

Successive Copper(I)-Catalyzed Cross-Couplings in One Pot: A Novel and Efficient Starting Point for Synthesis of Carbapenems

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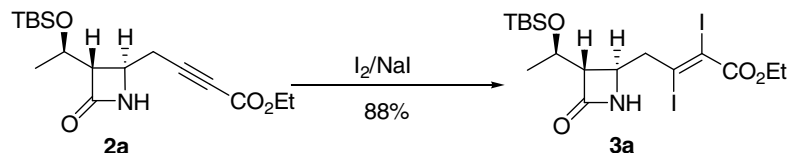
1. EXPERIMENTAL SECTION

1.1 General methods

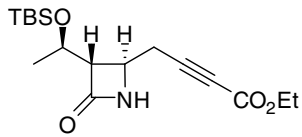
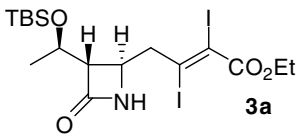
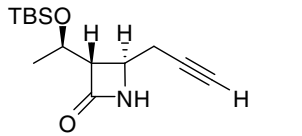
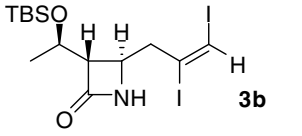
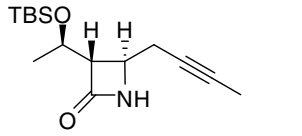
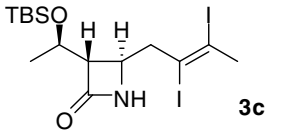
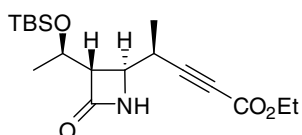
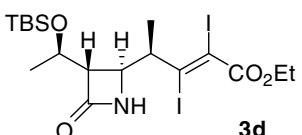
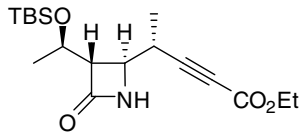
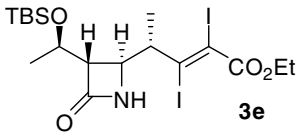
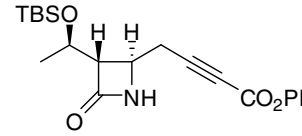
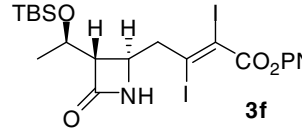
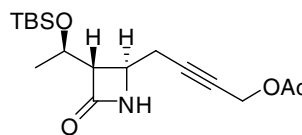
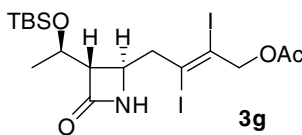
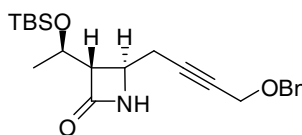
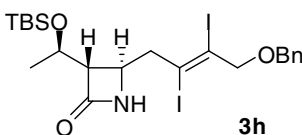
The solvents were dried and distilled by the standard methods. Unless otherwise indicated, all chemicals were used as provided by the supplier. CuI were purified according to *Purification of Laboratory Chemicals*, fifth edition, Butterworth–Heinemann, 2003. For thin-layer chromatography (TLC), Silica gel plates GF254 were used and compounds were visualized by irradiation with UV light, by treatment with aqueous solution of KMnO_4 and NaHCO_3 followed by heating. Column chromatography was carried out on silica gel H (10 ± 40 mm). ^1H NMR spectra were recorded on 300 MHz and ^{13}C NMR spectra were recorded on 75 MHz with TMS or solvent residue as the internal standard. IR spectra were recorded on a FT-IR spectrometer and only major peaks are reported. HRMS were recorded by using either FTMS-7 or IonSpec 4.7 spectrometers. Melting points were determined by microscope melting point instrument and are uncorrected. Optical rotations were measured on an Autopol III automatic polarimeter. Elemental analyses were performed by Element Analysis Lab of our institute.

1.2 General procedure for the synthesis of (*E*)-dihaloalkene 3 from 4-propargyl-2-azetidinone 2.

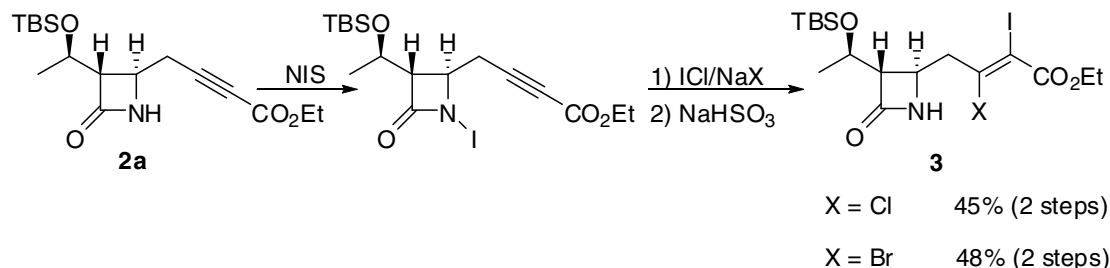
Representative procedure for the preparation of diiodoalkene (3a-3h):



A flask equipped with a magnetic stirring bar was charged with anhydrous sodium iodide (596 mg, 4.0 mmol) and iodine (369 mg, 1.5 mmol), then a solution of **2a** (450 mg, 1.3 mmol) in dry dichloromethane (8 mL) was added. After it was stirred for 24 h at 30 °C under dark, the mixture was allowed to pour into 10 mL of 10% Na_2SO_3 and extracted with ether (2 x 20 mL). The combined organic layers were washed with brine (15 mL), dried over sodium sulfate. Concentration under vacuum and purification by column chromatography gave the title compound 690 mg (88%) as a light yellow solid.

Entry	2	3	reat. time (h)	yield
1			24	88%
2			24	70%
3			24	78%
4			52	72%
5			48	81%
6			24	73%
7			26	90%
8			48	88%

3i and 3j were synthesized as the following method:

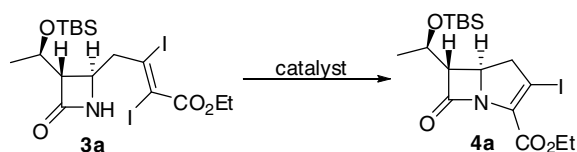


N-iodosuccinimide (210 mg, 0.93 mmol) was added to a solution of alkyne **2a** (300 mg, 0.88 mmol) in dry dichloromethane (6 mL) in a 25 mL flask equipped with a magnetic stirring bar and the mixture was stirred under argon at room temperature for 20 min. The product was purified directly by column chromatography on silica gel to give yellow solid in 95% yield (390 mg) with satisfied purity for the next step. 20% Product will be transformed back to the starting material after 24 h at r.t. (ESI or EI of **3** only show the peak of **2**), thus it should be used immediately. NMR data was shown as follows:

^1H NMR (300 MHz, CDCl_3) δ 4.28–4.16 (m, 3H), 3.93–3.88 (m, 1H), 3.39 (dd, $J = 2.1, 2.4$ Hz, 1H), 2.66 (dd, $J = 5.1, 15.4$ Hz, 1H), 2.55 (dd, $J = 6.9, 15.4$ Hz, 1H), 1.32 (t, $J = 6.9$ Hz, 3H), 1.19 (d, $J = 6.3$ Hz, 3H), 0.87 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 171.2, 153.1, 82.3, 75.7, 64.6, 64.3, 61.1, 55.8, 25.7, 22.7, 22.3, 17.7, 13.9, -4.3, -5.0.

A solution of above solid (280 mg, 0.6 mmol) in dry dichloromethane (6 mL) was added to dry NaCl (106 mg, 1.81 mmol) in 25 mL flask equipped with a magnetic stirring bar, then ICl (0.6 mL, 1 M in dichloromethane) was added and the whole mixture was stirred for 20 h at r.t.. It was washed with 10 mL of 10% Na_2SO_3 and extracted with ether (2 x 15 mL), the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 . Concentration under vacuum and purification by column chromatography gave 143 mg of the title compound (45% yield in two steps).

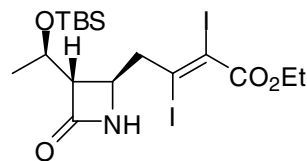
1.3 General procedure for the cyclization of compound 3.



A Schlenk tube (evacuated and back-filled with argon) was charged with **3a** (100 mg, 0.17 mmol), bpy (11 mg, 0.067 mmol), K_3PO_4 (73 mg, 0.34 mmol, purchased from Lancaster), CuI (6 mg, 0.034 mmol) and toluene (4.20 mL, 0.04 M for **3a**). The reaction mixture was stirred at 40°C for 15 min before the H_2O (3.00 μL , 0.168 mmol) was added to the red solution. After 21 h, the mixture was cooled to 0 °C, filtered over silica gel and washed with ethyl acetate (15 mL). After removal of solvent under vacuum, the residue was purified by flash chromatography on silica gel (hexane/EtOAc 8/1) to afford **4a** (74 mg, 94% yield).

1.6 Characterization data

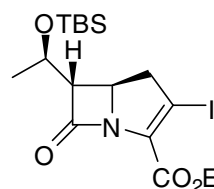
(*E*)-Ethyl 4-((2*R*,3*S*)-3-((*R*)-1-(tert-butyldimethylsilyloxy)ethyl)-4-oxoazetidin-2-yl)-2,3-diiodobut-2-enoate (**3a**)



m.p. 105-106 °C; $[\alpha]_D^{20}$ -10.8 (*c* 0.525, CHCl₃); IR (KBr): 3170, 3089, 2958, 2925, 2854, 1761, 1723, 1247 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.95 (brs, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 4.22 (dq, *J* = 2.1, 6.6 Hz, 1H), 4.14 (m, 1H), 3.11 (m, 2H), 3.01 (dd, *J* = 2.1, 4.2 Hz, 1H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.24 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 167.9, 166.0, 98.3, 86.5, 64.8, 63.8, 62.7, 52.4, 49.2, 25.7, 22.6, 17.8, 13.7, -4.4, -5.0; MS(ESI) *m/z*: 616 (M+Na⁺); Anal. Calcd for C₁₇H₂₉I₂NO₄Si: C, 34.41; H, 4.93; N, 2.36; Found: C, 34.60; H, 4.98; N, 2.14.

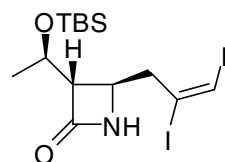
(5*R*,6*S*)-Ethyl

6-((*R*)-1-(tert-butyldimethylsilyloxy)ethyl)-3-iodo-7-oxo-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylate (**4a**)



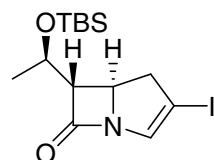
m.p. 107-110 °C; $[\alpha]_D^{20}$ +53.8 (*c* 0.670, CHCl₃); IR (KBr): 2977, 2929, 2887, 2856, 1770, 1714, 1579, 1308 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.29 (q, *J* = 4.2 Hz, 1H), 4.28 (q, *J* = 4.2 Hz, 1H), 4.25-4.15 (m, 2H), 4.21 (dd, *J* = 2.7, 5.7 Hz, 1H), 3.15 (d, *J* = 5.7 Hz, 1H), 3.11 (d, *J* = 4.8 Hz, 1H), 1.33 (t, *J* = 5.2 Hz, 3H), 1.22 (d, *J* = 6.3 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 171.7, 160.2, 134.8, 93.5, 67.6, 66.0, 61.7, 54.3, 48.8, 25.6, 22.4, 17.9, 14.0, -4.2, -5.1; HRMS(MALDI) *m/z* Calcd for C₁₇H₂₈INO₄Si (M+Na⁺) 488.0725, Found 488.0735; Anal. Calcd for C₁₇H₂₈INO₄Si: C, 43.87; H, 6.06; N, 3.01; Found: C, 43.83; H, 5.82; N, 2.95.

(3*S*,4*R*)-3-((*R*)-1-(tert-Butyldimethylsilyloxy)ethyl)-4-((*E*)-2,3-diiodoallyl)azetidin-2-one (**3b**)



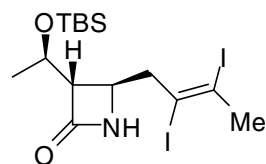
m.p. 109-110 °C; $[\alpha]_D^{20}$ -15.3 (*c* 0.580, CHCl₃); IR (KBr): 3148, 3048, 2954, 2927, 2856, 1761, 1347, 1252 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.03(s, 1H), 6.15 (brs, 1H), 4.20 (dq, *J* = 4.2, 6.3 Hz, 1H), 4.04 (dt, *J* = 1.8, 6.3 Hz, 1H), 3.01 (dd, *J* = 1.8, 6.0 Hz, 1H), 2.97-2.86 (m, 2H), 1.23 (d, *J* = 6.3 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 170.0, 97.1, 82.2, 65.0, 64.0, 49.5, 49.3, 25.7, 22.6, 17.8, -4.3, -5.0; MS(ESI) *m/z*: 522 (M+H⁺), 544 (M+Na⁺), 576 (M+MeOH+Na⁺); Anal. Calcd for C₁₄H₂₅I₂NO₂Si: C, 32.26; H, 4.83; N, 2.69; Found: C, 32.28; H, 4.89; N, 2.45;

(5*R*,6*S*)-6-((*R*)-1-(tert-Butyldimethylsilyloxy)ethyl)-3-iodo-1-aza-bicyclo[3.2.0]hept-2-en-7-one (**4b**)



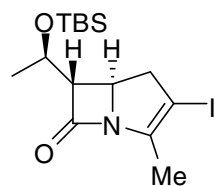
m.p. 45-46 °C; $[\alpha]_D^{20}$ -14.5 (*c* 0.83, CHCl₃); IR (KBr): 3087, 2955, 2929, 2855, 1760, 1253, 1146 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.36 (dd, *J* = 2.1, 3.0 Hz, 1H), 4.22-4.15 (m, 1H), 3.22 (dd, *J* = 3.0, 4.5 Hz, 1H), 2.88 (m, 2H), 1.20 (d, *J* = 6.6 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 176.6, 134.5, 80.2, 67.4, 65.3, 53.6, 44.5, 25.6, 22.3, 17.9, -4.3, -5.1; HRMS(MALDI) *m/z* Calcd for C₁₄H₂₅INO₂Si (M+H⁺) 394.0694, Found 394.0695.

(3*S*,4*R*)-3-((*R*)-1-(tert-Butyldimethylsilyloxy)ethyl)-4-((*E*)-2,3-diiodobut-2-enyl)azetidin-2-one (**3c**)



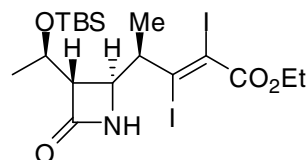
m.p. 135-136 °C; $[\alpha]_D^{20}$ -13.4 (c 0.425, CHCl₃); IR (KBr): 3167, 3082, 2964, 2926, 1760, 1088 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.28 (brs, 1H), 4.17 (dq, J = 6.0, 6.3 Hz, 1H), 4.10 (dt, J = 1.8, 5.7 Hz, 1H), 3.12-3.00 (m, 3H), 2.61 (s, 3H), 1.18 (d, J = 6.3 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 168.2, 96.4, 96.1, 64.9, 63.6, 54.7, 49.6, 40.6, 25.7, 22.6, 17.9, -4.3, -4.9; HRMS(MALDI) m/z Calcd for C₁₅H₂₇I₂NO₂Si (M+H⁺) 535.9973, Found 535.9976.

(5R,6S)-6-((R)-1-(tert-Butyldimethylsilyloxy)ethyl)-3-iodo-2-methyl-1-aza-bicyclo[3.2.0]hept-2-en-7-one (4c)



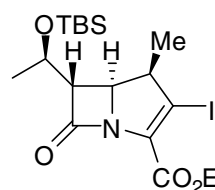
m.p. 81-82 °C; $[\alpha]_D^{20}$ +30.1 (c 0.570, CHCl₃); IR (KBr): 2954, 2930, 1757, 1251, 1137 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.17 (dq, J = 5.1, 6.3 Hz, 1H), 4.09 (dt, J = 3.0, 5.1 Hz, 1H), 2.94-2.88 (m, 2H), 2.03 (s, 3H), 1.19 (d, J = 6.3 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 177.0, 141.4, 75.7, 67.6, 65.5, 52.7, 45.4, 25.6, 22.3, 17.9, 16.1, -4.3, -5.1; MS(ESI) m/z : 536 (M+H⁺), 558 (M+Na⁺); HRMS(MALDI) m/z Calcd for C₁₅H₂₇INO₂Si (M+H⁺) 408.0850, Found 408.0870.

(R,E)-Ethyl 4-((2S,3S)-3-((R)-1-(tert-butyldimethylsilyloxy)ethyl)-4-oxoazetidin-2-yl)-2,3-diiodopent-2-enoate (3d)



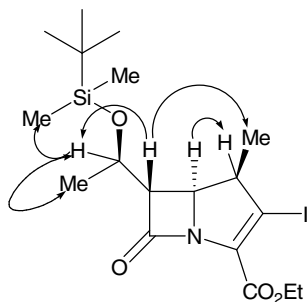
m.p. 155-156 °C; $[\alpha]_D^{20}$ +28.1 (c 0.320, CHCl₃); IR (KBr): 3158, 3087, 2959, 2924, 1761, 1723, 1247 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.94 (brs, 1H), 4.32 (q, J = 6.9 Hz, 2H), 4.25 (dq, J = 2.4, 6.3 Hz, 1H), 3.88 (dd, J = 2.4, 8.1 Hz, 1H), 3.06 (dd, J = 2.1, 2.4 Hz, 1H), 2.73 (dq, J = 8.1, 6.6 Hz, 1H), 1.36 (t, J = 6.9 Hz, 3H), 1.21 (d, J = 6.3 Hz, 3H), 1.15 (d, J = 6.6 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 169.0, 166.1, 109.3, 84.3, 64.1, 62.8, 62.6, 53.9, 50.2, 25.7, 22.7, 17.9, 17.6, 13.7, -4.5, -5.1; HRMS(MALDI) m/z Calcd for C₁₈H₃₁I₂NO₄Si (M+Na⁺) 630.0004, Found 630.0032.

(4R,5S,6S)-Ethyl 6-((R)-1-(tert-butyldimethylsilyloxy)ethyl)-3-iodo-4-methyl-7-oxo-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylate (4d)



m.p. 53-55 °C; $[\alpha]_D^{20}$ +27.8 (c 1.8, CHCl₃); IR (KBr): 2955, 2929, 2856, 1786, 1725, 1368, 1309 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.34-4.17 (m, 4H), 3.34 (dd, J = 3.6, 6.0 Hz, 1H), 3.18 (dq, J = 6.0, 7.2 Hz, 1H), 1.33 (t, J = 7.2 Hz, 3H), 1.22 (d, J = 6.6 Hz, 3H), 1.17 (d, J = 7.2 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 172.8, 160.2, 133.4, 101.9, 66.1, 61.7, 61.0, 56.3, 49.1, 25.6, 22.3, 17.9, 16.4, 14.0, -4.3, -5.1; HRMS(MALDI) m/z Calcd for C₁₈H₃₀INO₄Si (M+Na⁺) 502.0881, Found 502.0892.

NOESY of **4d**



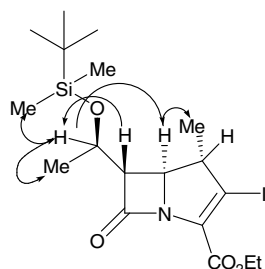
(*S,E*)-Ethyl 4-((2*S,3S*)-3-((*R*)-1-(tert-butyldimethylsilyloxy)ethyl)-4-oxoazetidin-2-yl)-2,3-diiodopent-2-enoate (3e)

m.p. 145-147 °C; $[\alpha]_D^{20}$ -22.7 (*c* 0.700 CHCl₃); IR (KBr): 3162, 3105, 2974, 2928, 1763, 1730, 1248 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.83 (brs, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 4.17 (dq, *J* = 6.0, 6.0 Hz, 1H), 3.74 (dd, *J* = 1.2, 6.3 Hz, 1H), 2.92 (d, *J* = 6.0 Hz, 1H), 2.55 (dq, *J* = 6.3, 6.9 Hz, 1H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.27 (d, *J* = 6.0 Hz, 3H), 1.08 (d, *J* = 7.2 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 167.3, 166.2, 109.7, 85.1, 65.7, 63.0, 62.8, 55.9, 51.9, 25.7, 22.9, 17.8, 17.2, 13.8, -4.4, -4.7; MS(ESI) *m/z*: 608 (M+H⁺), 630 (M+Na⁺); Anal. Calcd for C₁₈H₃₁I₂NO₄Si: C, 35.60; H, 5.14; N, 2.31; Found: C, 35.88; H, 5.09; N, 2.12.

(4*S,5S,6S*)-Ethyl 6-((*R*)-1-(tert-butyldimethylsilyloxy)ethyl)-3-iodo-4-methyl-7-oxo-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylate (4e)

IR (KBr): 2957, 2894, 2856, 1789, 1724, 1372, 1306, 1261 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.29 (q, *J* = 7.2 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 1H), 4.22 (dq, *J* = 6.9 Hz, 1H), 3.77 (dd, *J* = 3.0, 8.7 Hz, 1H), 3.21-3.16 (m, 2H), 3.18 (dq, *J* = 6.0, 7.2 Hz, 1H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.29 (d, *J* = 7.2 Hz, 3H), 1.24 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 174.2, 160.2, 134.1, 104.4, 67.2, 66.1, 61.7, 59.9, 51.9, 25.6, 22.6, 20.3, 17.9, 14.0, -4.3, -5.0; MS(ESI) *m/z*: 480 (M+H⁺), 502 (M+Na⁺), 512 (M+MeOH+H⁺); Anal. Calcd for C₁₈H₃₀INO₄Si: C, 45.09; H, 6.31; N, 2.92; Found: C, 45.07; H, 6.36; I, 26.47; N, 2.64.

NOESY of 4e

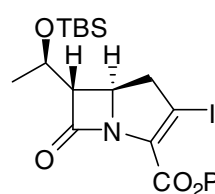


(*E*)-4-((2*R,3S*)-3-((*R*)-1-(tert-Butyldimethylsilyloxy)ethyl)-4-oxoazetidin-2-yl)-2,3-diiodobut-2-enoic 4-nitrobenzoic anhydride (3f)

m.p. 125-127 °C; $[\alpha]_D^{20}$ -6.8 (*c* 0.710, CHCl₃); IR (KBr): 3167, 3092, 2964, 2917, 1761, 1736, 1522, 1348, 1254 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.26 (d, *J* = 9.0 Hz, 2H), 7.61 (d, *J* = 9.0 Hz, 2H), 6.01 (brs,

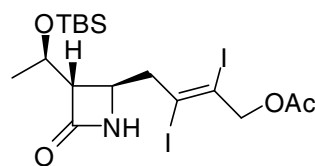
1H), 5.34 (s, 2H), 4.22 (dq, $J = 4.2, 6.2$ Hz, 1H), 4.14 (dt, $J = 2.1, 6.6$ Hz, 1H), 3.12 (d, $J = 6.6$ Hz, 2H), 3.05 (dd, $J = 2.1, 4.2$ Hz, 1H), 1.23 (d, $J = 6.6$ Hz, 3H), 0.88 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 167.8, 165.3, 147.7, 141.6, 128.7, 99.7, 85.2, 66.5, 64.7, 63.8, 52.5, 49.2, 25.6, 22.6, 17.8, -4.4, -5.0; MS(ESI) m/z : 723 ($\text{M}+\text{Na}^+$); Anal. Calcd for $\text{C}_{22}\text{H}_{30}\text{I}_2\text{N}_2\text{O}_6\text{Si}$: C, 37.73; H, 4.32; N, 4.00; Found: C, 37.96; H, 4.28; N, 3.82.

