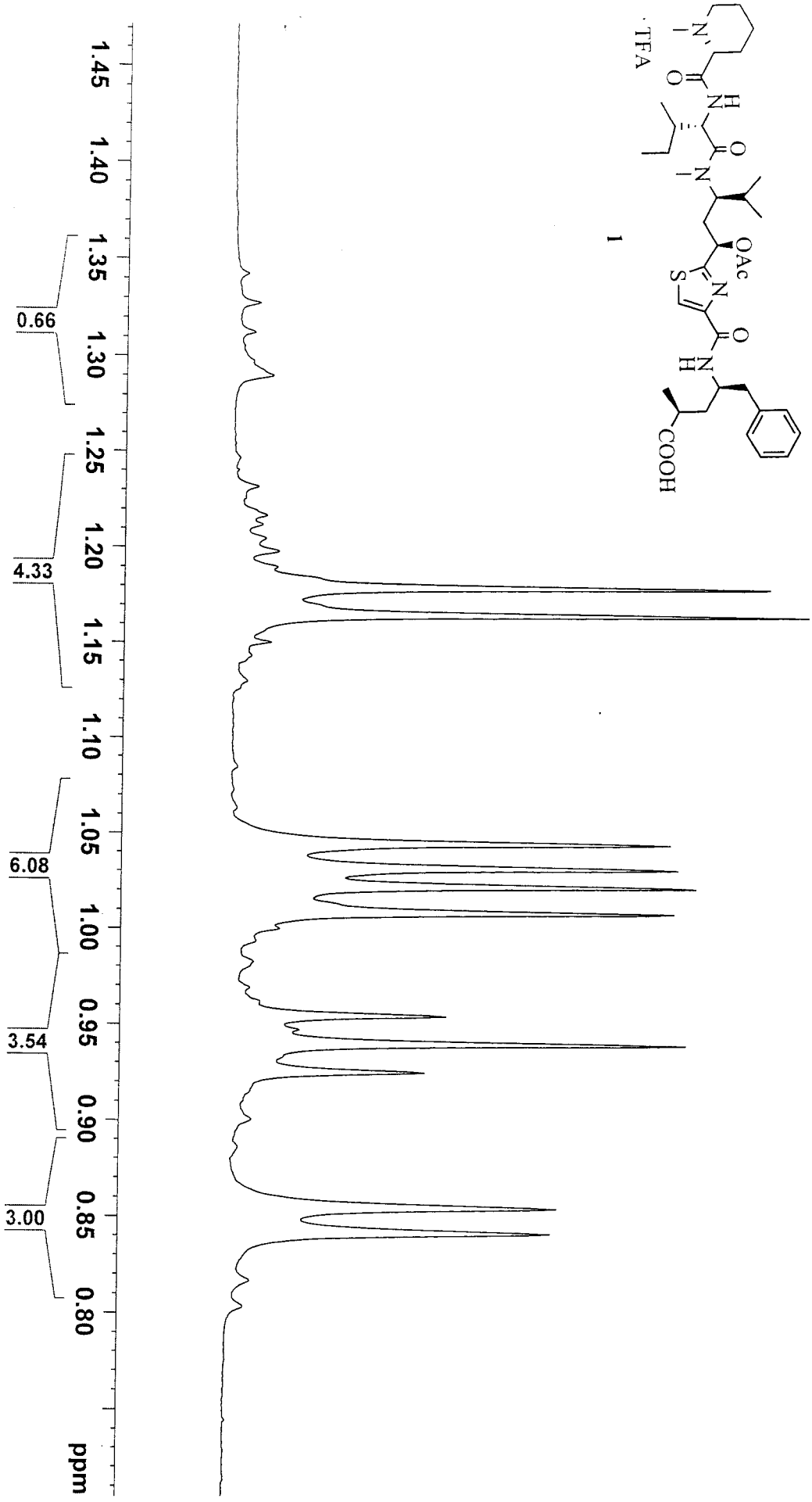


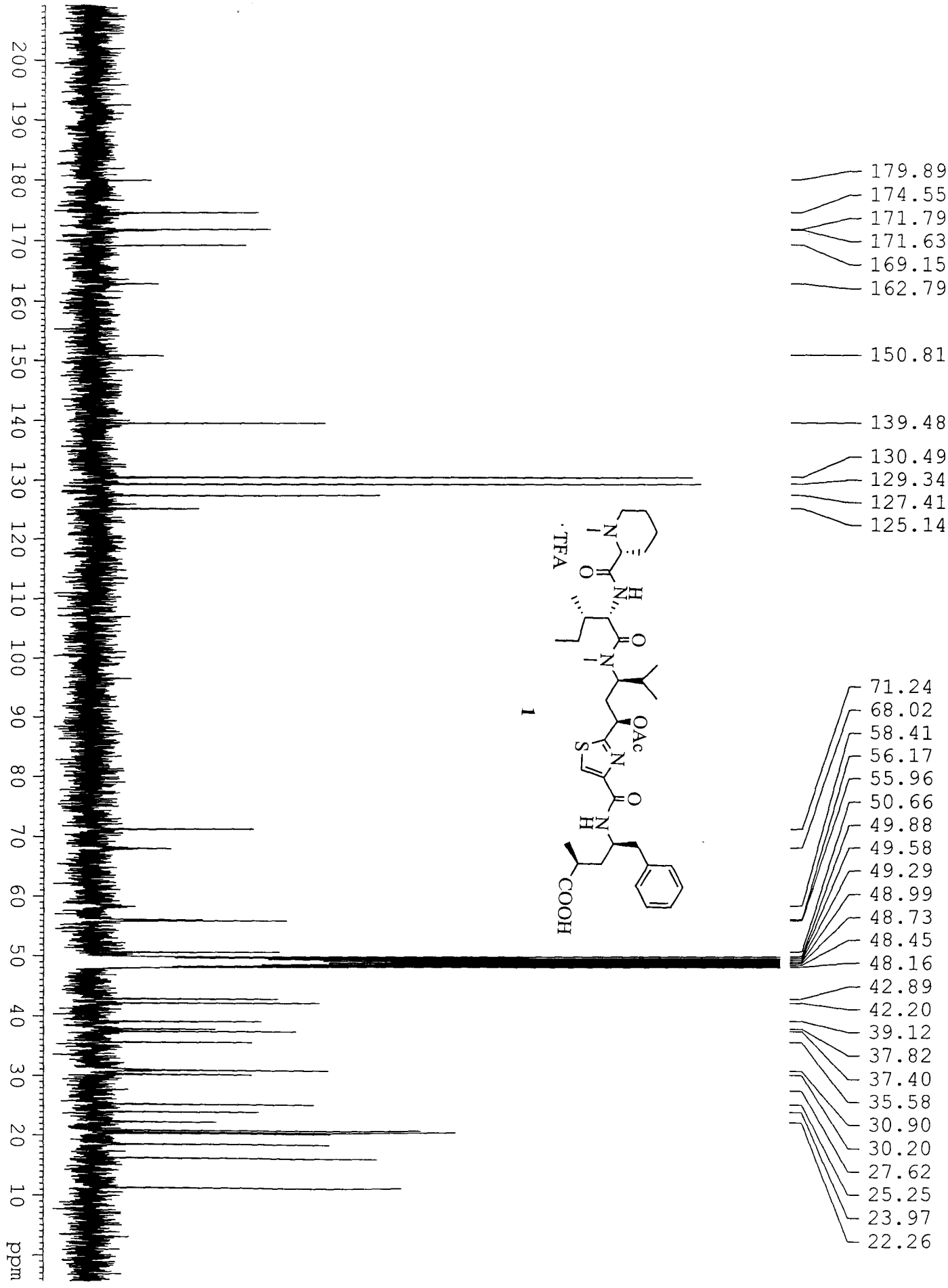
WZYII163C (CD3OD, NMR 500)