(5R,6S)-6-((R)-1-(tert-Butyldimethylsilyloxy)ethyl)-3-iodo-7-oxo-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylic 4-nitrobenzoic anhydride (4f)



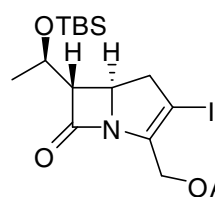
m.p. 123-125 °C; $[\alpha]_{\text{D}}^{20} +17.8$ (c 0.605, CHCl_3); IR (KBr): 2950, 2922, 2888, 2857, 1763, 1722, 1606, 1581, 1520 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.20 (d, $J = 5.4$ Hz, 2H), 7.65 (d, $J = 5.4$ Hz, 2H), 5.43 (d, $J = 14.4$ Hz, 1H), 5.27 (d, $J = 14.4$ Hz, 1H), 4.30-4.22 (m, 2H), 3.24 (dd, $J = 3.0, 4.8$ Hz, 1H), 3.20 (dd, $J = 9.9, 15.6$ Hz, 1H), 3.12 (dd, $J = 6.3, 15.6$ Hz, 1H), 1.23 (d, $J = 6.3$ Hz, 3H), 0.85 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 175.0, 159.6, 147.5, 142.5, 133.9, 128.1, 123.6, 95.6, 67.7, 65.6, 65.5, 53.9, 48.9, 25.6, 22.3, 17.8, -4.3, -5.2; HRMS(MALDI) m/z Calcd for $\text{C}_{22}\text{H}_{29}\text{IN}_2\text{O}_6\text{Si}$ ($\text{M}+\text{H}^+$) 573.0912, Found 573.0911.

(E)-4-((2R,3S)-3-((R)-1-(tert-Butyldimethylsilyloxy)ethyl)-4-oxoazetidin-2-yl)-2,3-diiodobut-2-enyl acetate (3g)



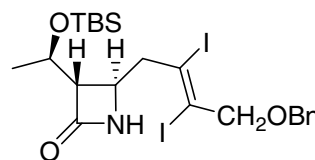
$[\alpha]_{\text{D}}^{20} -9.8$ (c 0.480, CHCl_3); IR (KBr): 3176, 3006, 2926, 2852, 1763, 1250, 1233 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 6.40 (brs, 1H), 4.90 (d, $J = 16.5$ Hz, 1H), 4.85 (d, $J = 16.5$ Hz, 1H), 4.16 (dq, $J = 4.5, 7.2$ Hz, 1H), 4.10 (dt, $J = 2.1, 6.6$ Hz, 1H), 3.14 (d, $J = 6.6$ Hz, 2H), 3.03 (dd, $J = 2.1, 4.5$ Hz, 1H), 2.10 (s, 3H), 1.19 (d, $J = 7.2$ Hz, 3H), 0.84 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 169.9, 168.0, 100.1, 97.2, 76.5, 64.8, 63.6, 54.5, 49.2, 25.7, 22.6, 20.8, 17.8, -4.4, -5.0; MS(ESI) m/z : 594 ($\text{M}+\text{H}^+$), 616 ($\text{M}+\text{Na}^+$), 626 ($\text{M}+\text{MeOH}+\text{H}^+$); Anal. Calcd for $\text{C}_{17}\text{H}_{29}\text{I}_2\text{NO}_4\text{Si}$: C, 34.41; H, 4.93; N, 2.36; Found: C, 34.64; H, 5.01; N, 2.20.

((5R,6S)-6-((R)-1-(tert-Butyldimethylsilyloxy)ethyl)-3-iodo-7-oxo-1-aza-bicyclo[3.2.0]hept-2-en-2-yl)methyl acetate (4g)



$[\alpha]_{\text{D}}^{20} +30.0$ (c 0.45, CHCl_3); IR (KBr): 2954, 2927, 2855, 1781, 1257, 1229 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 4.88 (d, $J = 13.5$ Hz, 1H), 4.75 (d, $J = 13.5$ Hz, 1H), 4.21-4.16 (m, 2H), 3.18 (dd, $J = 2.0, 4.5$ Hz, 1H), 3.02 (dd, $J = 9.6, 16.8$ Hz, 1H), 2.94 (dd, $J = 9.0, 16.8$ Hz, 1H), 2.09 (s, 3H), 1.20 (d, $J = 6.3$ Hz, 3H), 0.86 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 175.9, 170.5, 139.4, 81.5, 67.6, 65.6, 60.0, 53.3, 45.8, 25.6, 22.3, 20.7, 17.9, -4.3, -5.1; MS(ESI) m/z : 466 ($\text{M}+\text{H}^+$), 488 ($\text{M}+\text{Na}^+$), 498 ($\text{M}+\text{MeOH}+\text{H}^+$), 520 ($\text{M}+\text{MeOH}+\text{Na}^+$); Anal. Calcd for $\text{C}_{17}\text{H}_{28}\text{INO}_4\text{Si}$: C, 43.87; H, 6.06; N, 3.01; Found: C, 44.04; H, 6.26; N, 2.72.

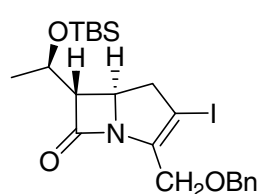
(3S,4R)-4-((E)-4-(Benzyloxy)-2,3-diiodobut-2-enyl)-3-((R)-1-(tert-butyldimethylsilyloxy)ethyl)azetidin-2-one (3h)



$[\alpha]_{\text{D}}^{20} +69.4$ (c 0.650, CHCl_3); IR (KBr): 3176, 3111, 2951, 2931, 1757, 1717, 1101 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.45-7.30 (m, 5H), 5.96 (brs, 1H), 4.53 (s, 2H), 4.41 (d, $J = 13.0$ Hz, 1H), 4.36 (d, $J = 13.0$ Hz,

1H), 4.21 (dq, $J = 4.2, 6.0$ Hz, 1H), 4.18-11 (m, 1H), 3.29-3.15 (m, 2H), 3.06 (dd, $J = 4.2, 2.1$ Hz, 1H), 1.19 (d, $J = 6.0$ Hz, 3H), 0.88 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 168.1, 137.3, 128.3, 128.0, 127.8, 102.3, 98.2, 82.0, 71.8, 64.9, 63.6, 54.6, 49.3, 25.7, 22.6, 17.8, -4.3, -5.0; MS(ESI) m/z : 664 ($\text{M}+\text{Na}^+$); Anal. Calcd for $\text{C}_{22}\text{H}_{33}\text{I}_2\text{NO}_3\text{Si}$: C, 41.20; H, 5.19; N, 2.18; Found: C, 41.26; H, 5.14; N, 2.03.

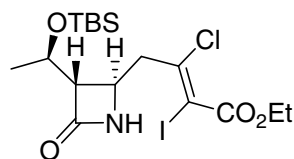
(5R,6S)-2-(Benzyloxymethyl)-6-((R)-1-(tert-butyldimethylsilyloxy)ethyl)-3-iodo-1-aza-bicyclo[3.2.0]hept-2-en-7-one (4h)



m.p. 56-58 °C; $[\alpha]_{\text{D}}^{20} +2.0$ (c 0.485, CHCl_3); IR (KBr): 3059, 3022, 2954, 2928, 2856, 1777, 1256, 1130 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.37-7.23 (m, 5H), 4.62 (d, $J = 12.3$ Hz, 1H), 4.56 (d, $J = 12.3$ Hz, 1H), 4.31 (s, 2H), 4.26-4.12 (m, 2H), 3.17 (dd, $J = 2.7, 5.4$ Hz, 1H), 3.04-2.86 (m, 2H), 1.23 (d, $J = 6.3$ Hz, 3H), 0.87 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.3, 141.4, 137.8, 128.3, 127.9, 127.6, 80.5, 72.8, 67.7, 65.8, 65.7, 53.3, 45.8, 25.6, 22.4, 17.9, -4.3, -5.1; HRMS(MALDI) m/z Calcd for $\text{C}_{22}\text{H}_{33}\text{NO}_3\text{ISi}$ ($\text{M}+\text{H}^+$) 514.1269, Found 514.1267.

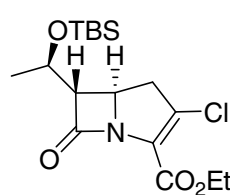
(E)-Ethyl

4-((2R,3S)-3-((R)-1-(tert-butyldimethylsilyloxy)ethyl)-4-oxoazetidin-2-yl)-3-chloro-2-iodobut-2-enoate (3i)



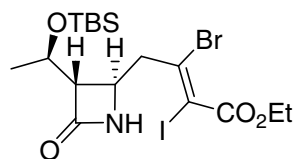
m.p. 93-95 °C; $[\alpha]_{\text{D}}^{20} -2.2$ (c 0.380, CHCl_3); IR (KBr): 3159, 3080, 2958, 2928, 2855, 1762, 1722, 1253, 1091 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 6.24 (brs, 1H), 4.28 (q, $J = 6.9$ Hz, 2H), 4.22-4.19 (m, 1H), 4.08-4.02 (m, 1H), 3.10-2.98 (m, 3H), 1.31 (t, $J = 6.9$ Hz, 3H), 1.20 (d, $J = 6.3$ Hz, 3H), 0.86 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 167.8, 164.6, 134.2, 82.9, 64.9, 64.2, 62.7, 48.3, 46.3, 25.7, 22.4, 17.9, 13.8, -4.3, -5.0; MS(ESI) m/z : 524.1 ($\text{M}+\text{Na}^+$); Anal. Calcd for $\text{C}_{17}\text{H}_{29}\text{ClINO}_4\text{Si}$: C, 40.69; H, 5.82; N, 2.79; Found: C, 40.65; H, 5.95; N, 2.52.

(5R,6S)-Ethyl 6-((R)-1-(tert-butyldimethylsilyloxy)ethyl)-3-chloro-7-oxo-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylate (4i)



m.p. 54-55 °C; $[\alpha]_{\text{D}}^{20} +69.4$ (c 0.650, CHCl_3); IR (KBr): 2956, 2930, 2857, 1790, 1725, 1275, 1207, 1130 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 4.28 (q, $J = 7.2$ Hz, 2H), 4.23-4.14 (m, 2H), 3.18 (dd, $J = 2.7, 3.0$ Hz, 1H), 3.12-2.96 (m, 2H), 1.34 (t, $J = 6.6$ Hz, 3H), 1.22 (d, $J = 6.3$ Hz, 3H), 0.86 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.0, 159.6, 135.1, 128.6, 67.7, 65.9, 61.5, 51.7, 42.6, 25.7, 25.6, 22.4, 17.9, 14.0, -4.3, -5.1; HRMS(MALDI) m/z Calcd for $\text{C}_{13}\text{H}_{19}\text{NO}_4\text{ClSi}$ ($\text{M}-\text{tBu}^+$) 316.0772, Found 316.0764.

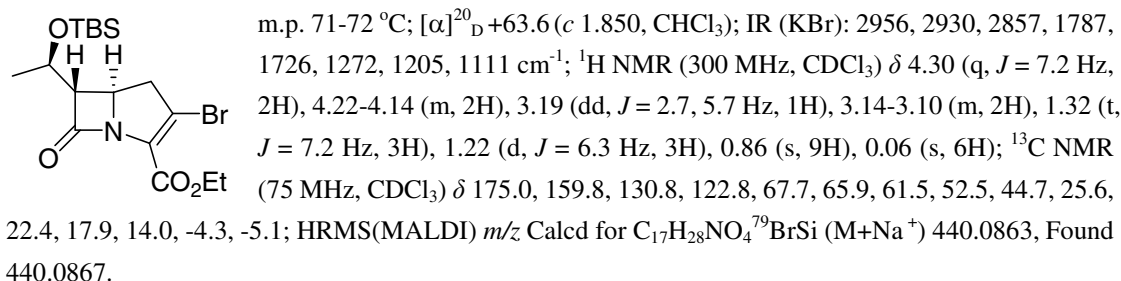
(E)-Ethyl 3-bromo-4-((2R,3S)-3-((R)-1-(tert-butyldimethylsilyloxy)ethyl)-4-oxoazetidin-2-yl)-2-iodobut-2-enoate (3j)



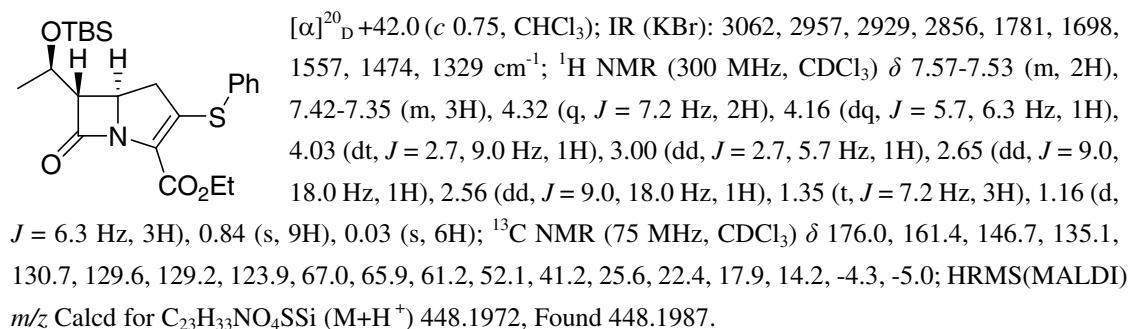
m.p. 96-97 °C; $[\alpha]_{\text{D}}^{20} -5.1$ (c 0.530, CHCl_3); IR (KBr): 3156, 3096, 2958, 2926, 1762, 1723, 1251 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 6.26, 4.28 (q, $J = 7.2$ Hz, 2H), 4.24-4.18 (m, 1H), 4.16-4.05 (m, 1H), 3.14-3.05 (m, 2H), 3.02-2.98 (m, 1H), 1.32 (t, $J = 6.9$ Hz, 3H), 1.20 (d, $J = 6.0$ Hz, 3H), 0.85 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 167.8, 165.2, 122.7, 83.5, 64.8, 64.1, 62.7, 48.7, 48.2,

25.7, 22.4, 17.9, 13.8, -4.3, -5.0; Anal. Calcd for C₁₇H₂₉BrINO₄Si: C, 37.37; H, 5.35; N, 2.56; Found: C, 37.48; H, 5.44; N, 2.33.

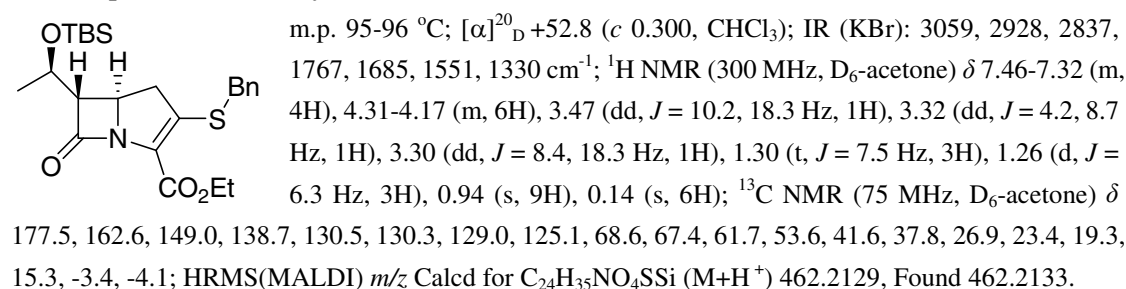
(5R,6S)-Ethyl 3-bromo-6-((R)-1-(tert-butyldimethylsilyloxy)ethyl)-7-oxo-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylate (4j)



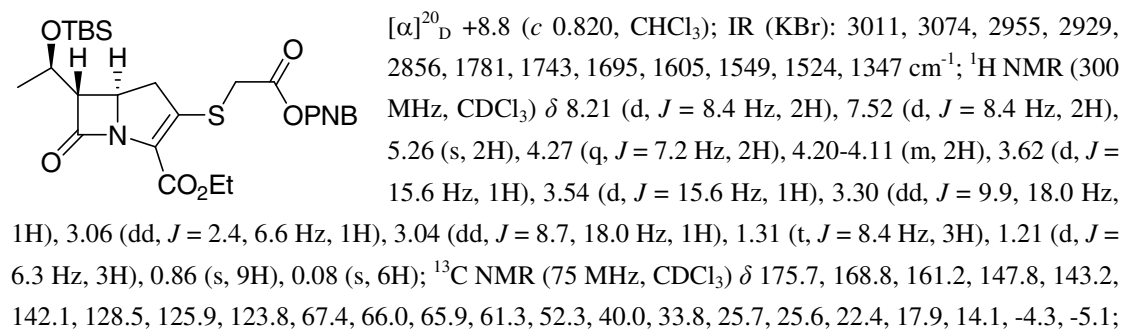
(5R,6S)-Ethyl 6-((R)-1-(tert-butyldimethylsilyloxy)ethyl)-7-oxo-3-(phenylthio)-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylate (5a)



(5R,6S)-Ethyl 3-(benzylthio)-6-((R)-1-(tert-butyldimethylsilyloxy)ethyl)-7-oxo-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylate (5c)

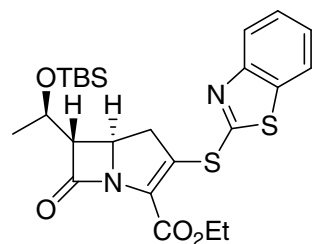


(5R,6S)-Ethyl 6-((R)-1-(tert-butyldimethylsilyloxy)ethyl)-3-(2-(4-nitrobenzyloxy)-2-oxoethylthio)-7-oxo-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylate (5d)



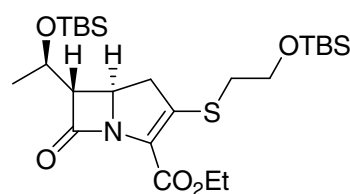
HRMS(ESI) m/z Calcd for $C_{26}H_{36}N_2O_8SSi$ ($M+H^+$) 587.1854, Found 587.1850.

(5*R*,6*S*)-Ethyl 3-(benzo[d]thiazol-2-ylthio)-6-((*R*)-1-(tert-butyldimethylsilyloxy)ethyl)-7-oxo-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylate (5b)



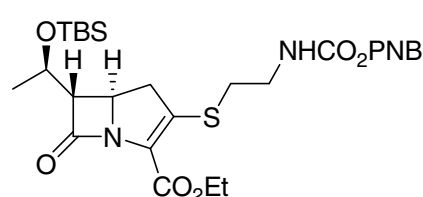
$[\alpha]_D^{20} +6.3$ (c 1.450, $CHCl_3$); IR (KBr): 3052, 2955, 2929, 2856, 1786, 1725, 1699, 1568, 1456 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.51 (dd, J = 7.2, 7.8 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 4.32 (q, J = 6.9 Hz, 2H), 4.25-4.18 (m, 2H), 3.27 (dd, J = 9.9, 18.3 Hz, 1H), 3.13 (dd, J = 2.4, 5.1 Hz, 1H), 3.04 (dd, J = 9.0, 18.3 Hz, 1H), 1.35 (t, J = 6.9 Hz, 3H), 1.18 (d, J = 6.0 Hz, 3H), 0.85 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 160.8, 159.5, 153.2, 138.8, 136.9, 128.2, 126.7, 125.9, 123.2, 121.3, 67.5, 65.6, 61.6, 52.3, 40.7, 25.6, 22.3, 17.9, 14.1, -4.3, -5.1; HRMS(MALDI) m/z Calcd for $C_{24}H_{32}N_2O_4S_2Si$ ($M+H^+$) 505.1646, Found 505.1631.

(5*R*,6*S*)-Ethyl 6-((*R*)-1-(tert-butyldimethylsilyloxy)ethyl)-3-(2-(tert-butyldimethylsilyloxy)ethylthio)-7-oxo-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylate (5e)