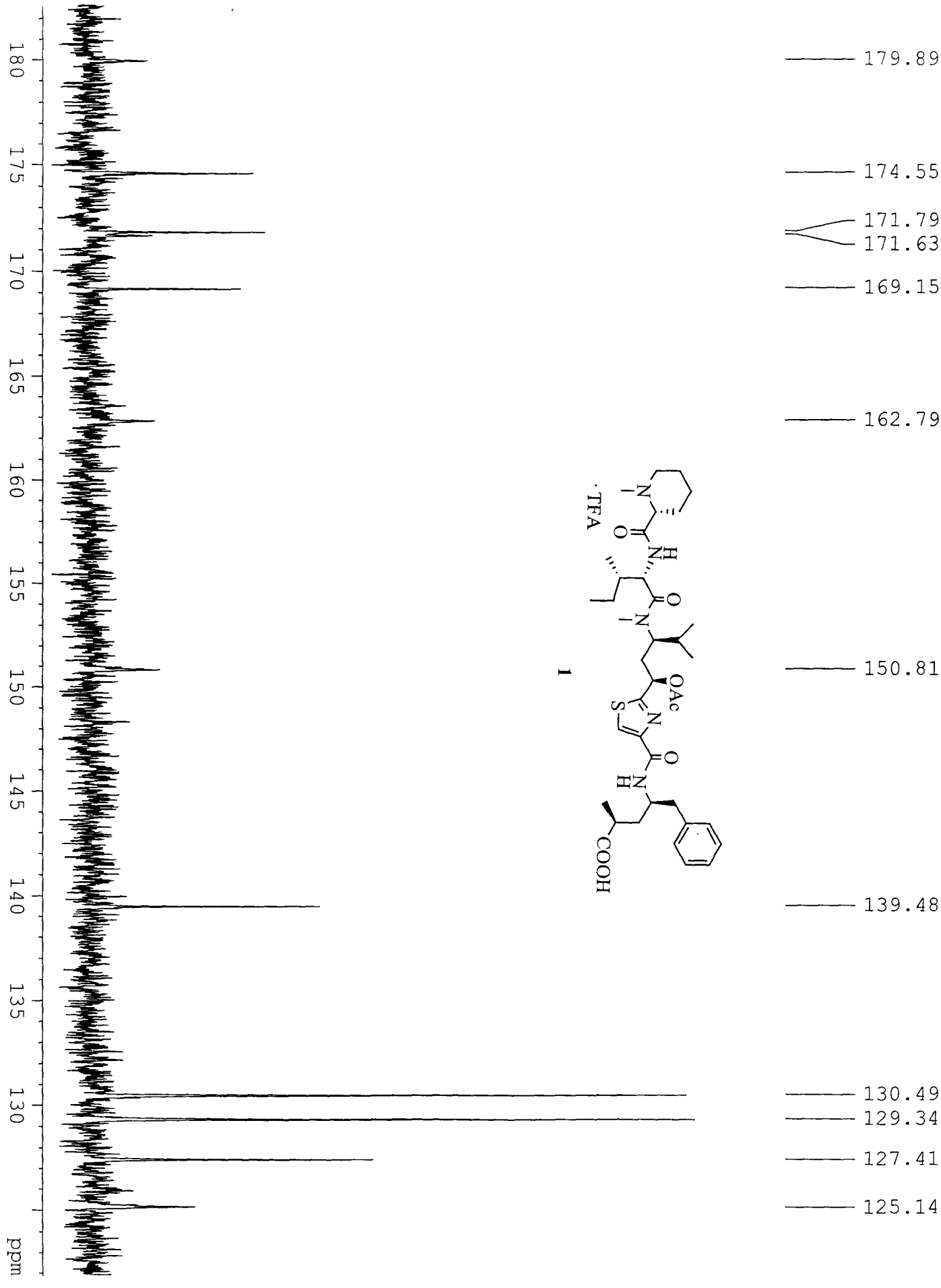


1

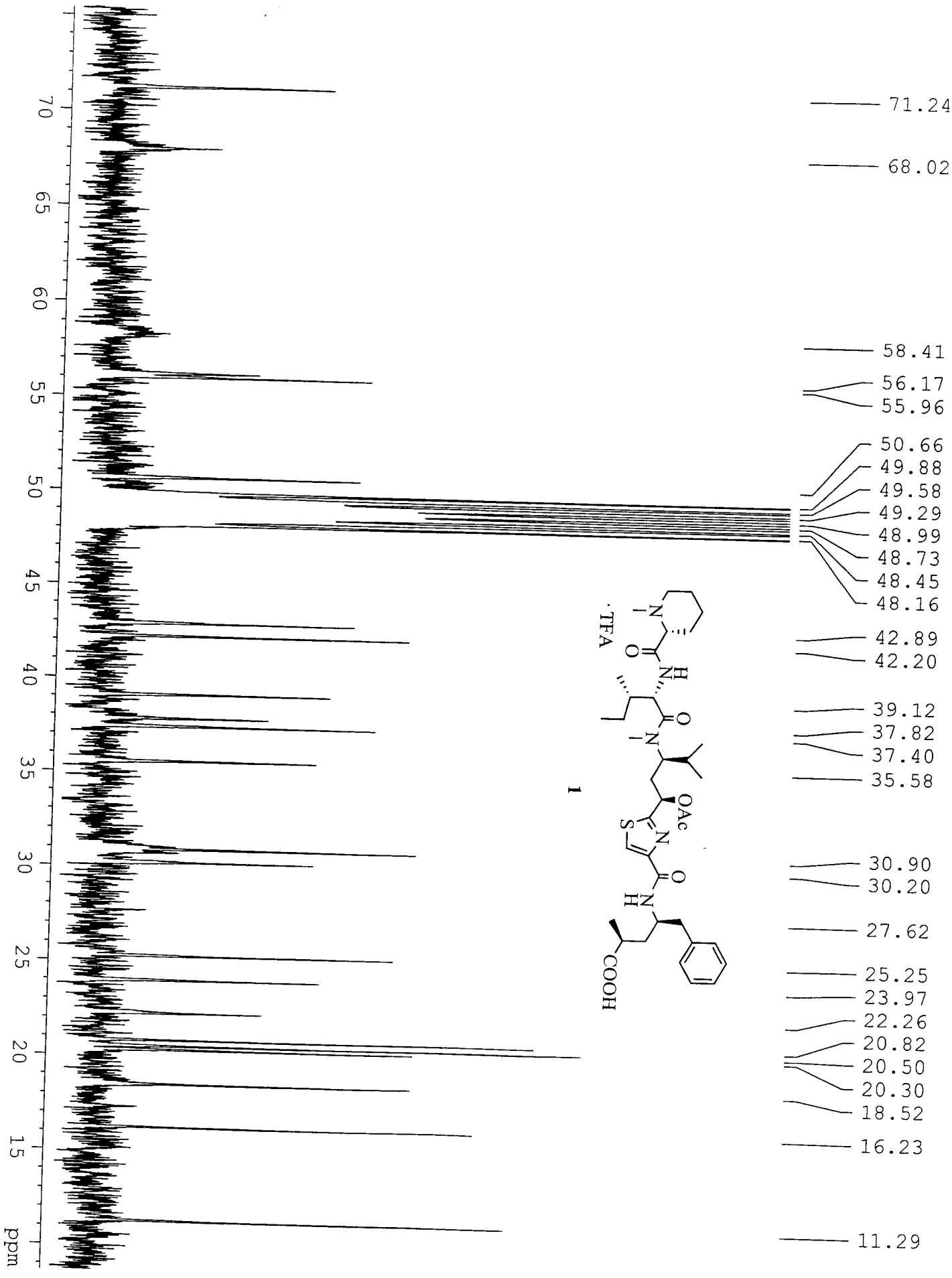
WZYII163C (CD3OD, NMR 500)