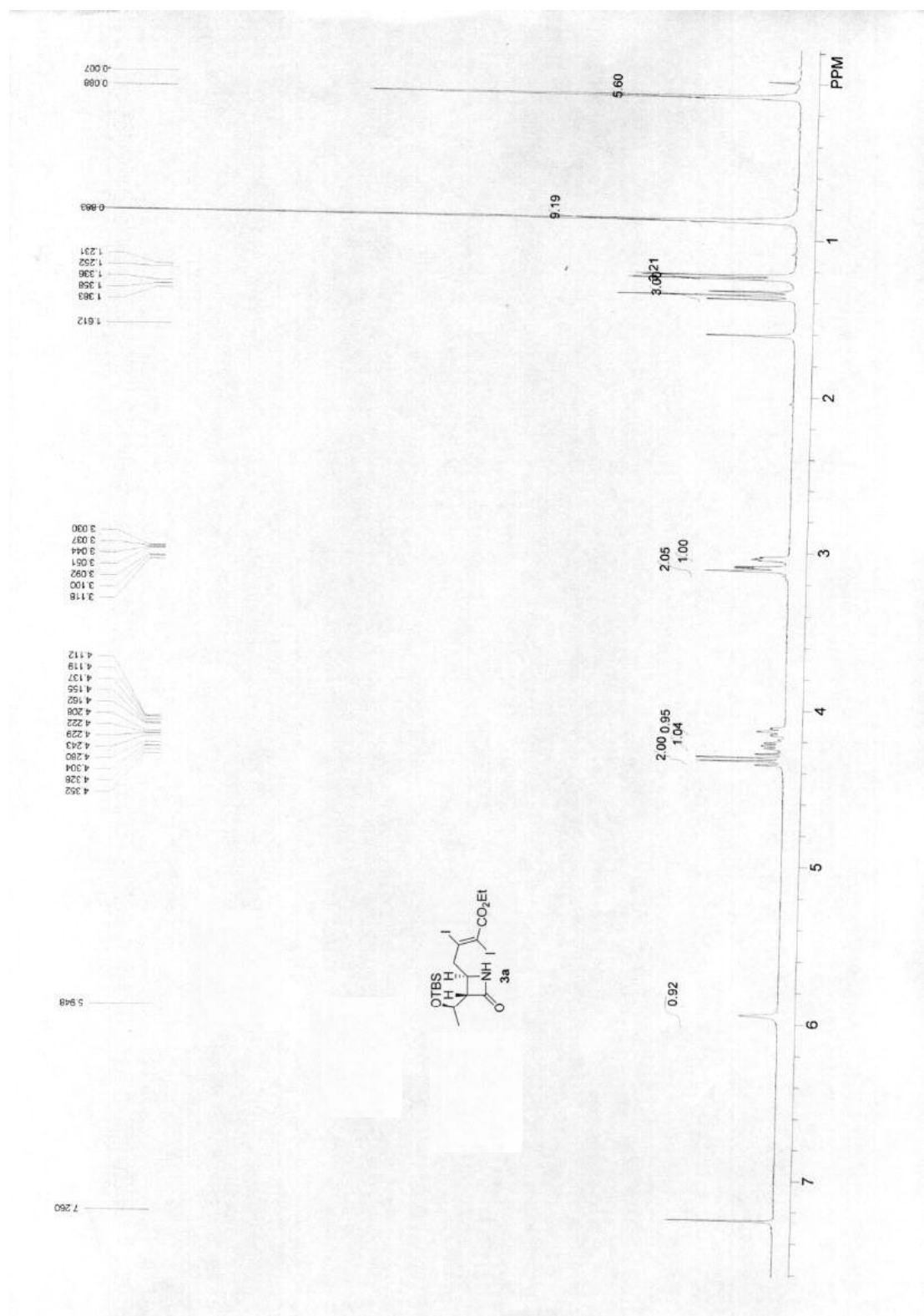


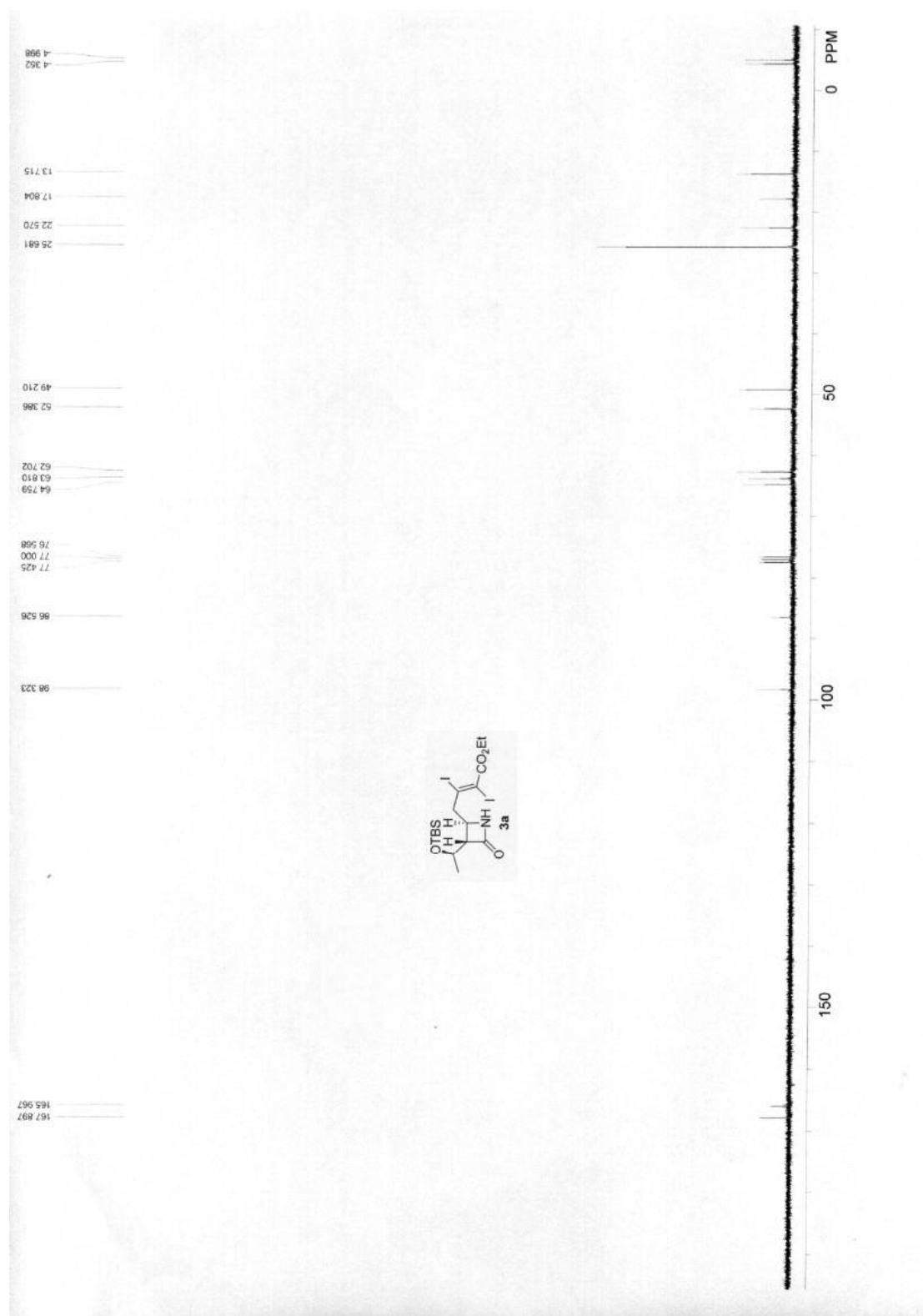
m.p. 81-82 °C; $[\alpha]_D^{20} +72.9$ (c 2.450, $CHCl_3$); IR (KBr): 2955, 2886, 2857, 1782, 1704, 1471 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 4.28 (q, J = 7.5 Hz, 2H), 4.18 (dq, J = 6.3, 6.3 Hz, 1H), 4.12 (dt, J = 2.4, 9.3 Hz, 1H), 3.81 (m, 2H), 3.28 (dd, J = 9.9, 15.7 Hz, 1H), 3.08 (dd, J = 2.7, 6.9 Hz, 1H), 4.05-2.85 (m, 3H), 1.32 (t, J = 7.5 Hz, 3H), 1.25 (d, J = 6.3 Hz, 3H), 0.88 (s, 18H), 0.09 (s, 6H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 161.4, 146.7, 124.3, 67.2, 66.5, 63.1, 61.0, 52.6, 40.5, 34.5, 25.8, 25.7, 22.5, 18.3, 17.9, 14.2, -4.2, -5.0, -5.4; MS(ESI) m/z : 552 ($M+Na^+$); Anal. Calcd for $C_{25}H_{47}NO_5SSi_2$: C, 56.67; H, 8.94; N, 2.64; Found: C, 56.74; H, 9.09; N, 2.57.

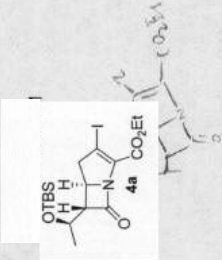
(5*R*,6*S*)-Ethyl 6-((*R*)-1-(tert-butyldimethylsilyloxy)ethyl)-3-(2-((4-nitrobenzyloxy)carbonylamino)ethylthio)-7-oxo-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylate (5f)

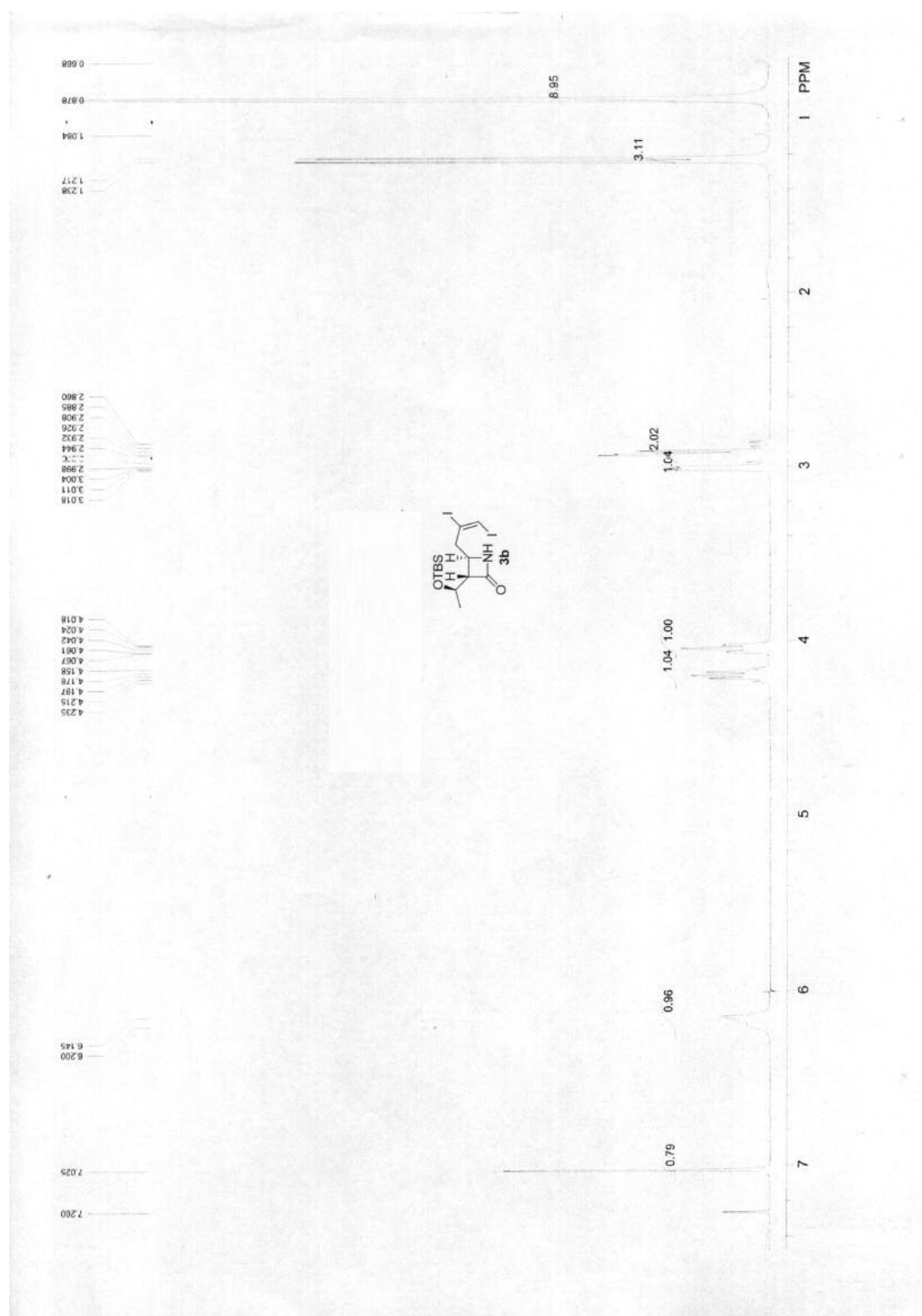


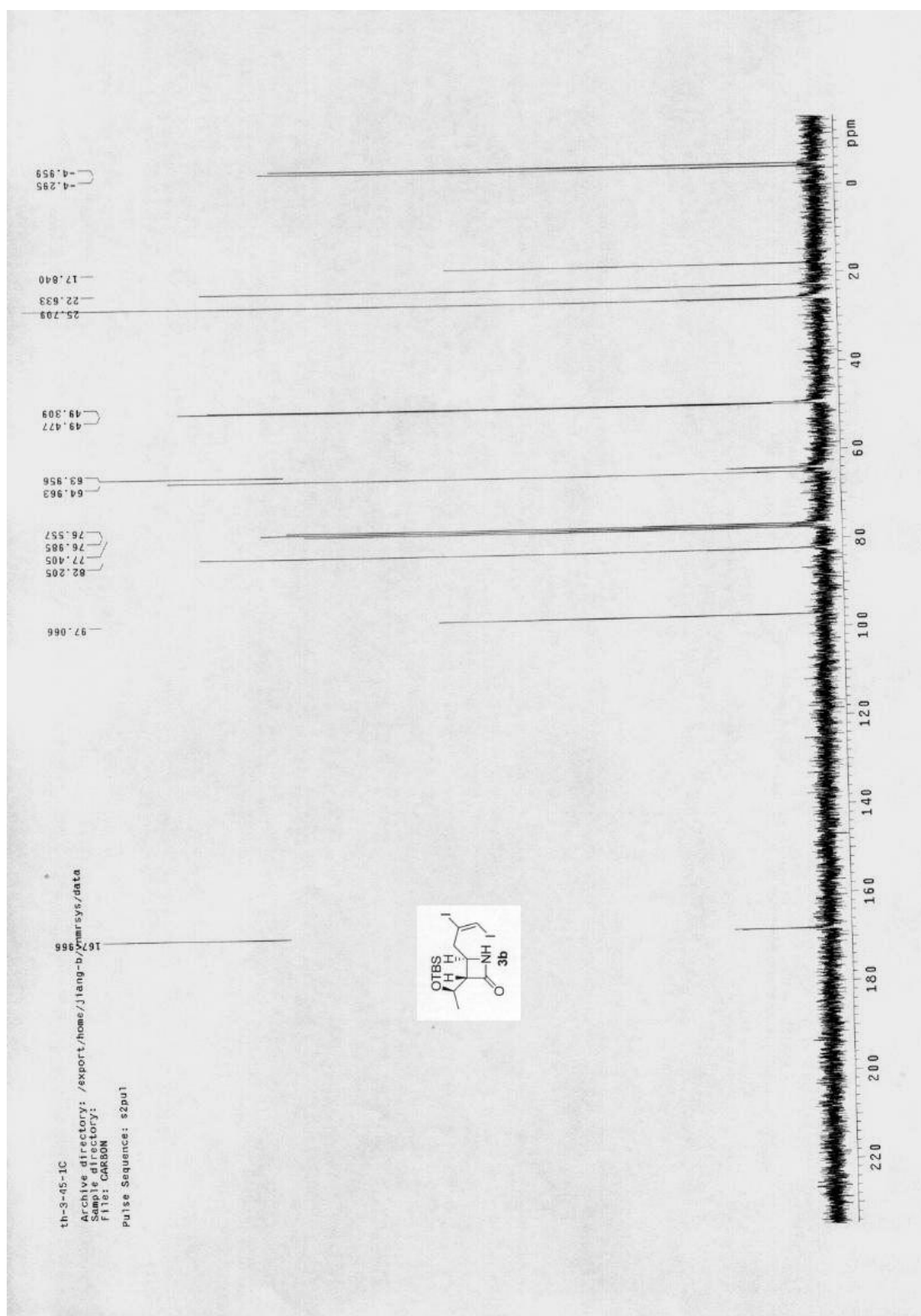
$[\alpha]_D^{20} +44.9$ (c 0.500, $CHCl_3$); IR (KBr): 3367, 3073, 2955, 2930, 2856, 1779, 1724, 1522, 1347 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 8.7 Hz, 2H), 5.41 (t, J = 6.0 Hz, 1H), 5.28 (s, 2H), 4.25 (q, J = 7.5 Hz, 2H), 4.20-4.12 (m, 2H), 3.41 (dt, J = 6.0, 6.9 Hz, 2H), 3.25 (dd, J = 9.6, 17.7 Hz, 1H), 3.09 (dd, J = 2.1, 6.0 Hz, 1H), 3.04-2.89 (m, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.22 (d, J = 6.3 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 161.4, 155.8, 147.6, 144.9, 143.7, 128.0, 125.4, 123.7, 67.3, 66.0, 65.3, 61.1, 52.4, 41.1, 40.0, 32.0, 25.6, 22.4, 17.9, 14.1, -4.3, -5.1; HRMS(MALDI) m/z Calcd for $C_{27}H_{39}N_3O_8SSi$ ($M+Na^+$) 616.2119, Found 616.2102.

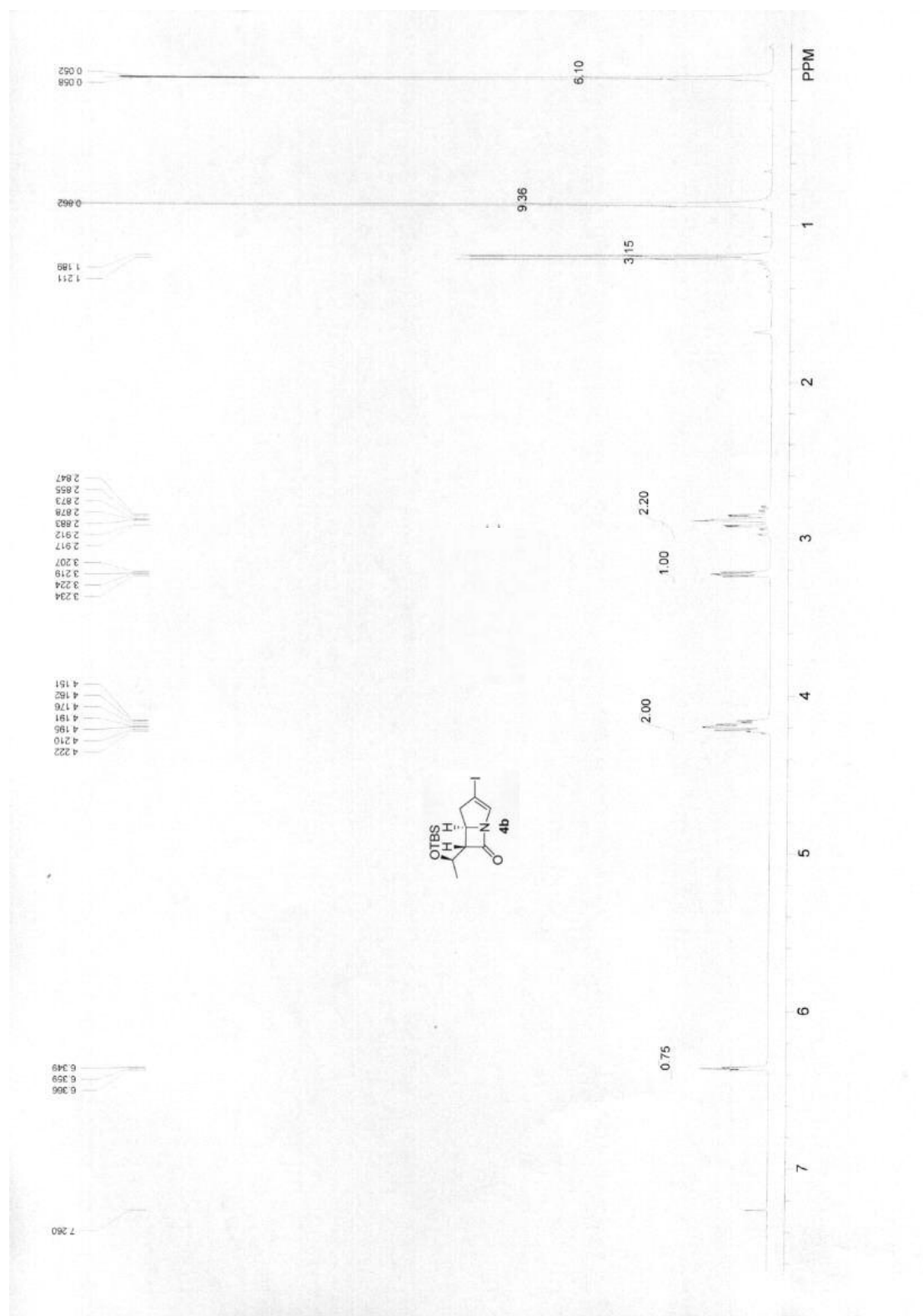


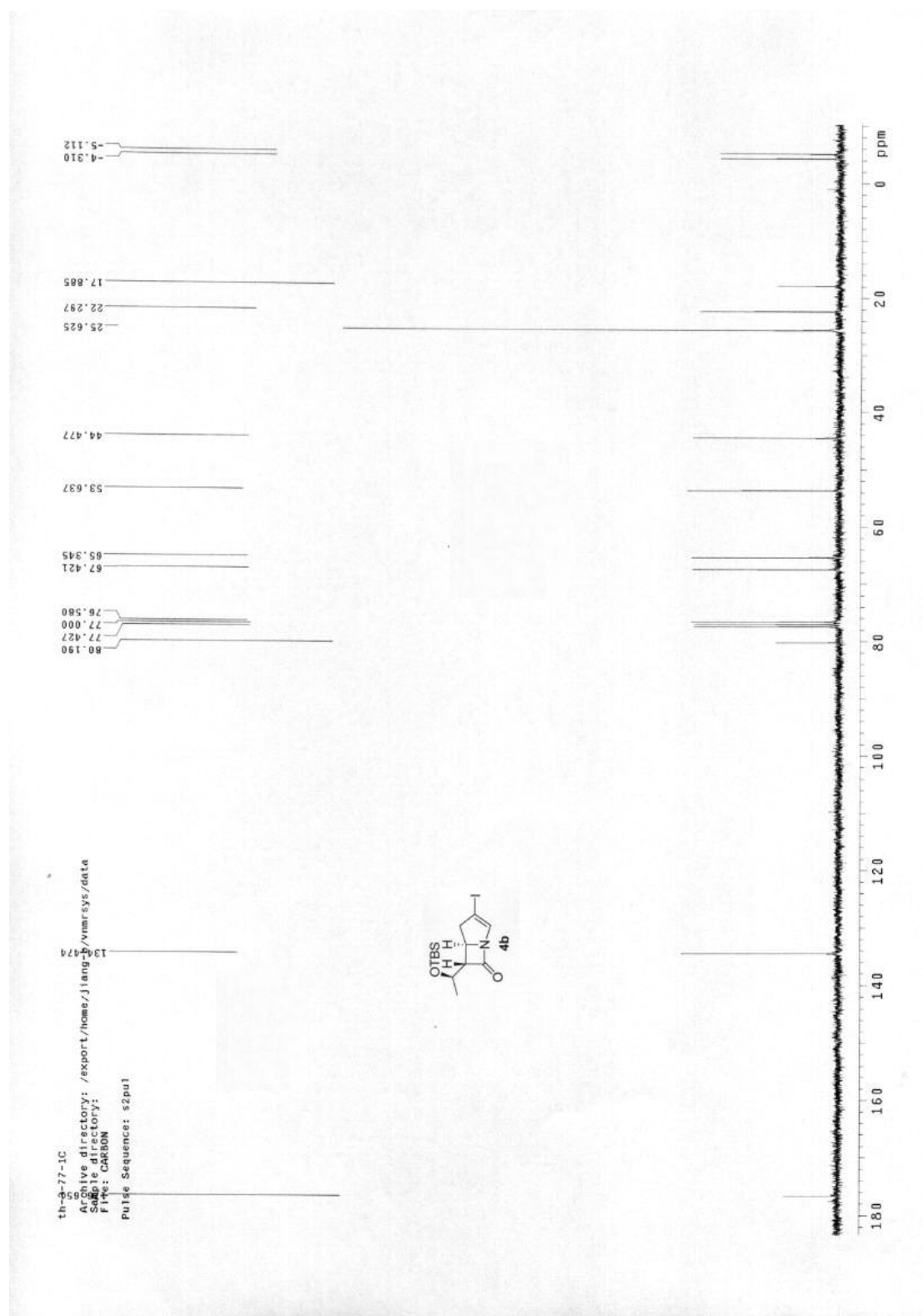




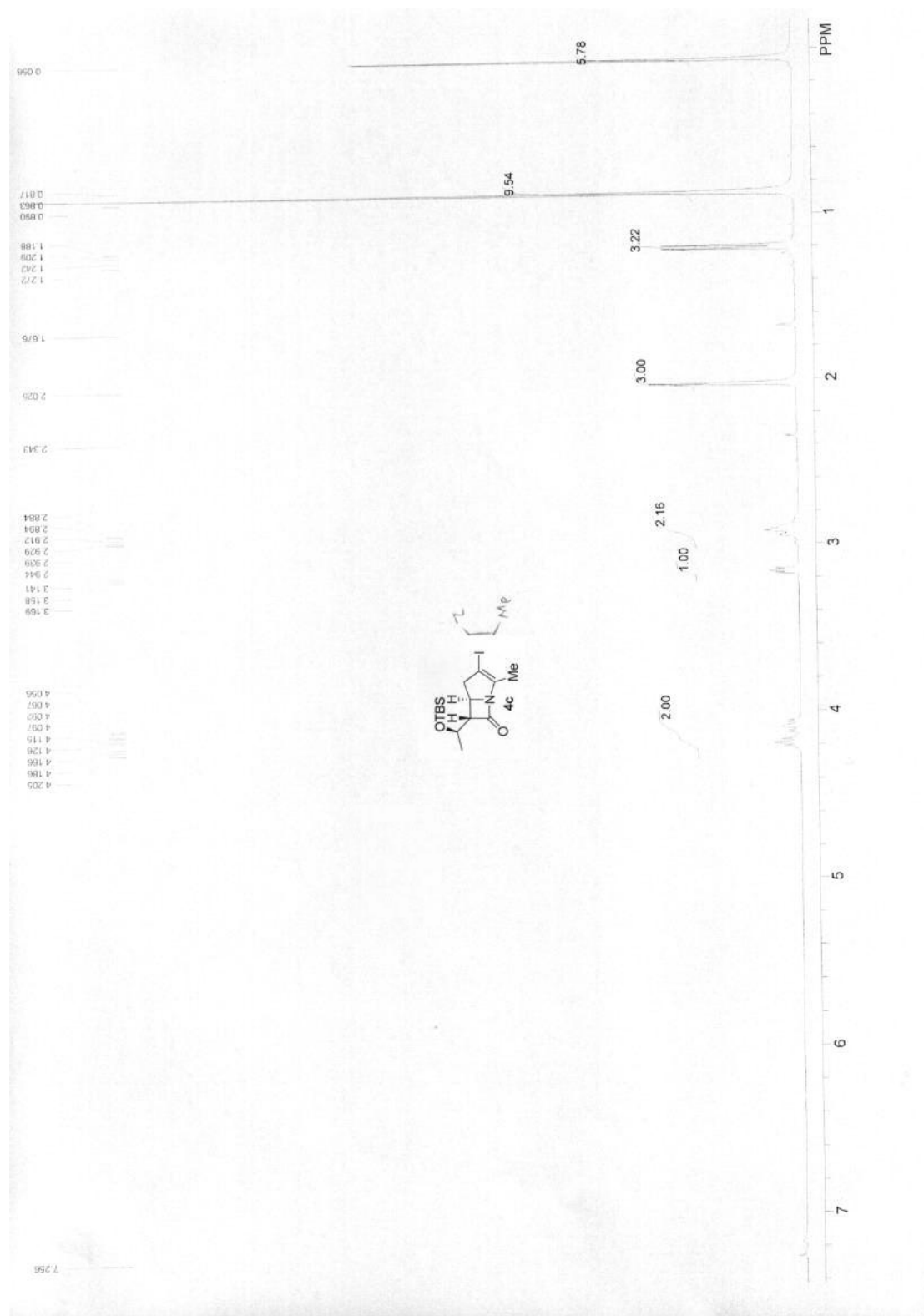


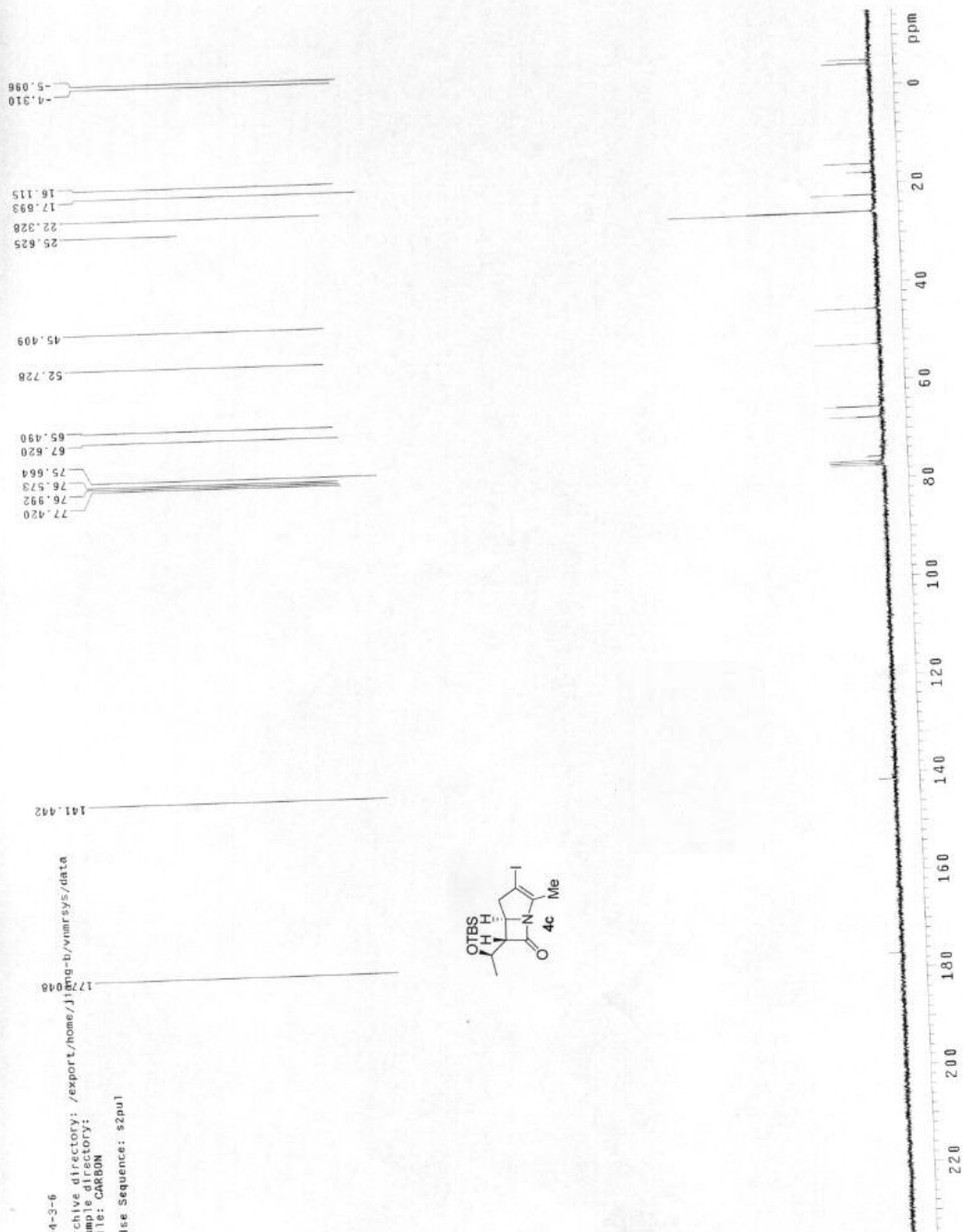


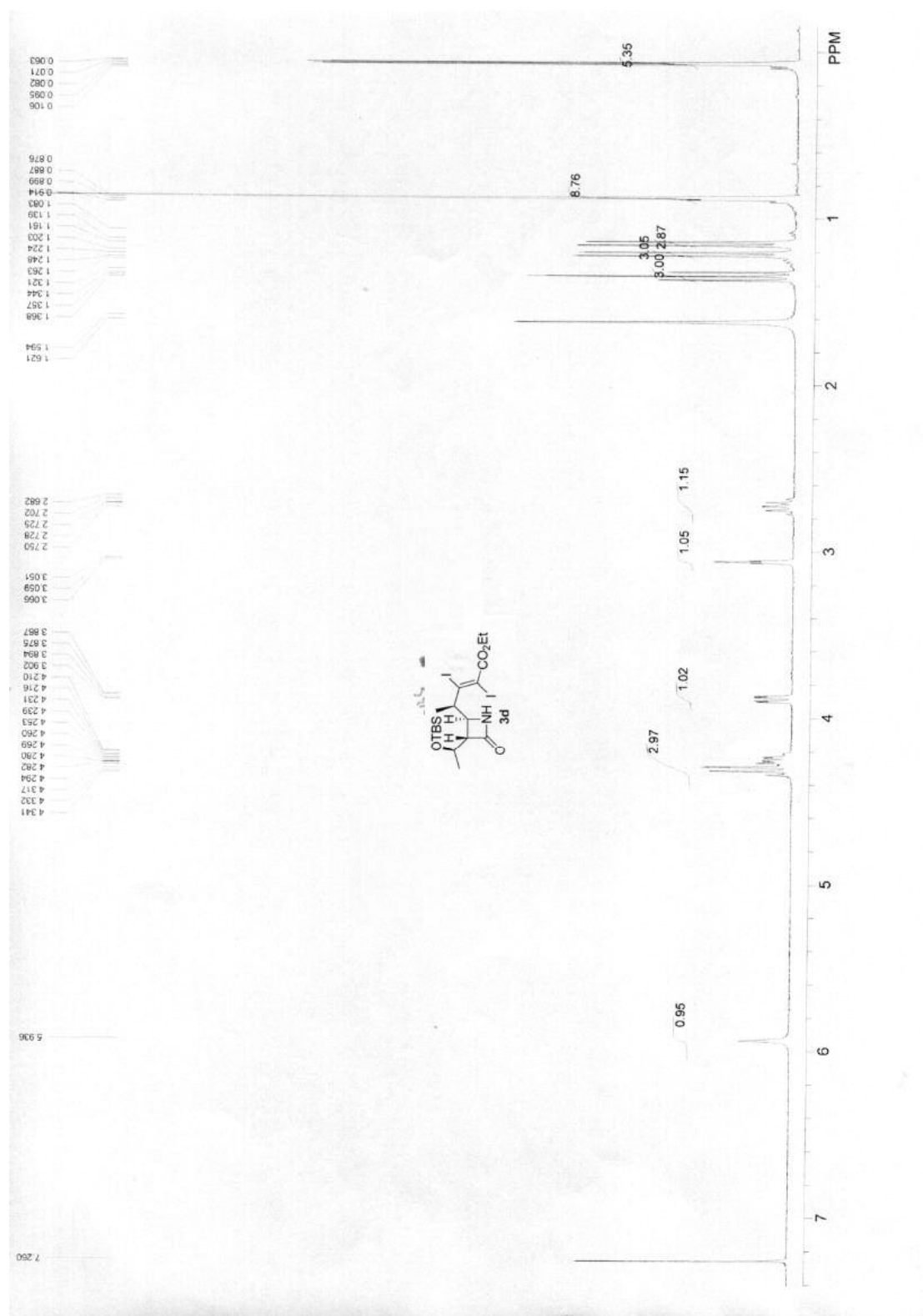


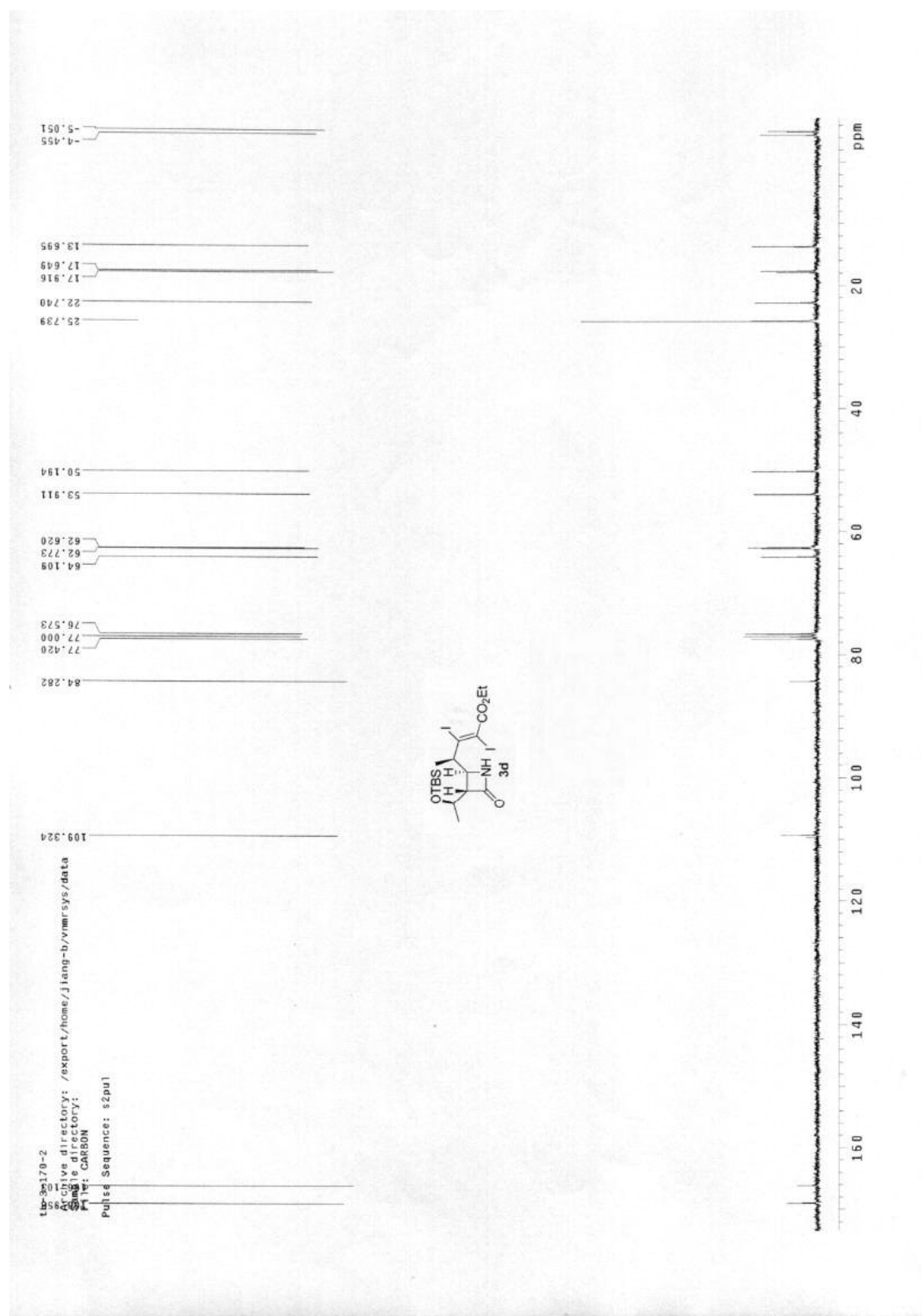




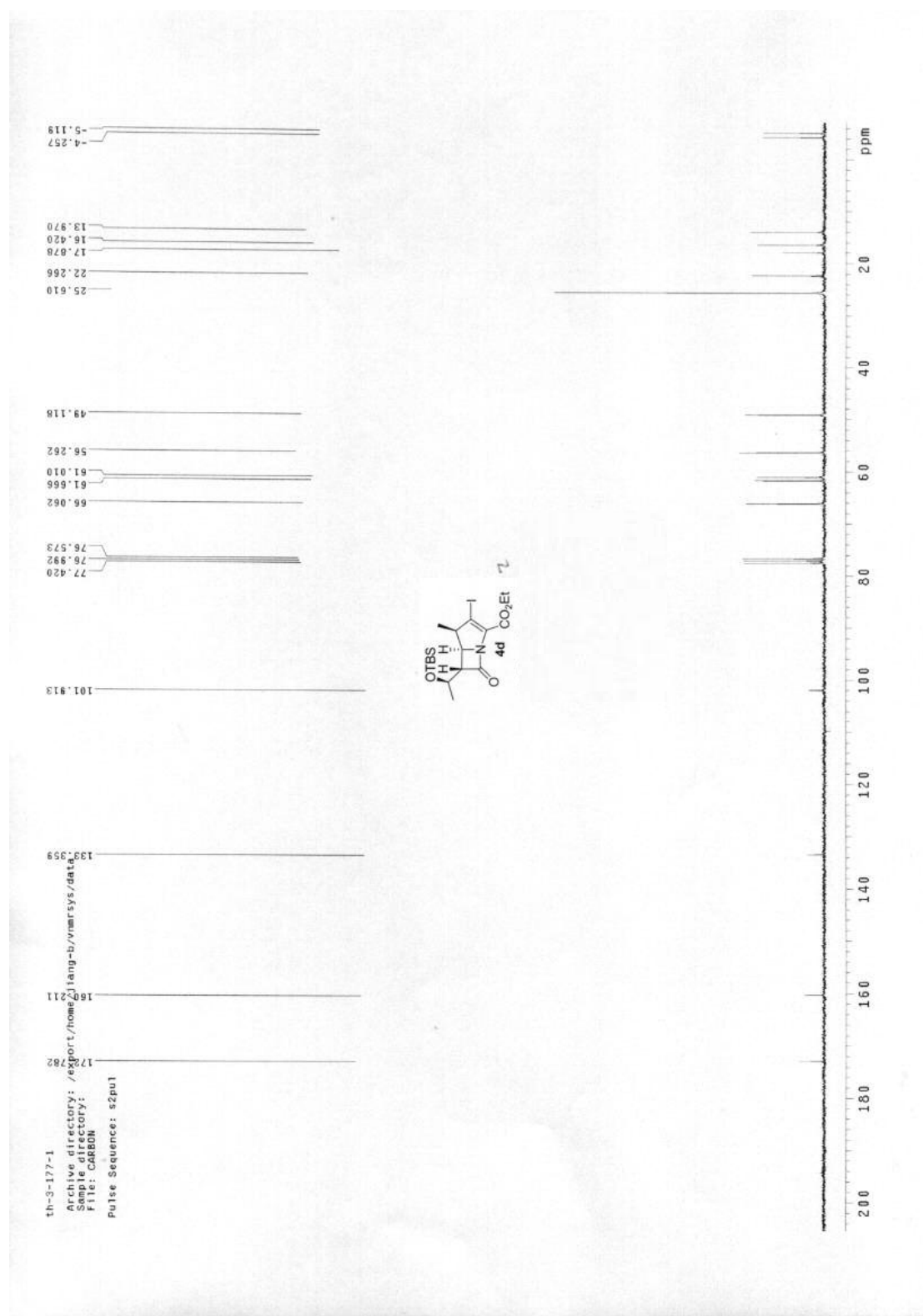




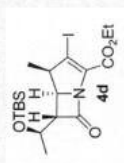
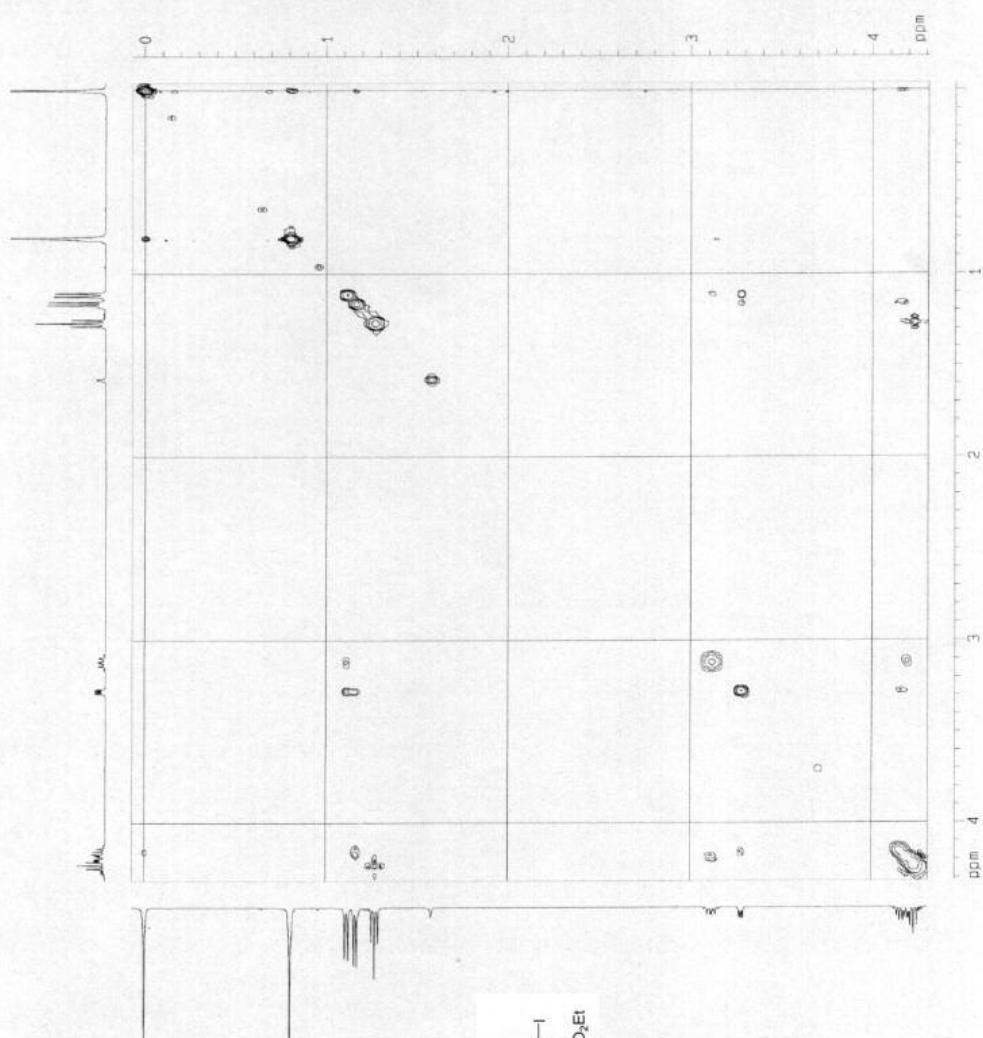




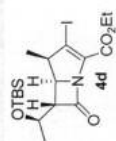
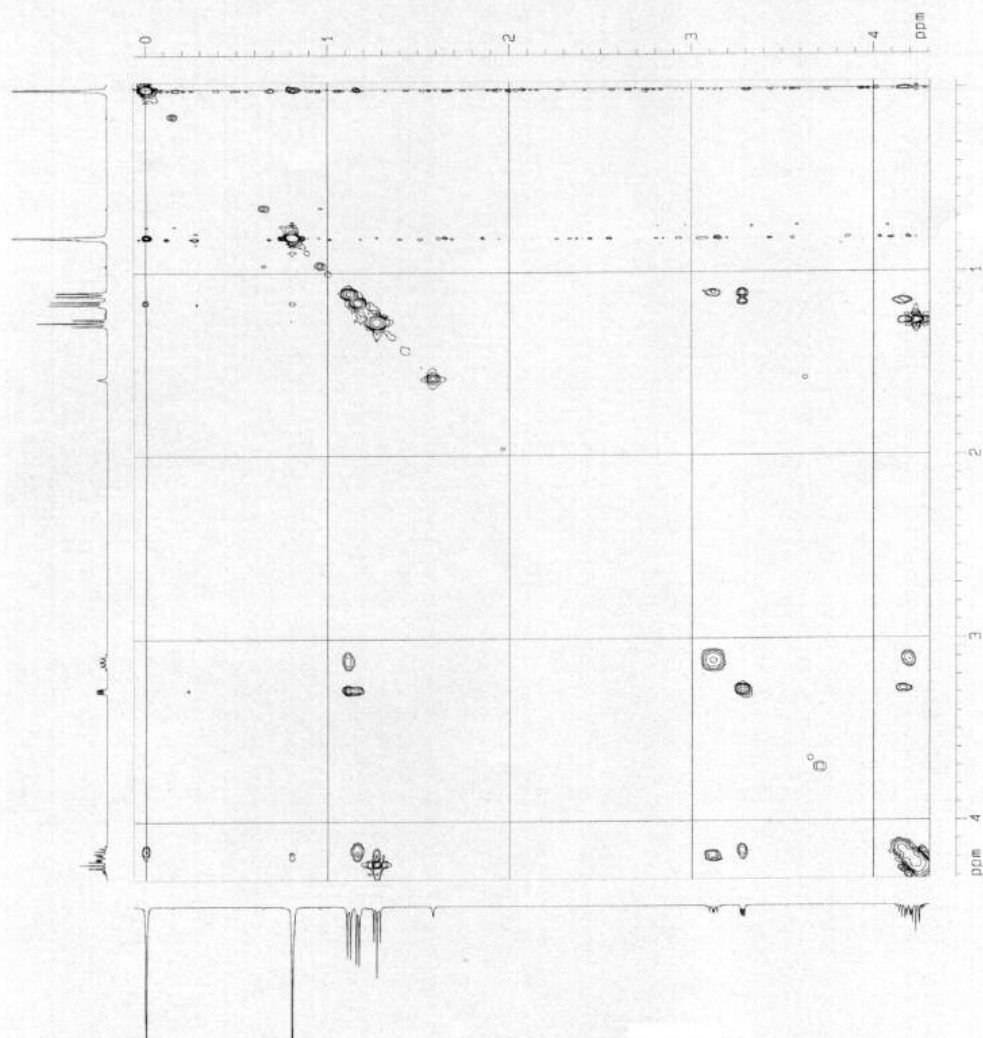