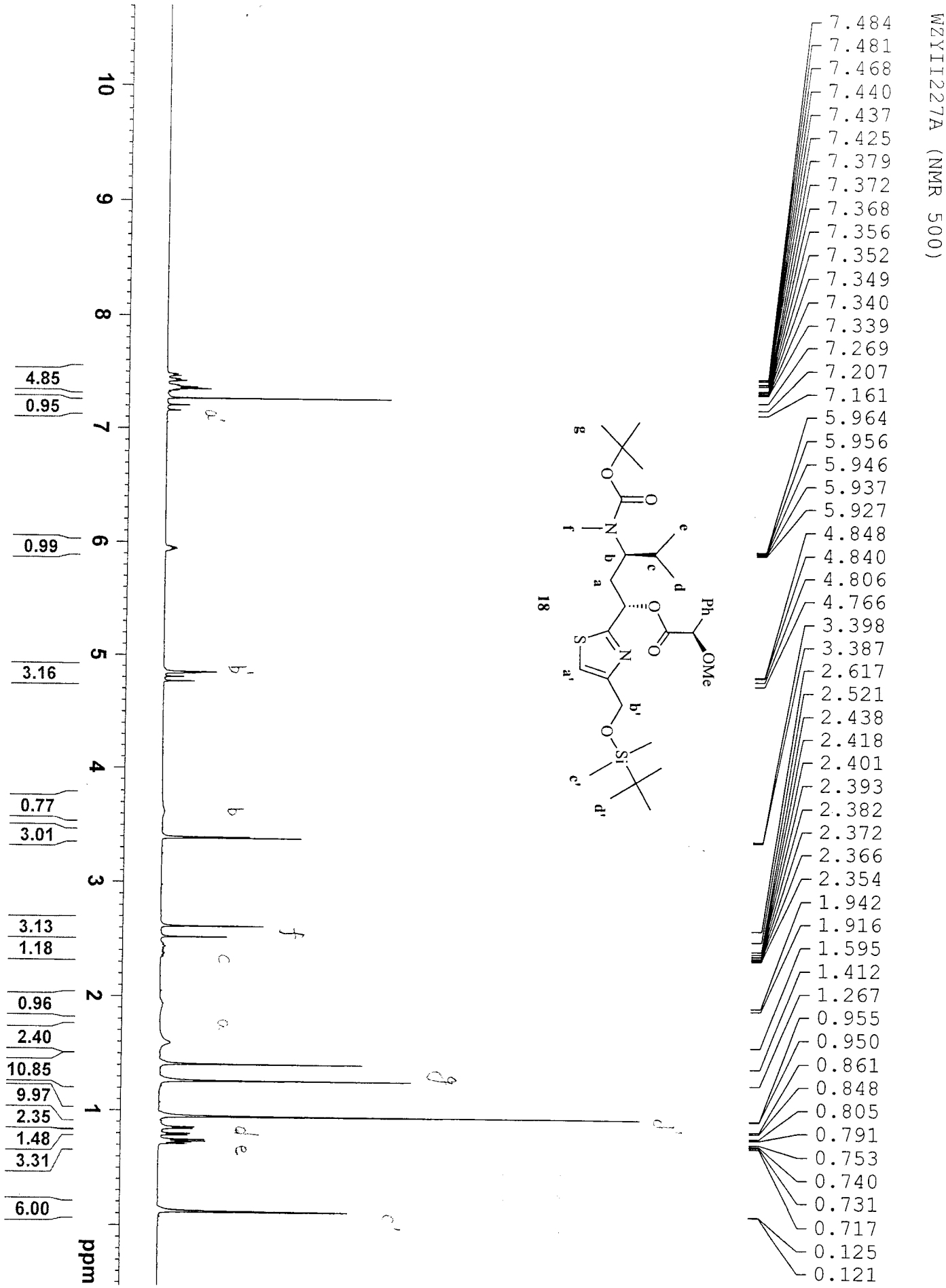


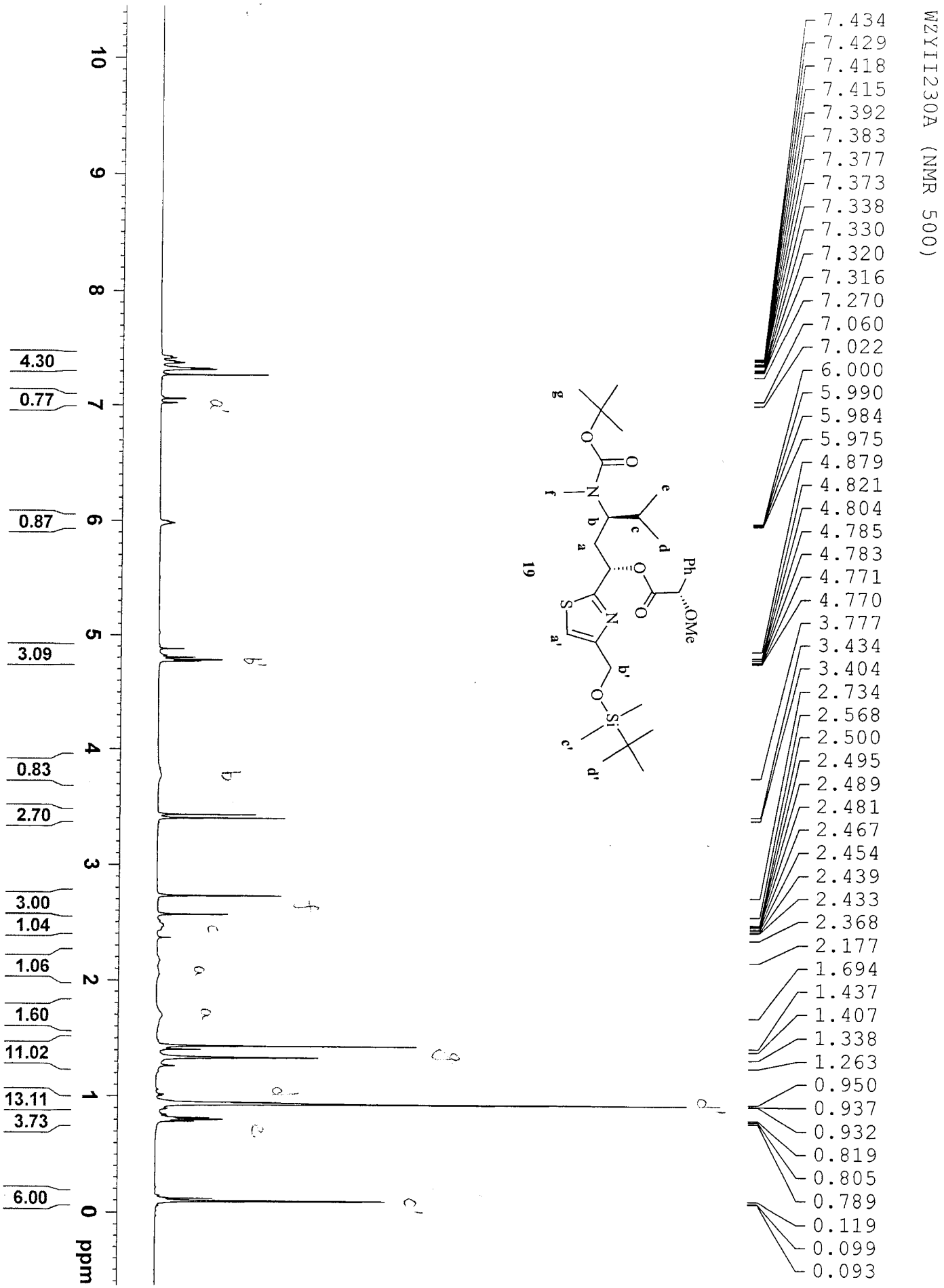

179.89
174.55
171.79
171.63
169.15
162.79
150.81
139.48
130.49
129.34
127.41
125.14
71.24
68.02
58.41
56.17
55.96
50.66
49.88
49.58
49.29
48.99
48.73
48.45
48.16
42.89
42.20
39.12
37.82
37.40
35.58
30.90
30.20
27.62
25.25
23.97
22.26
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
·TFA
OAc
COOH
1

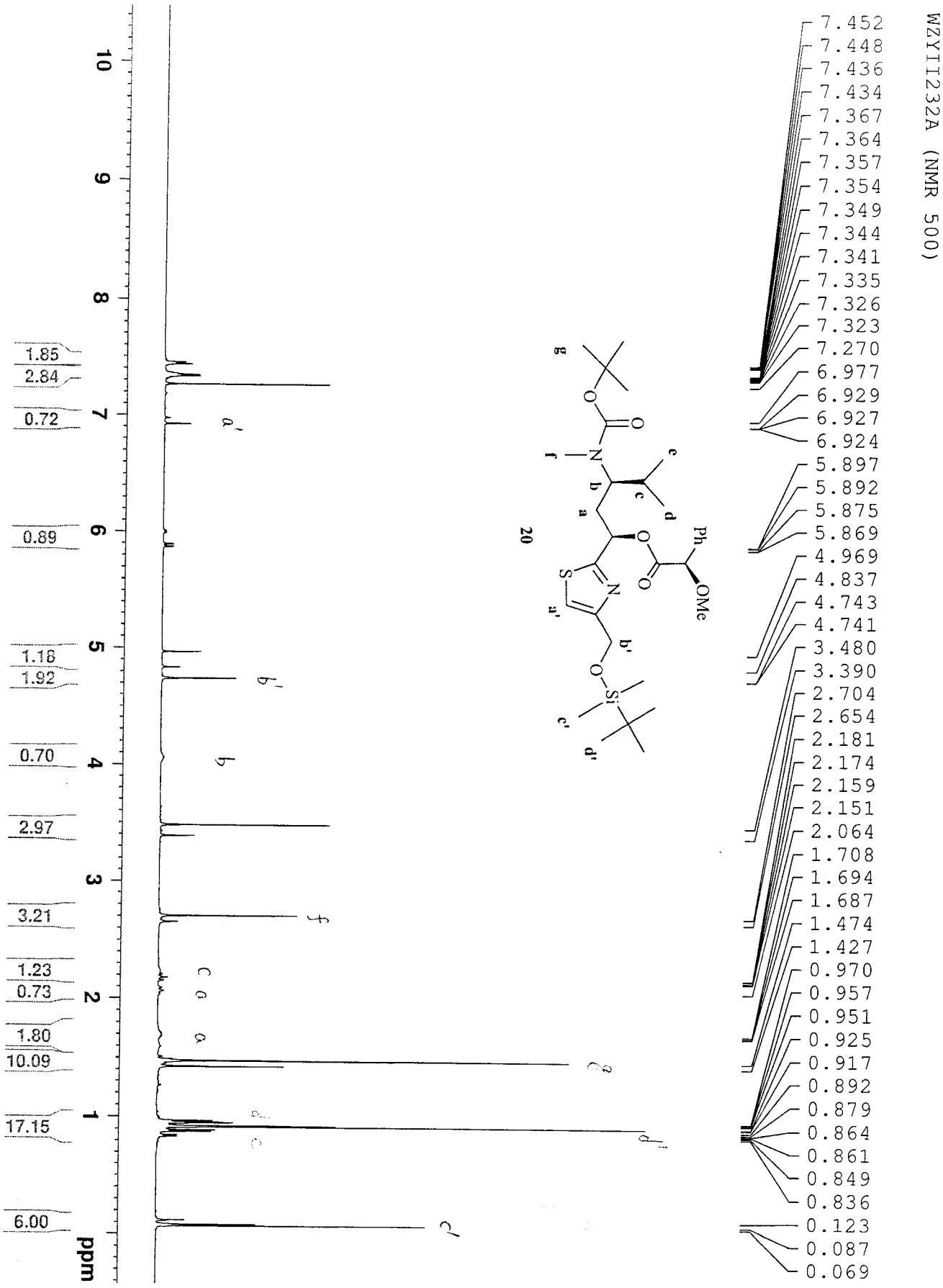

179.89
174.55
171.79
171.63
169.15
162.79
150.81
139.48
130.49
129.34
127.41
125.14
180
175
170
165
160
155
150
145
140
135
130
ppm
·TFA
OAc
COOH