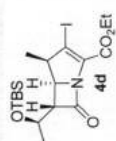
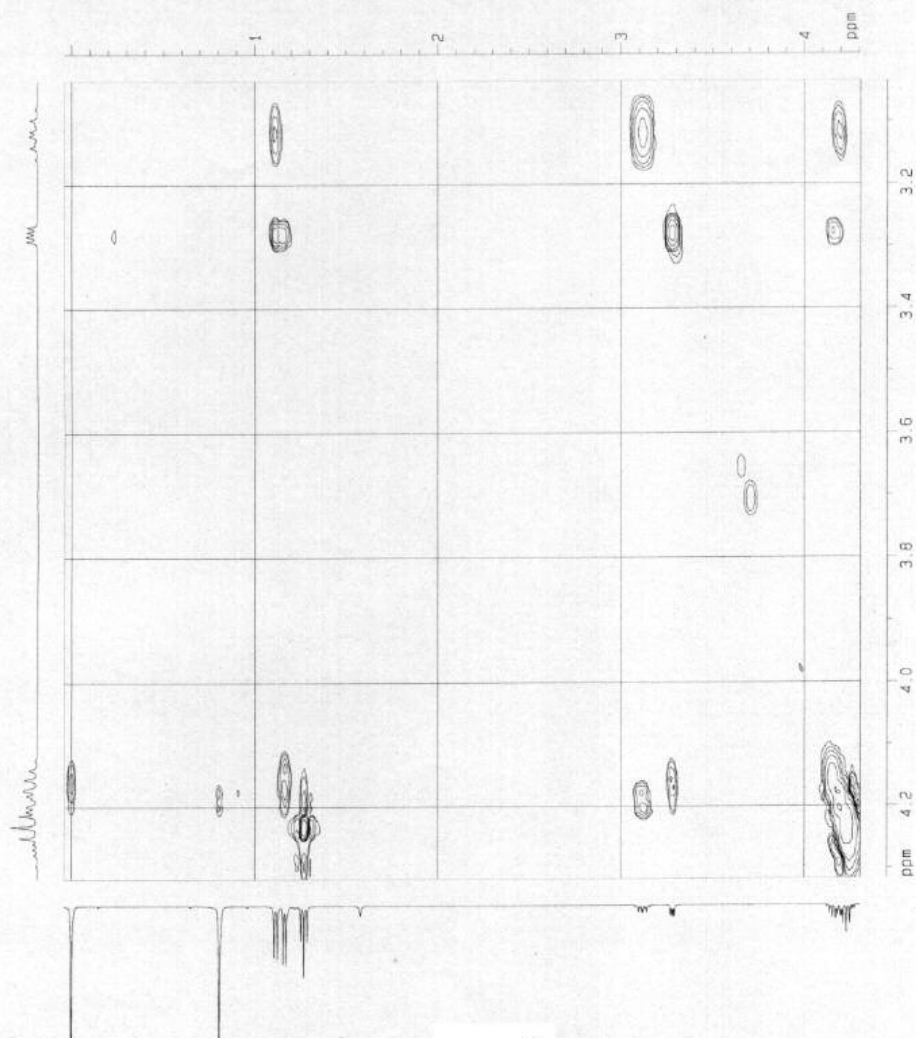
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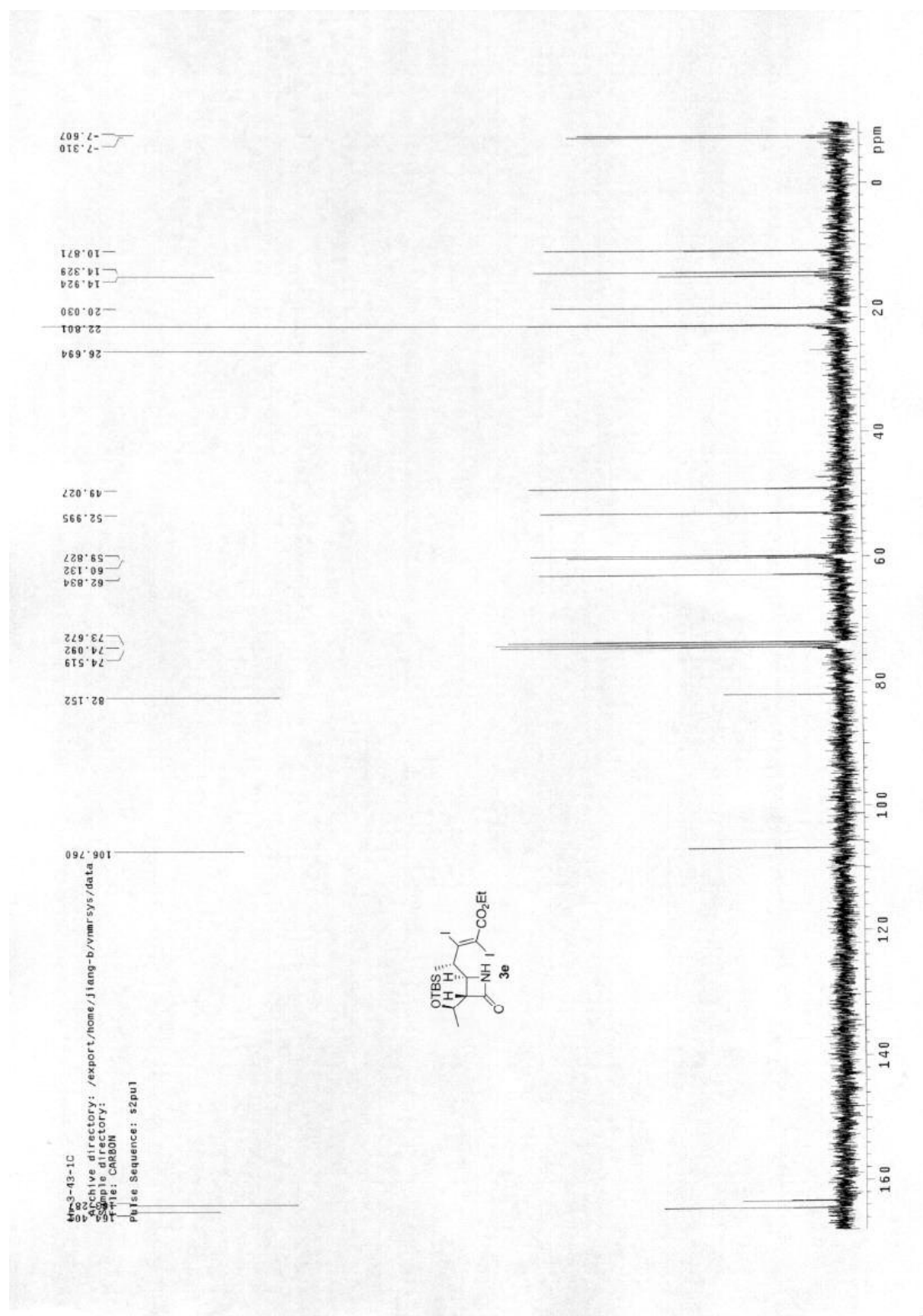


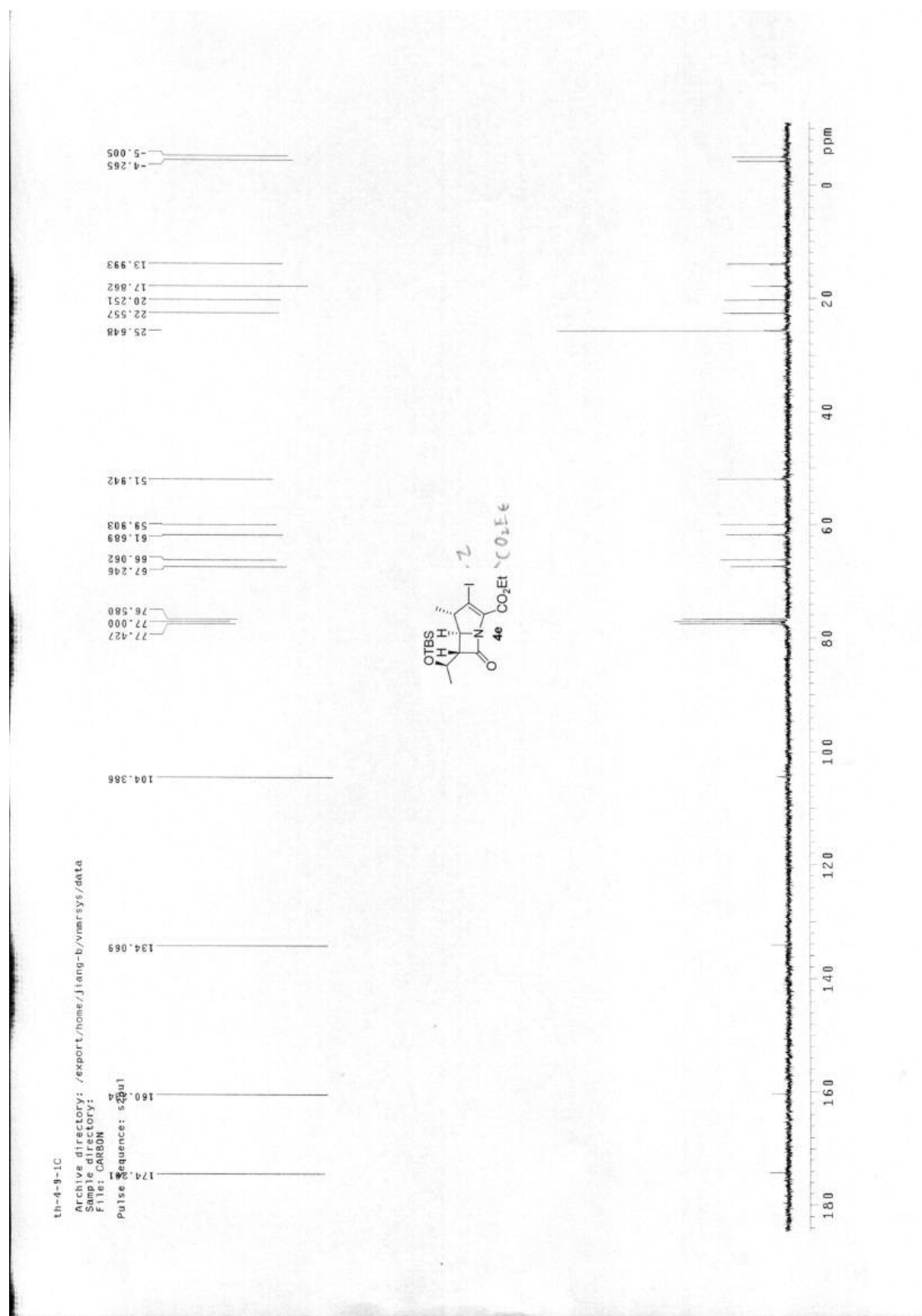
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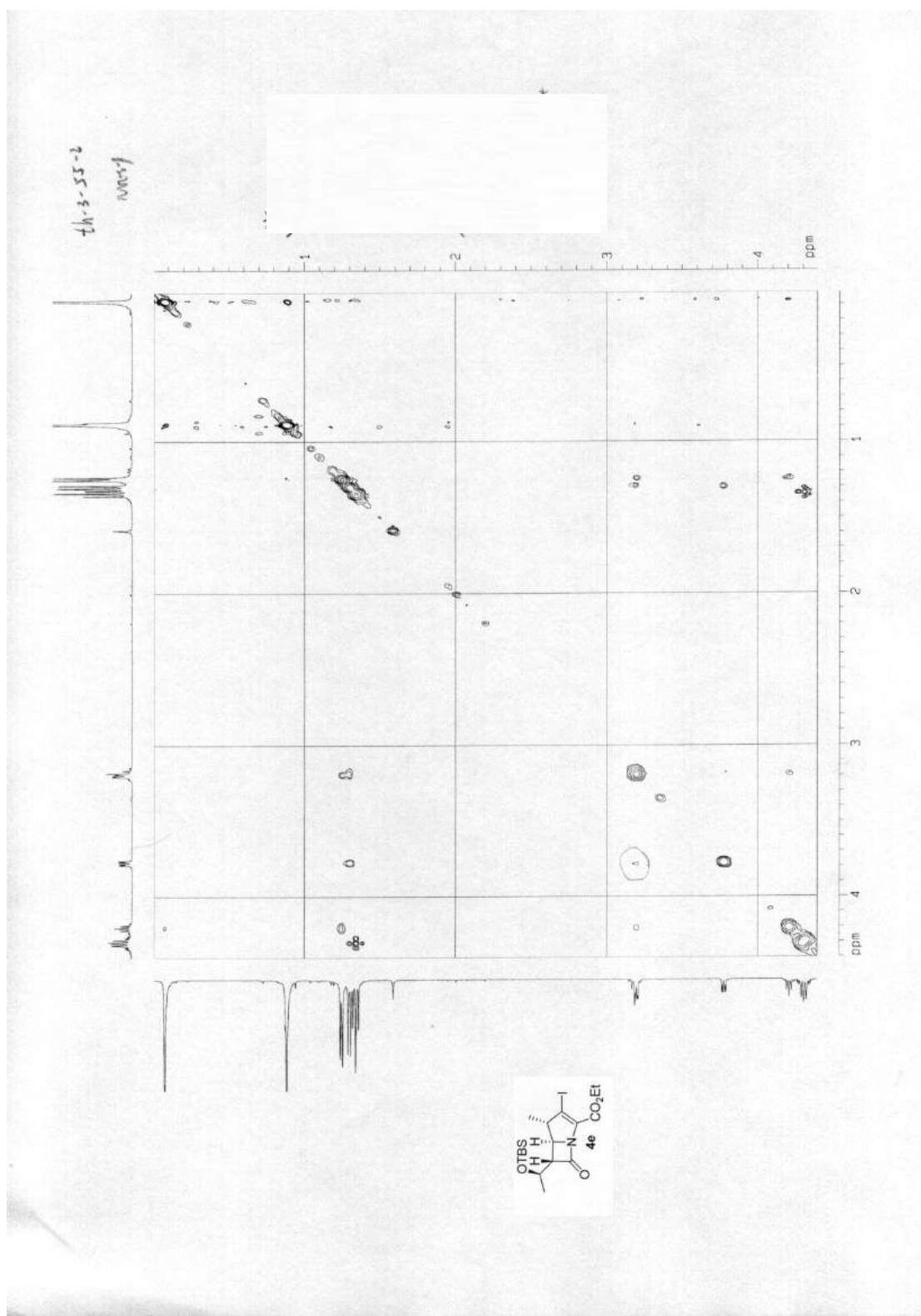


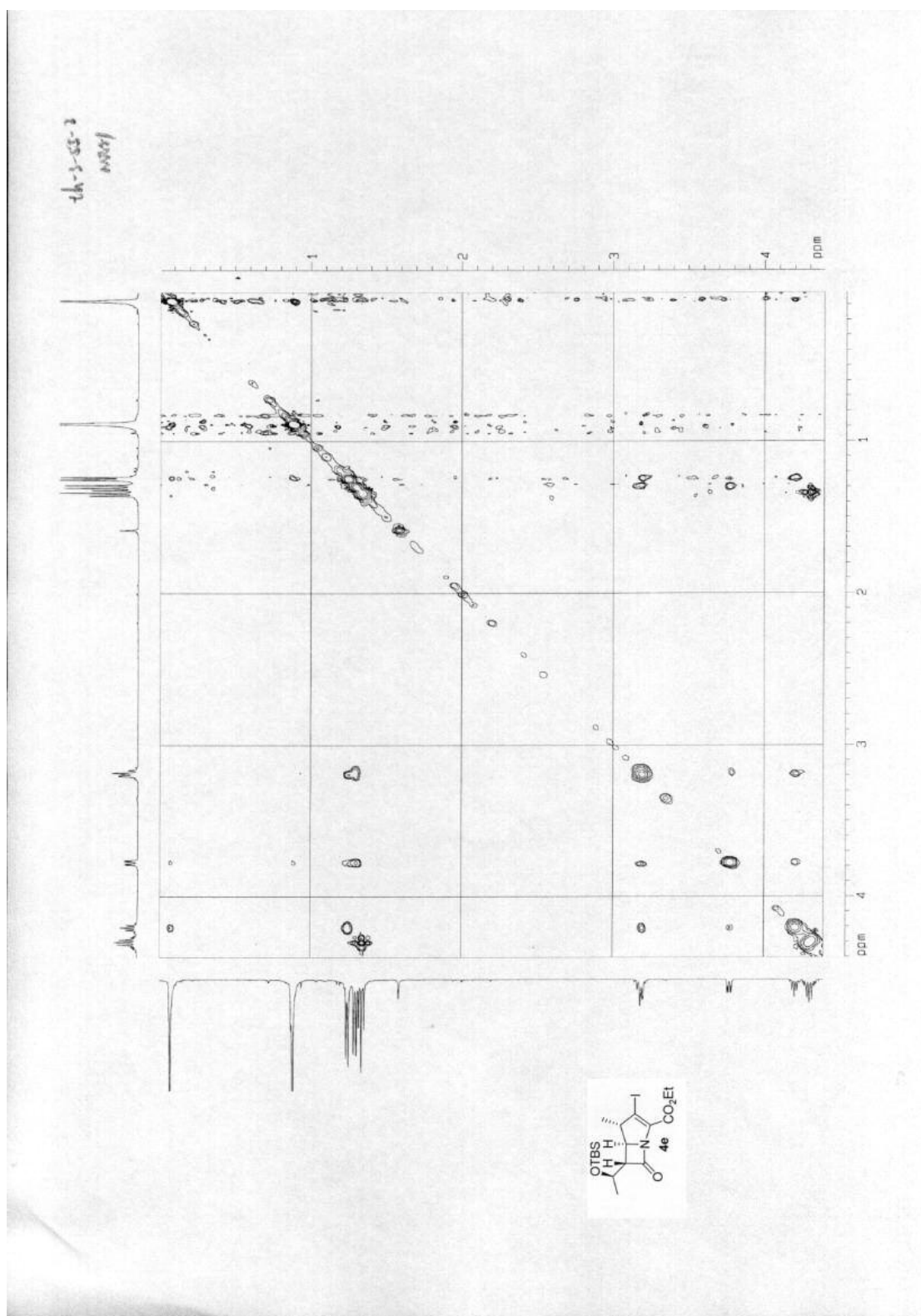
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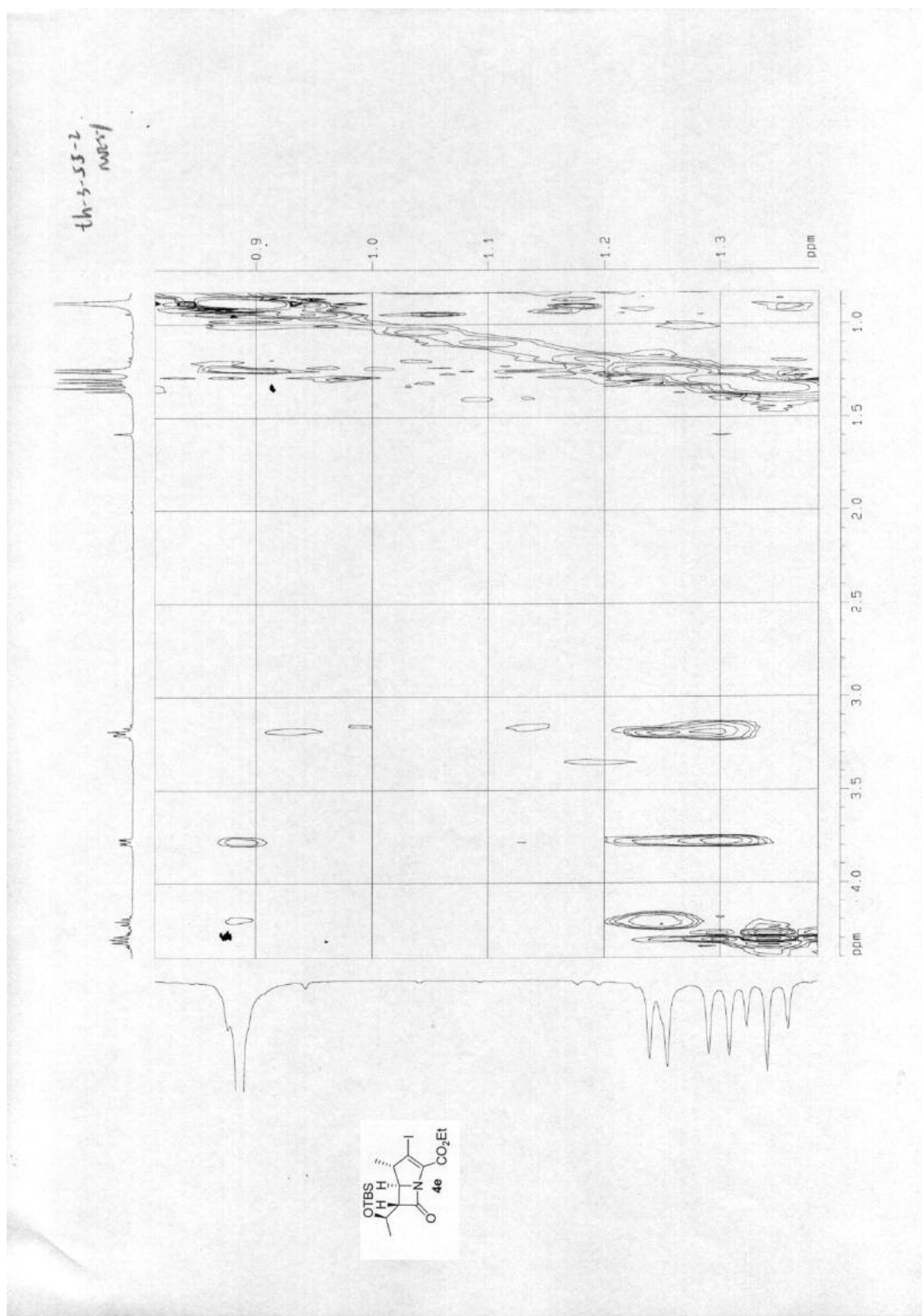


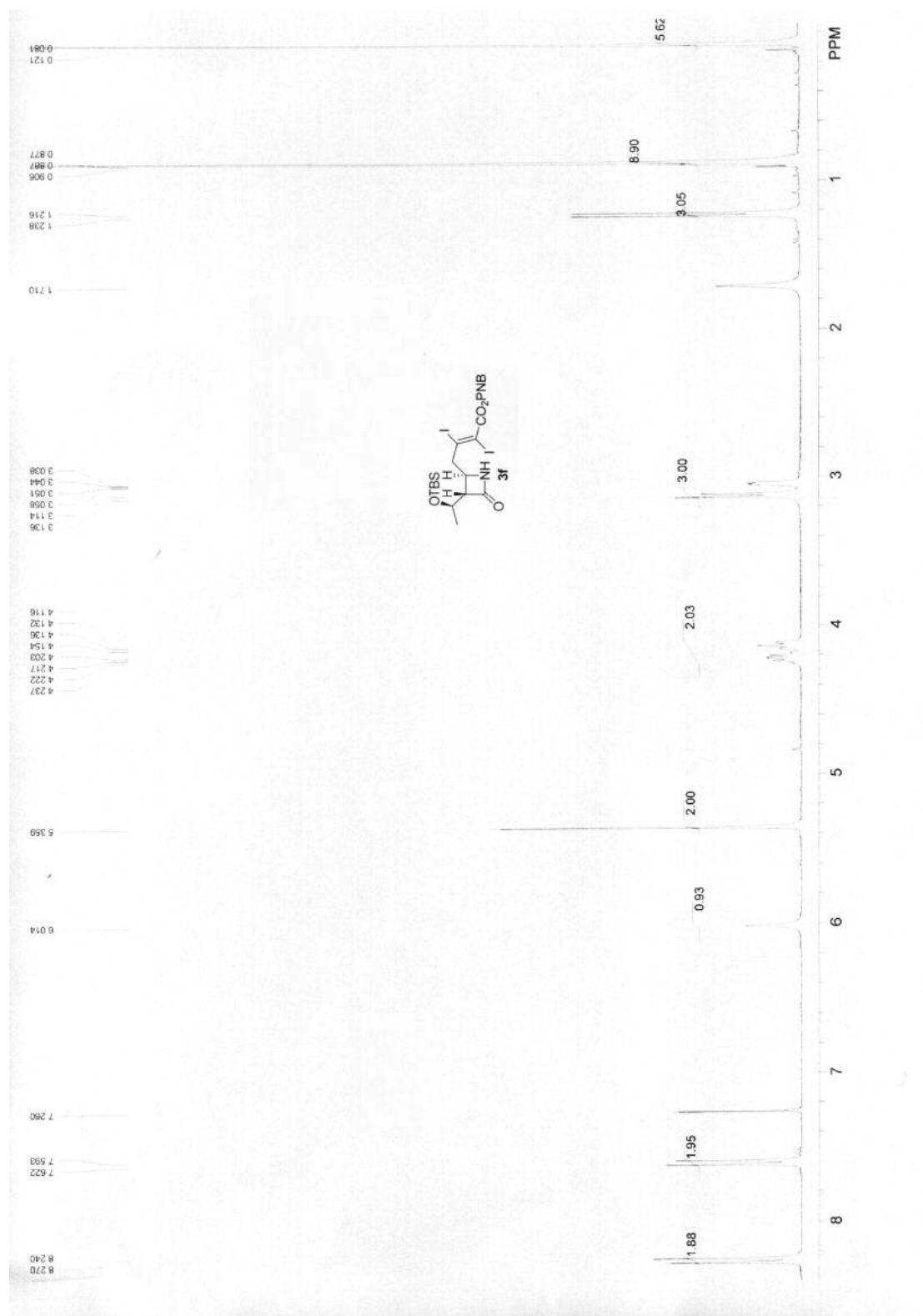


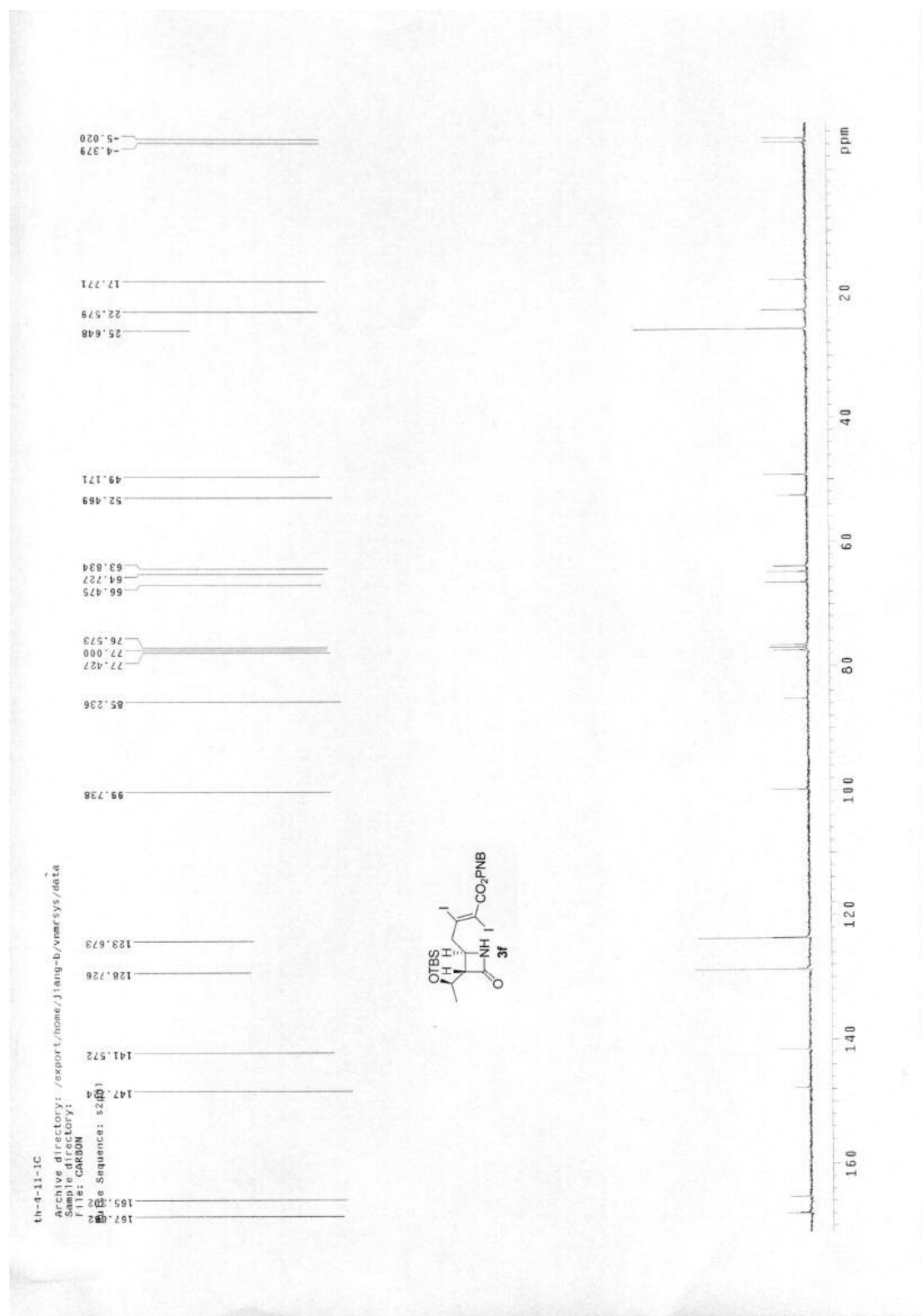


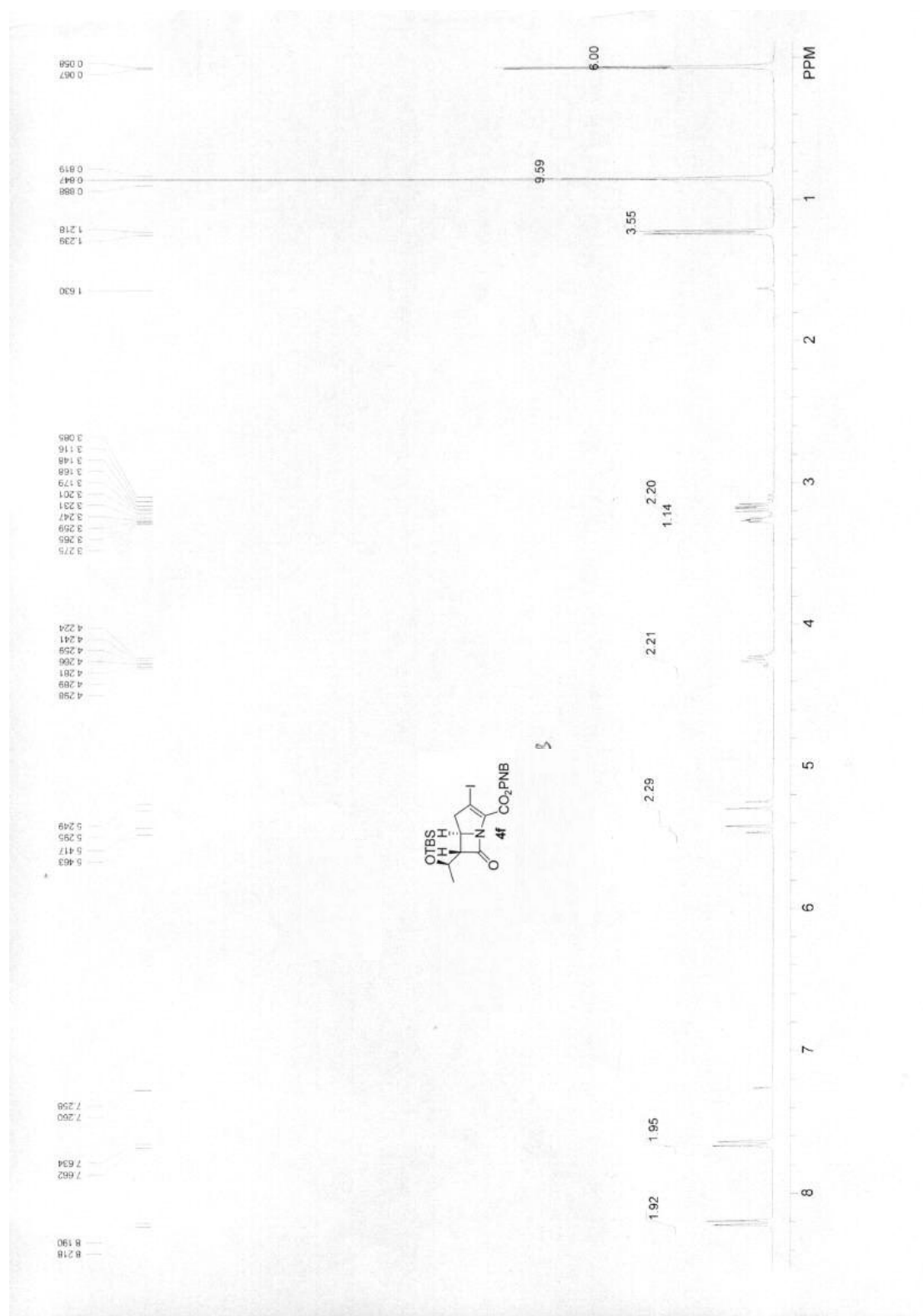


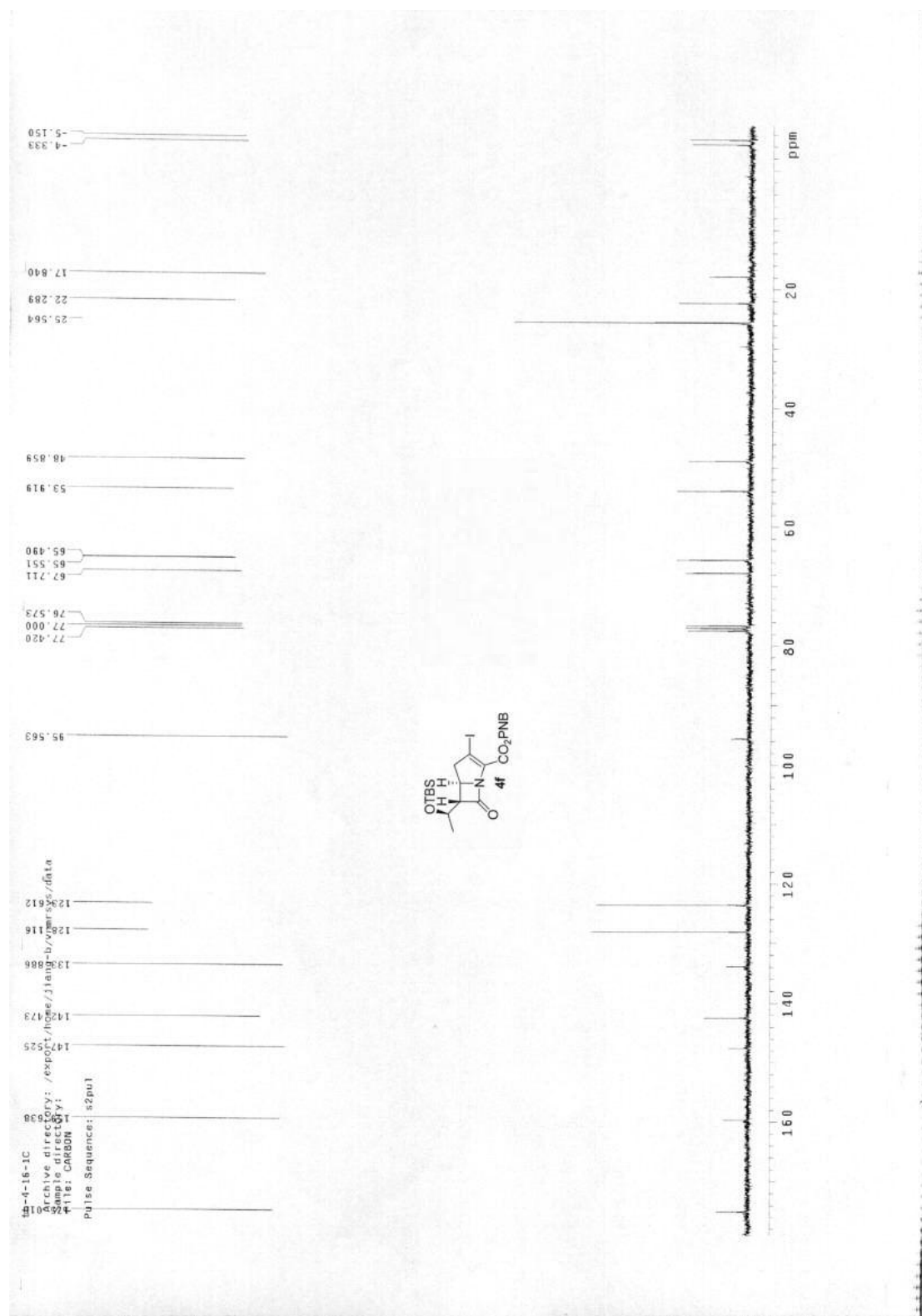


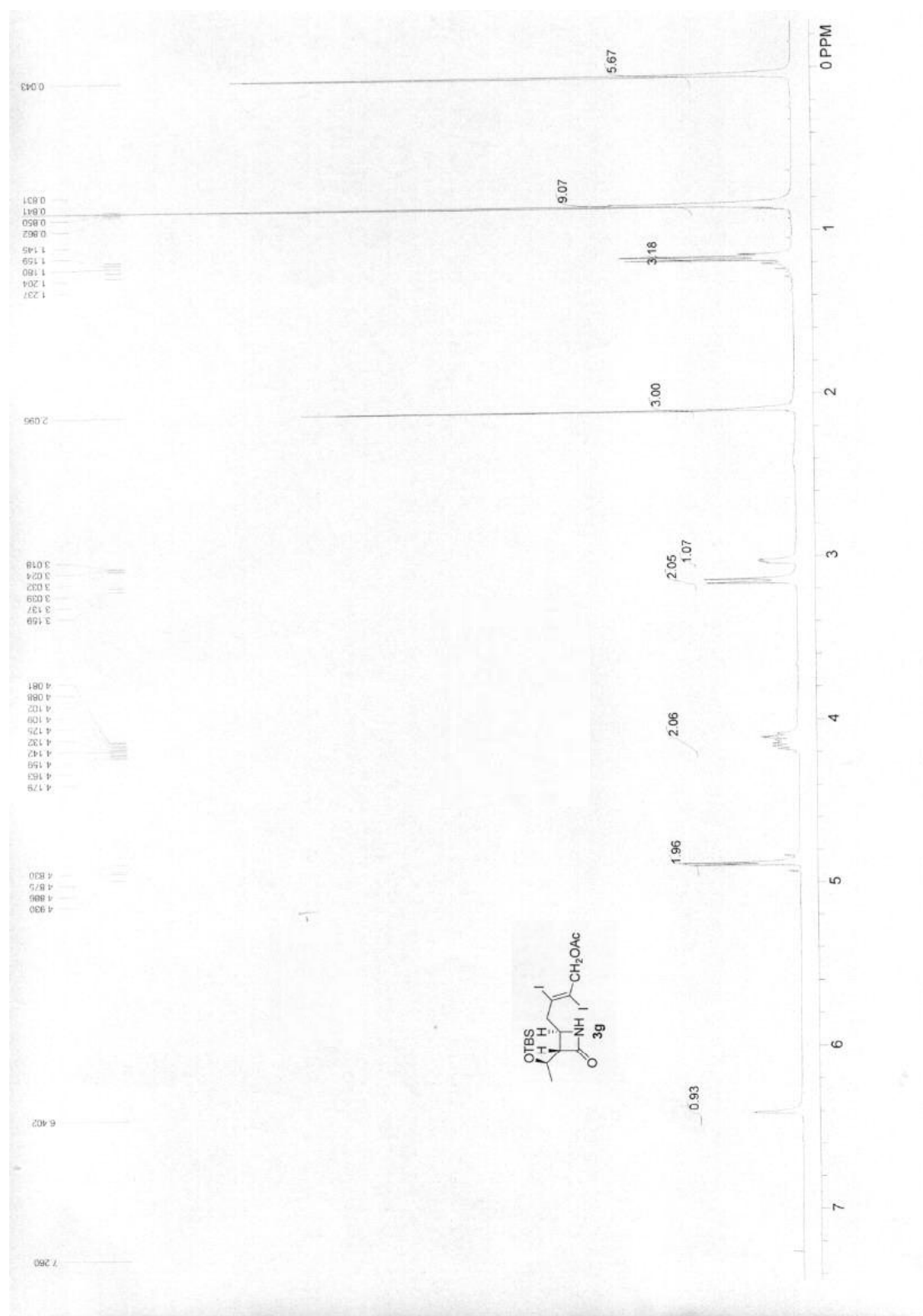


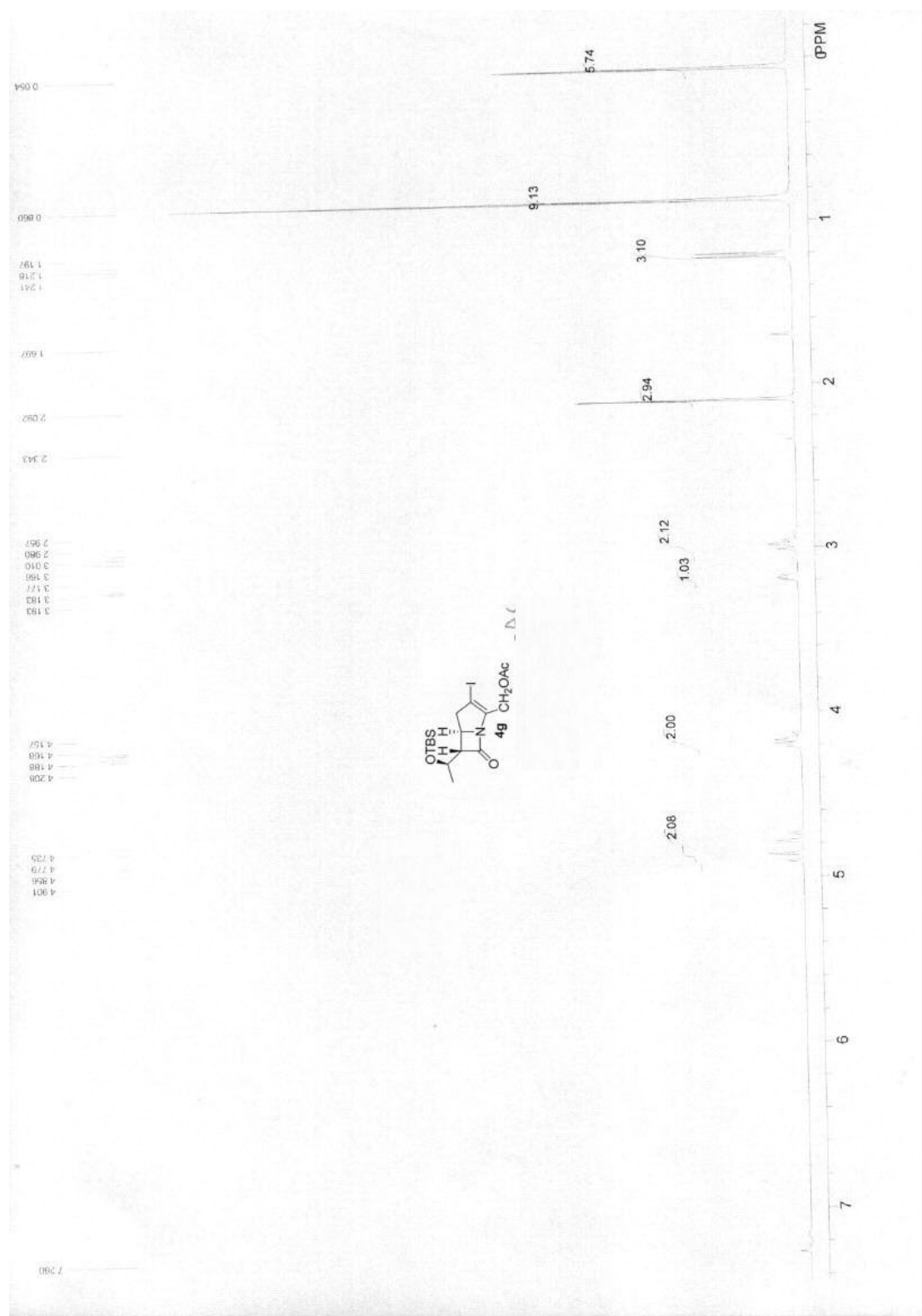












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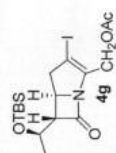
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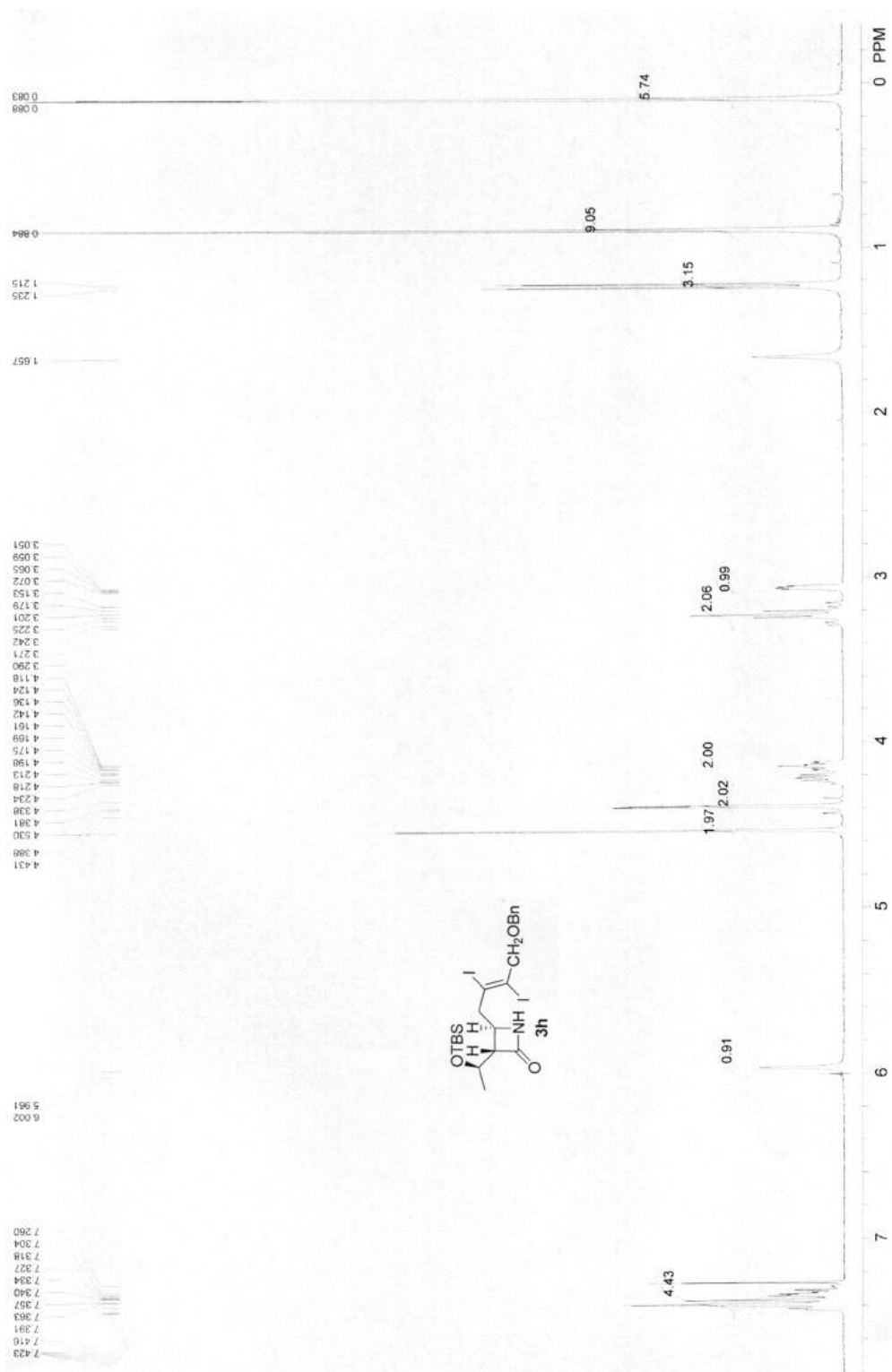
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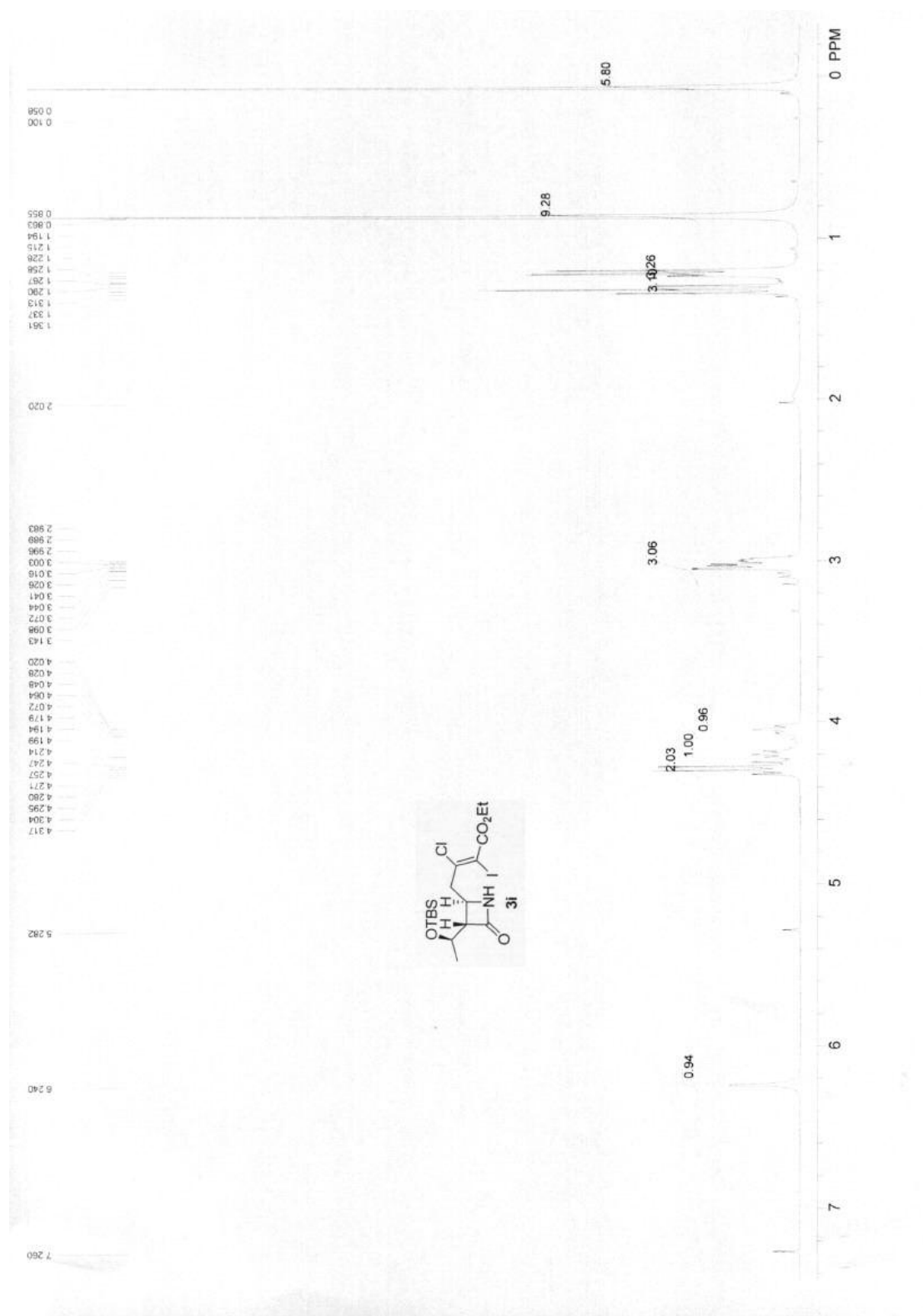
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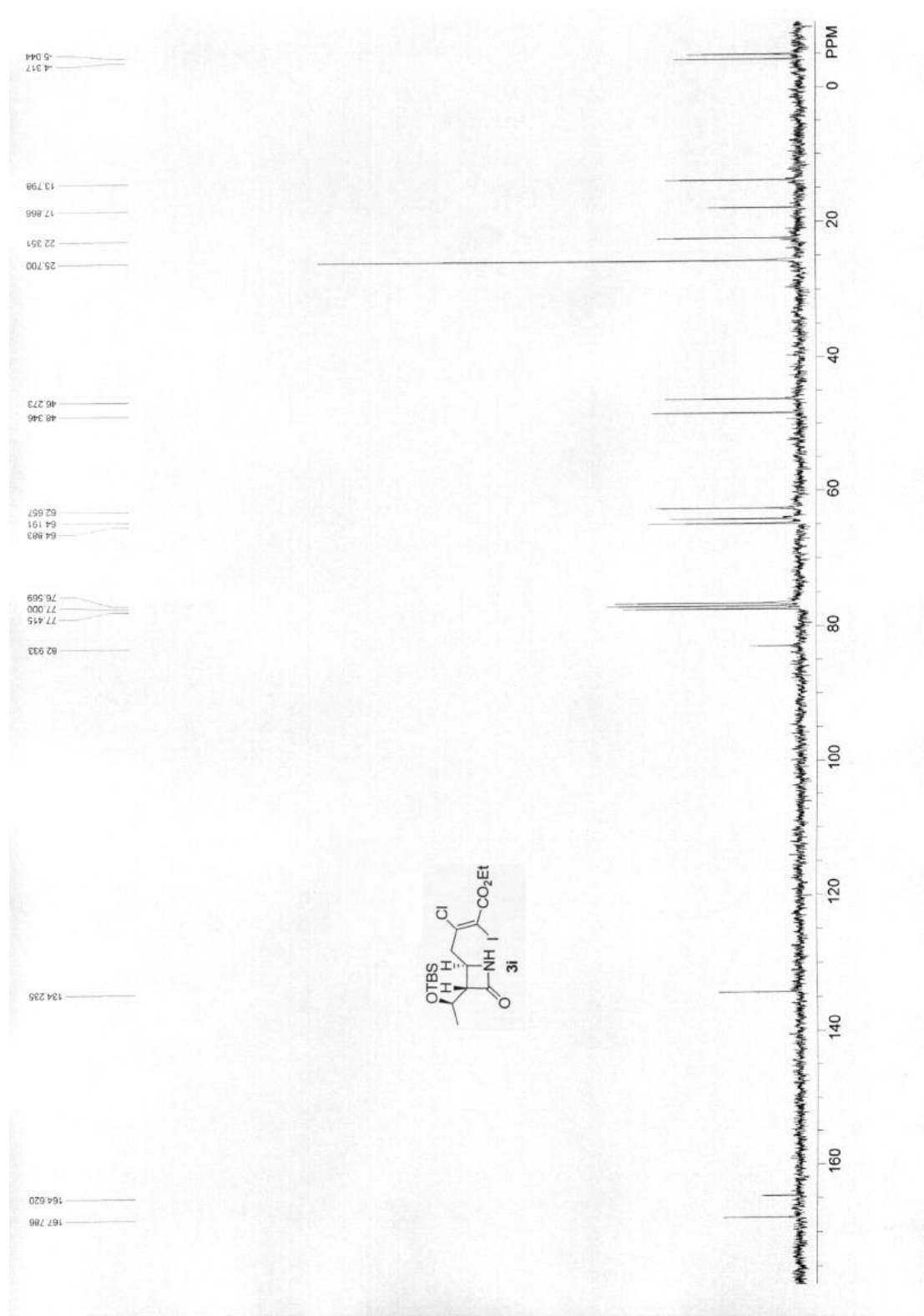