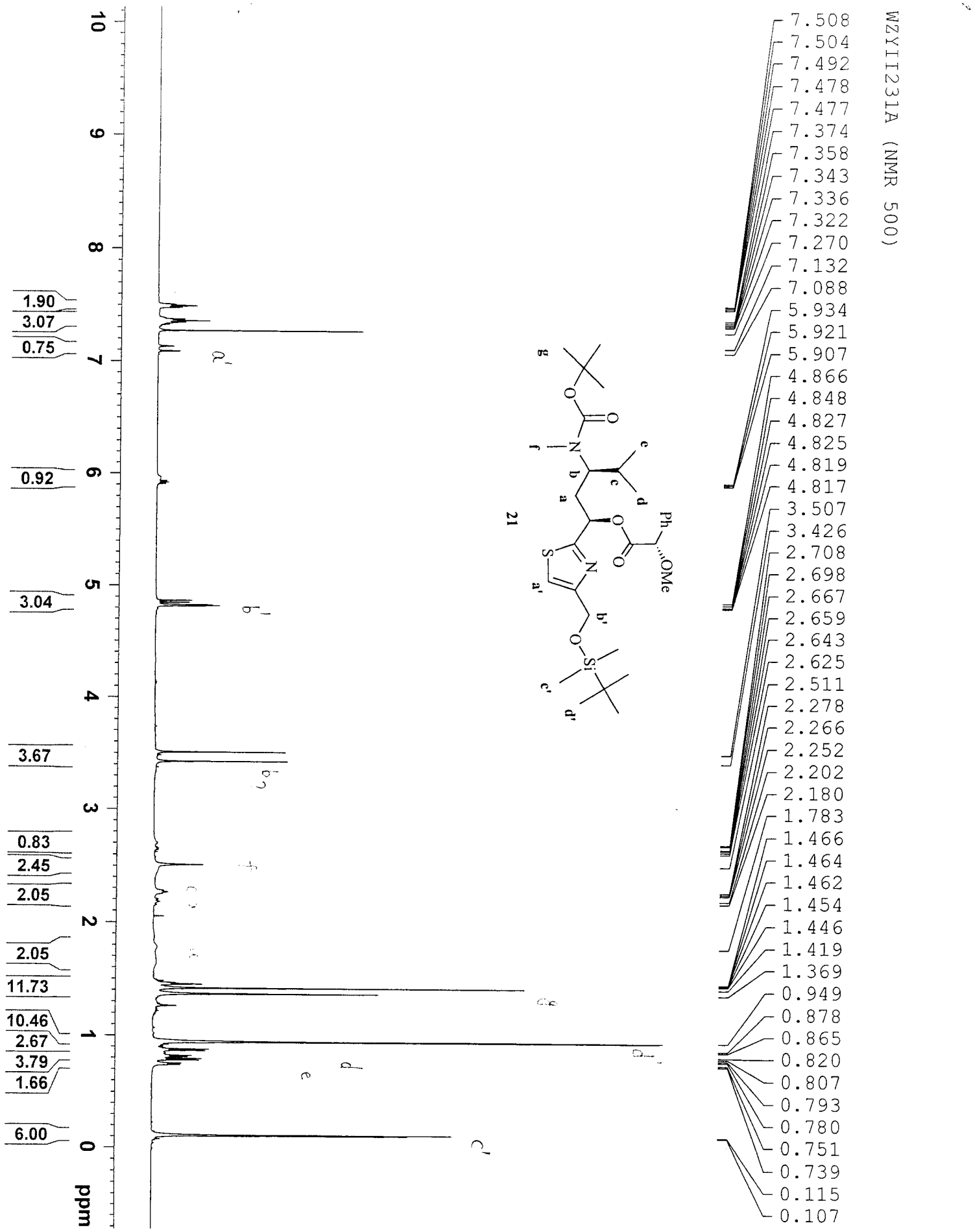
1


71.24
68.02
58.41
56.17
55.96
50.66
49.88
49.58
49.29
48.99
48.73
48.45
48.16
42.89
42.20
39.12
37.82
37.40
35.58
30.90
30.20
27.62
25.25
23.97
22.26
20.82
20.50
20.30
18.52
16.23
11.29
70
65
60
55
50
45
40
35
30
25
20
15
ppm
.TFA
OAc
COOH
1


WZYII227A (NMR 500)
7.484
7.481
7.468
7.440
7.437
7.425
7.379
7.372
7.368
7.356
7.352
7.349
7.340
7.339
7.269
7.207
7.161
5.964
5.956
5.946
5.937
5.927
4.848
4.840
4.806
4.766
3.398
3.387
2.617
2.521
2.438
2.418
2.401
2.393
2.382
2.372
2.366
2.354
1.942
1.916
1.595
1.412
1.267
0.955
0.950
0.861
0.848
0.805
0.791
0.753
0.740
0.731
0.717
0.125
0.121
4.85
0.95
0.99
3.16
0.77
3.01
3.13
1.18
0.96
2.40
10.85
9.97
2.35
1.48
3.31
6.00
ppm
18


WZYII230A (NMR 500)
7.434
7.429
7.418
7.415
7.392
7.383
7.377
7.373
7.338
7.330
7.320
7.316
7.270
7.060
7.022
6.000
5.990
5.984
5.975
4.879
4.821
4.804
4.785
4.783
4.771
4.770
3.777
3.434
3.404
2.734
2.568
2.500
2.495
2.489
2.481
2.467
2.454
2.439
2.433
2.368
2.177
1.694
1.437
1.407
1.338
1.263
0.950
0.937
0.932
0.819
0.805
0.789
0.119
0.099
0.093
4.30
0.77
0.87
3.09
0.83
2.70
3.00
1.04
1.06
1.60
11.02
13.11
3.73
6.00
ppm
19


WZYII232A (NMR 500)
7.452
7.448
7.436
7.434
7.367
7.364
7.357
7.354
7.349
7.344
7.341
7.335
7.326
7.323
7.270
6.977
6.929
6.927
6.924
5.897
5.892
5.875
5.869
4.969
4.837
4.743
4.741
3.480
3.390
2.704
2.654
2.181
2.174
2.159
2.151
2.064
1.708
1.694
1.687
1.474
1.427
0.970
0.957
0.951
0.925
0.917
0.892
0.879
0.864
0.861
0.849
0.836
0.123
0.087
0.069
20
Ph
OMe
1.85
2.84
0.72
0.89
1.18
1.92
0.70
2.97
3.21
1.23
0.73
1.80
10.09
17.15
6.00
ppm


WZYII231A (NMR 500)
7.508
7.504
7.492
7.478
7.477
7.374
7.358
7.343
7.336
7.322
7.270
7.132
7.088
5.934
5.921
5.907
4.866
4.848
4.827
4.825
4.819
4.817
3.507
3.426
2.708
2.698
2.667
2.659
2.643
2.625
2.511
2.278
2.266
2.252
2.202
2.180
1.783
1.466
1.464
1.462
1.454
1.446
1.419
1.369
0.949
0.878
0.865
0.820
0.807
0.793
0.780
0.751
0.739
0.115
0.107
1.90
3.07
0.75
0.92
3.04
3.67
0.83
2.45
2.05
2.05
11.73
10.46
2.67
3.79
1.66
6.00
ppm
21
OMe
Ph
OMe