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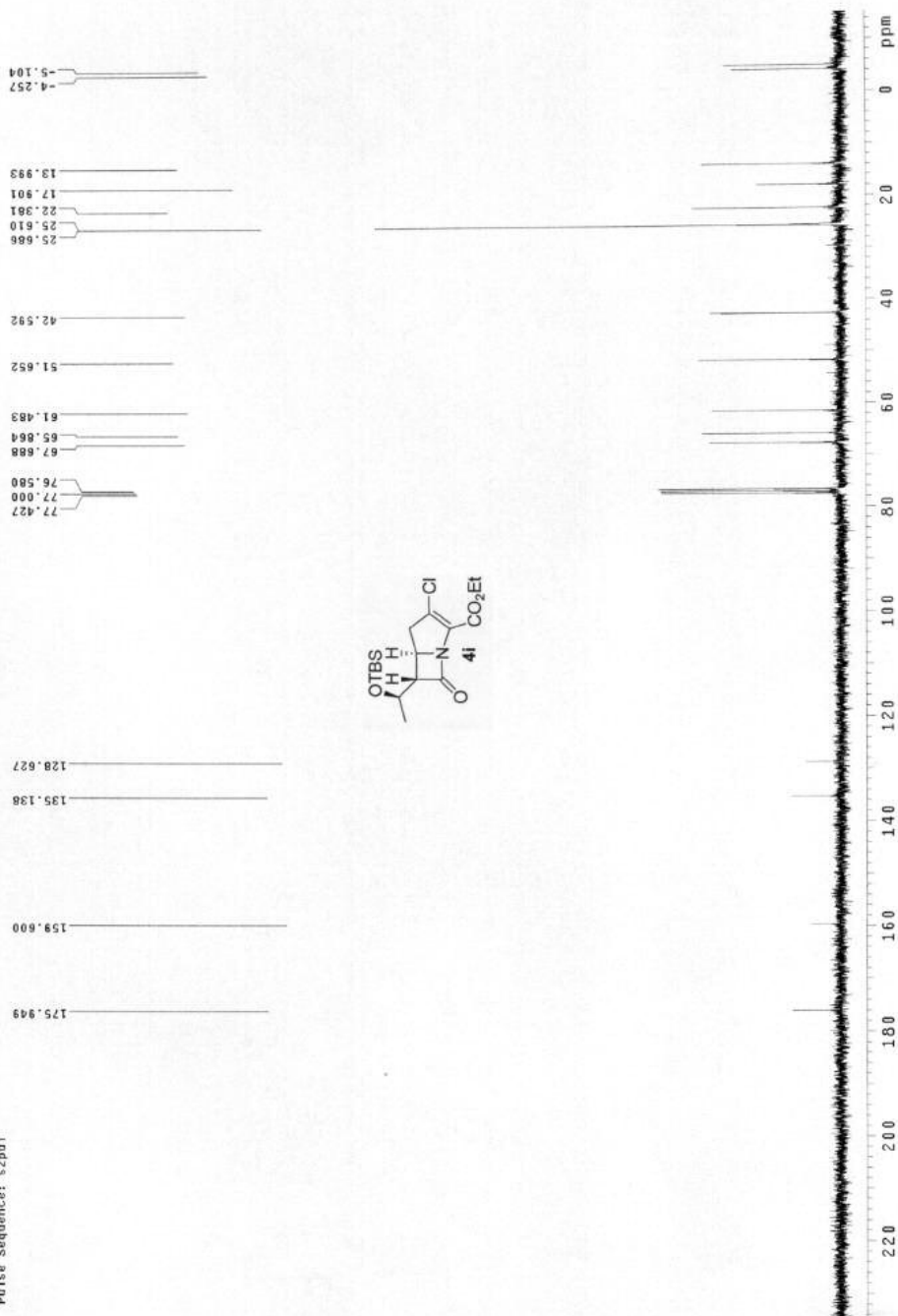
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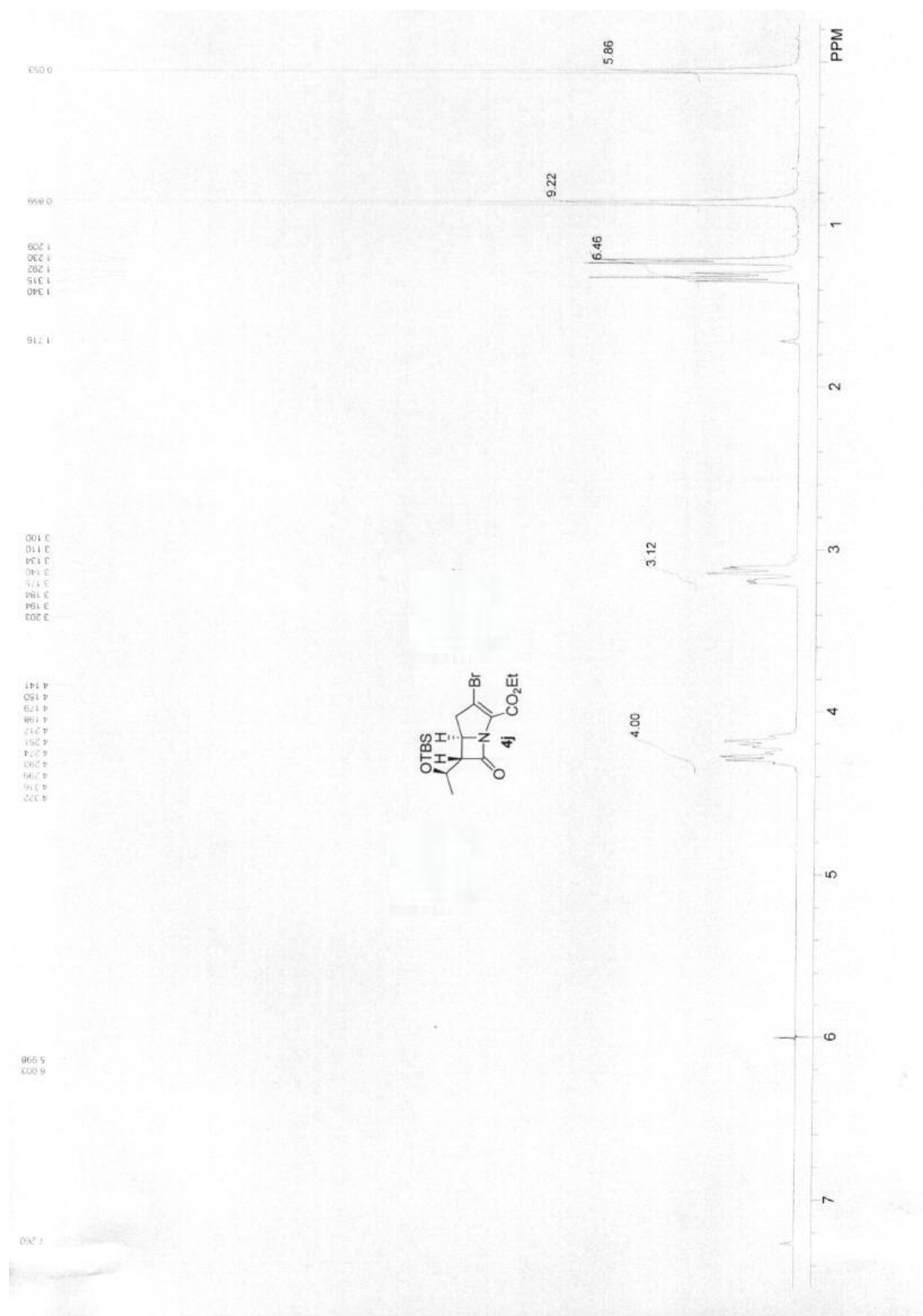
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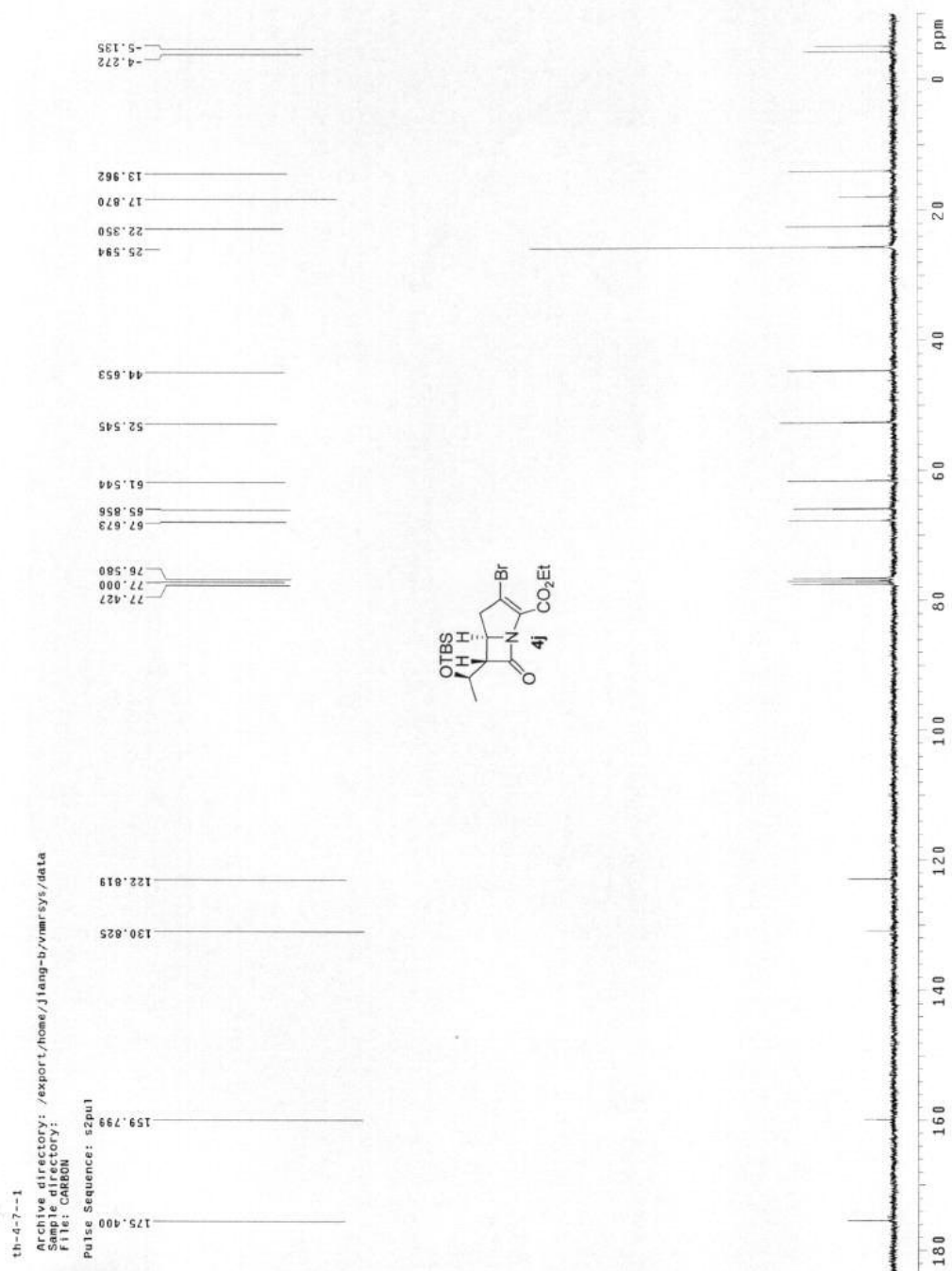
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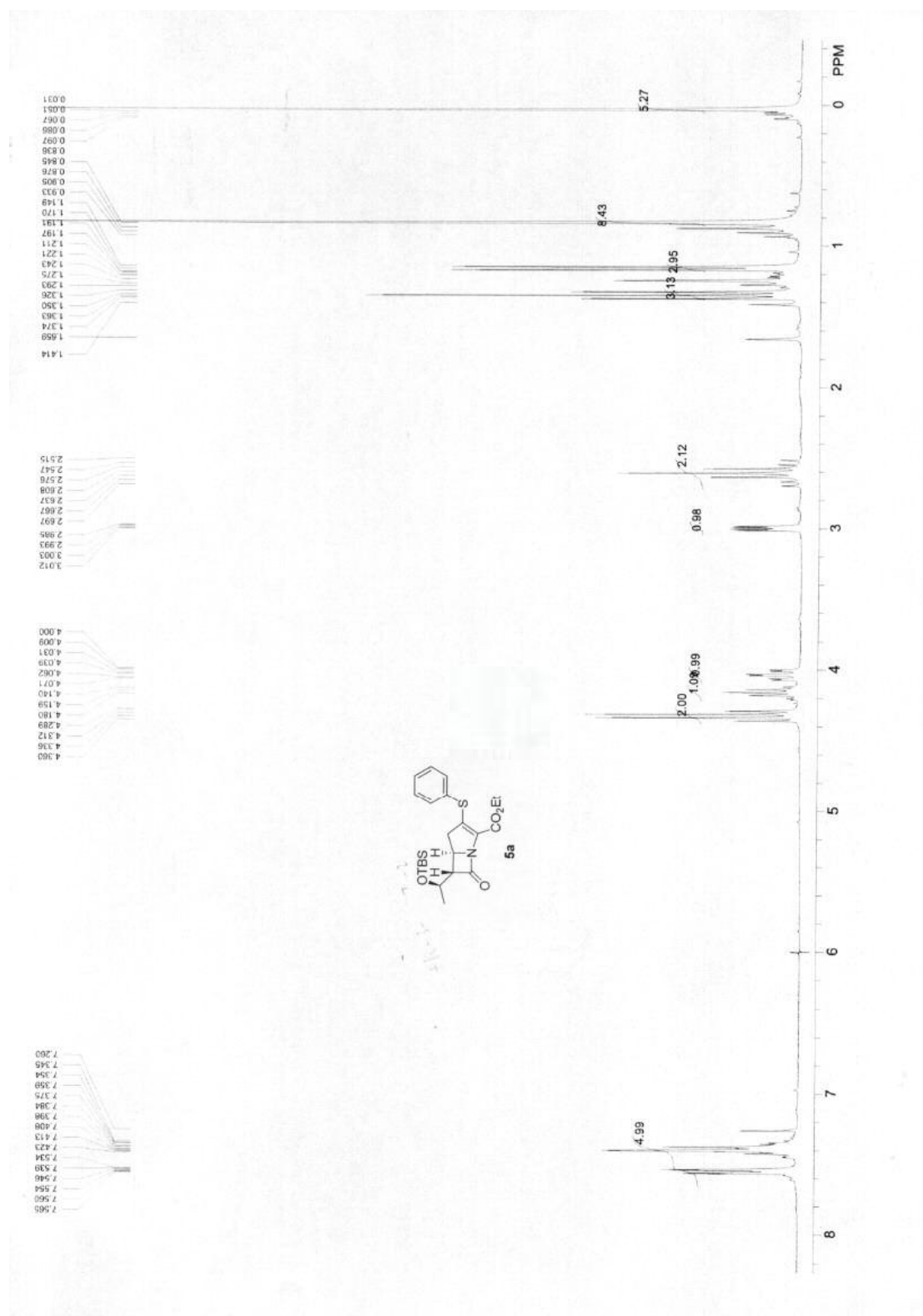
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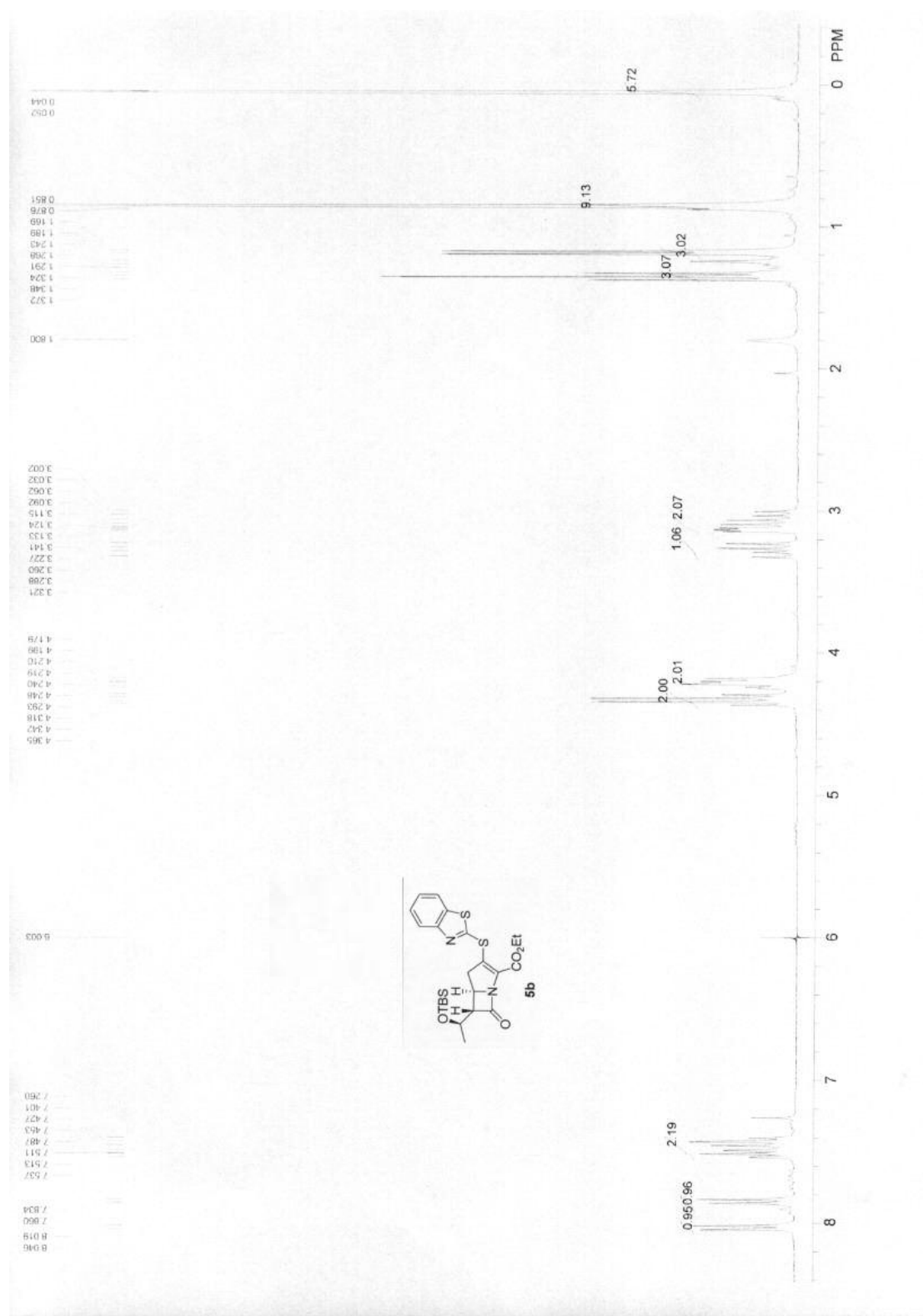
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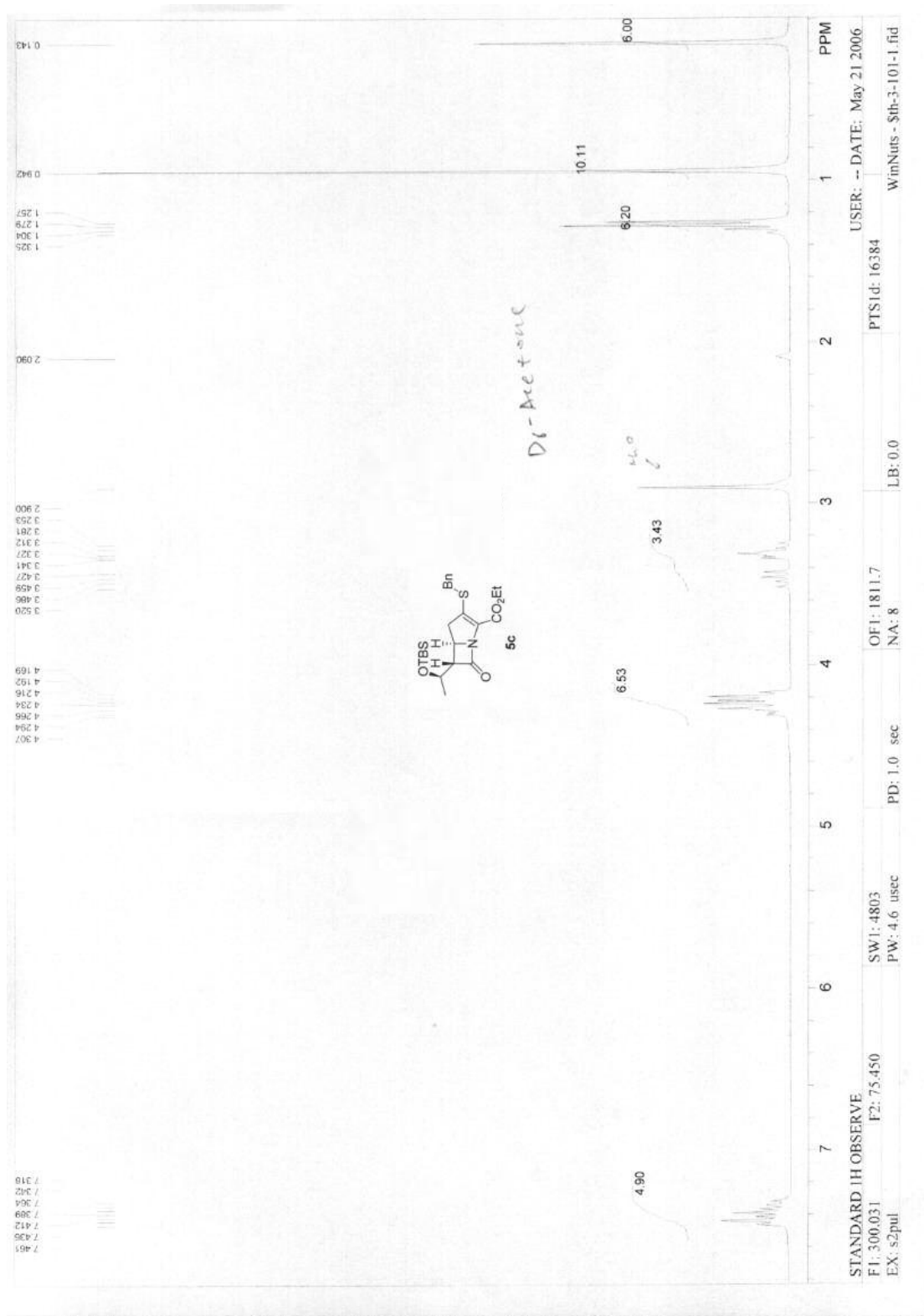


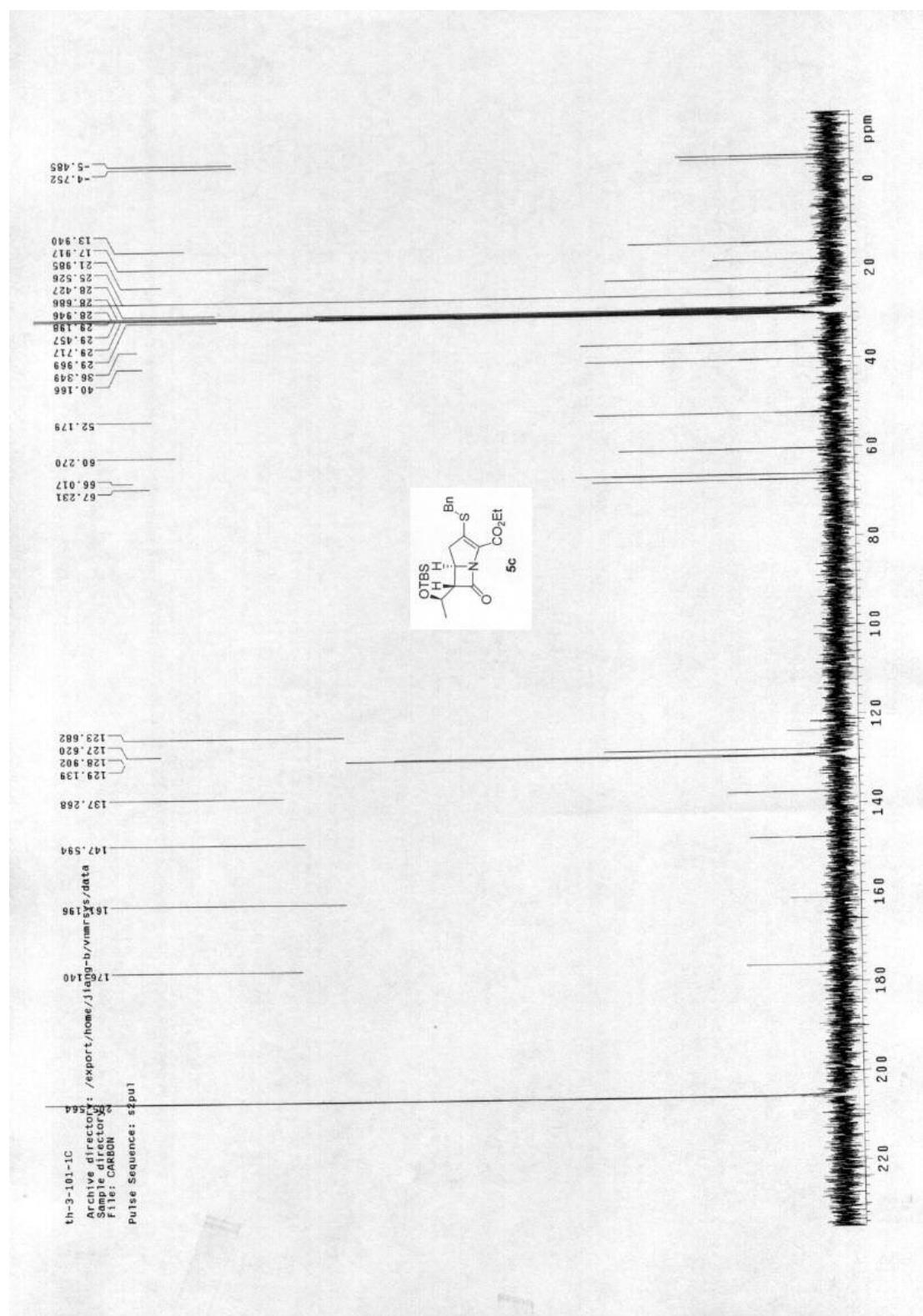


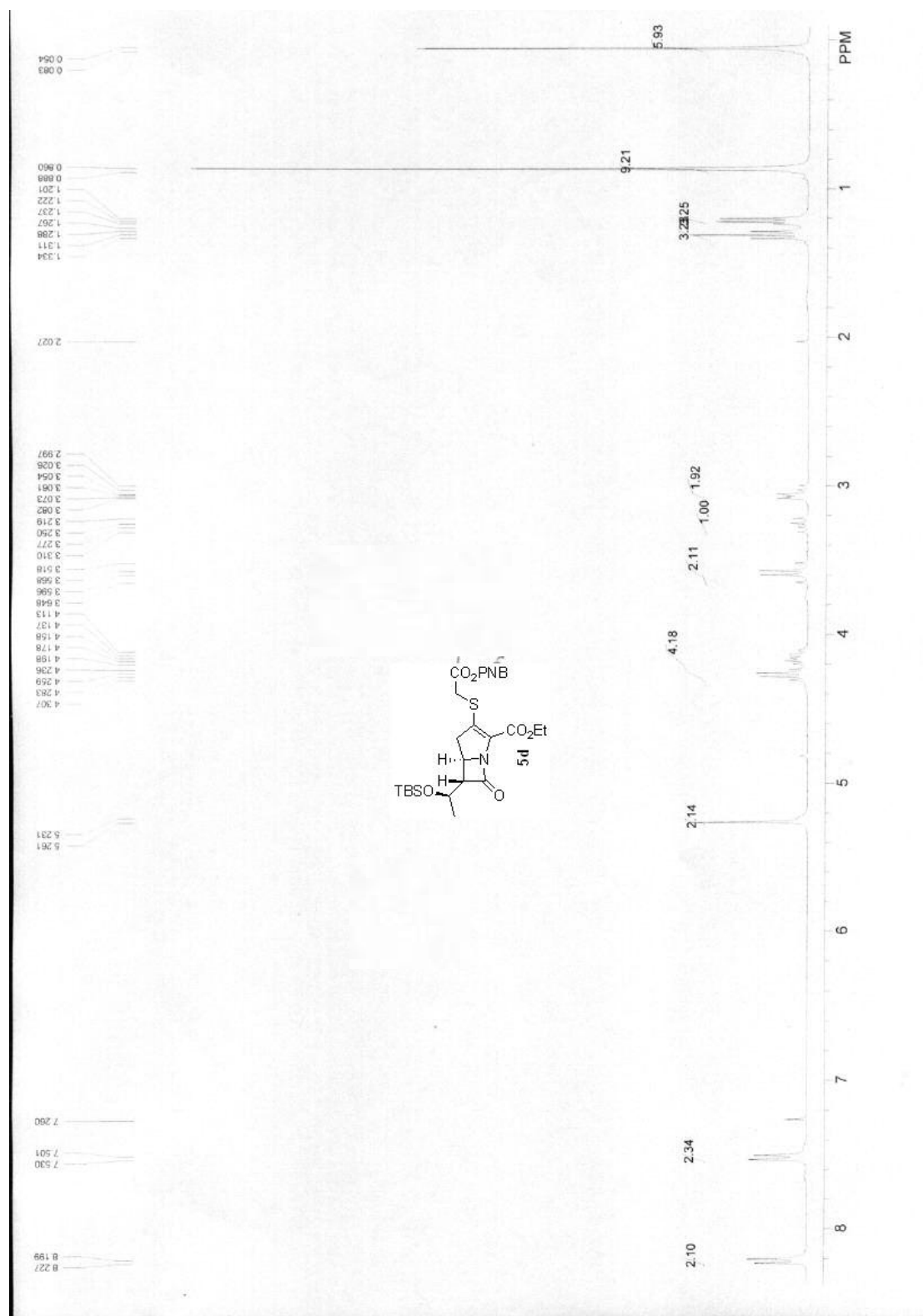


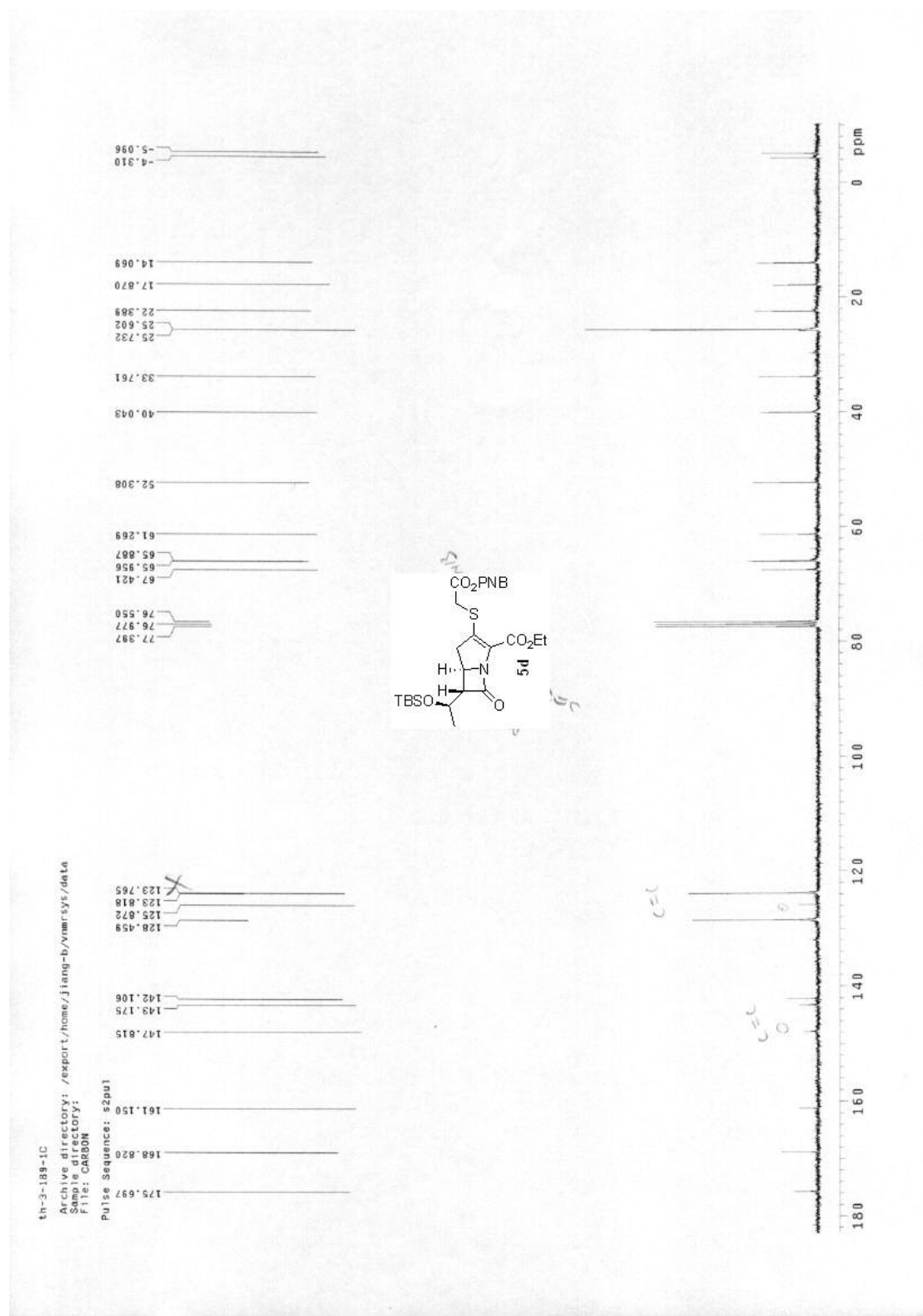


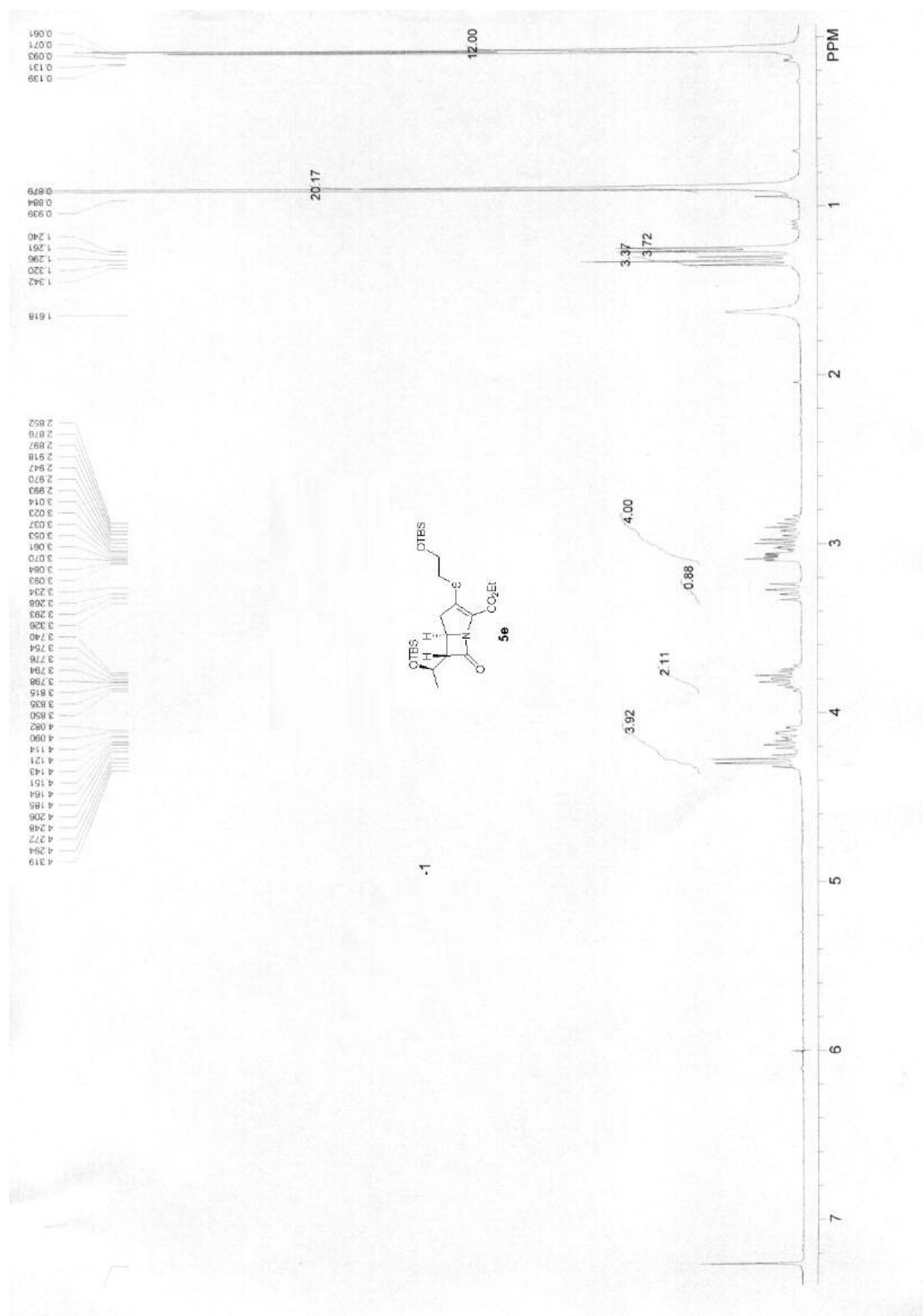


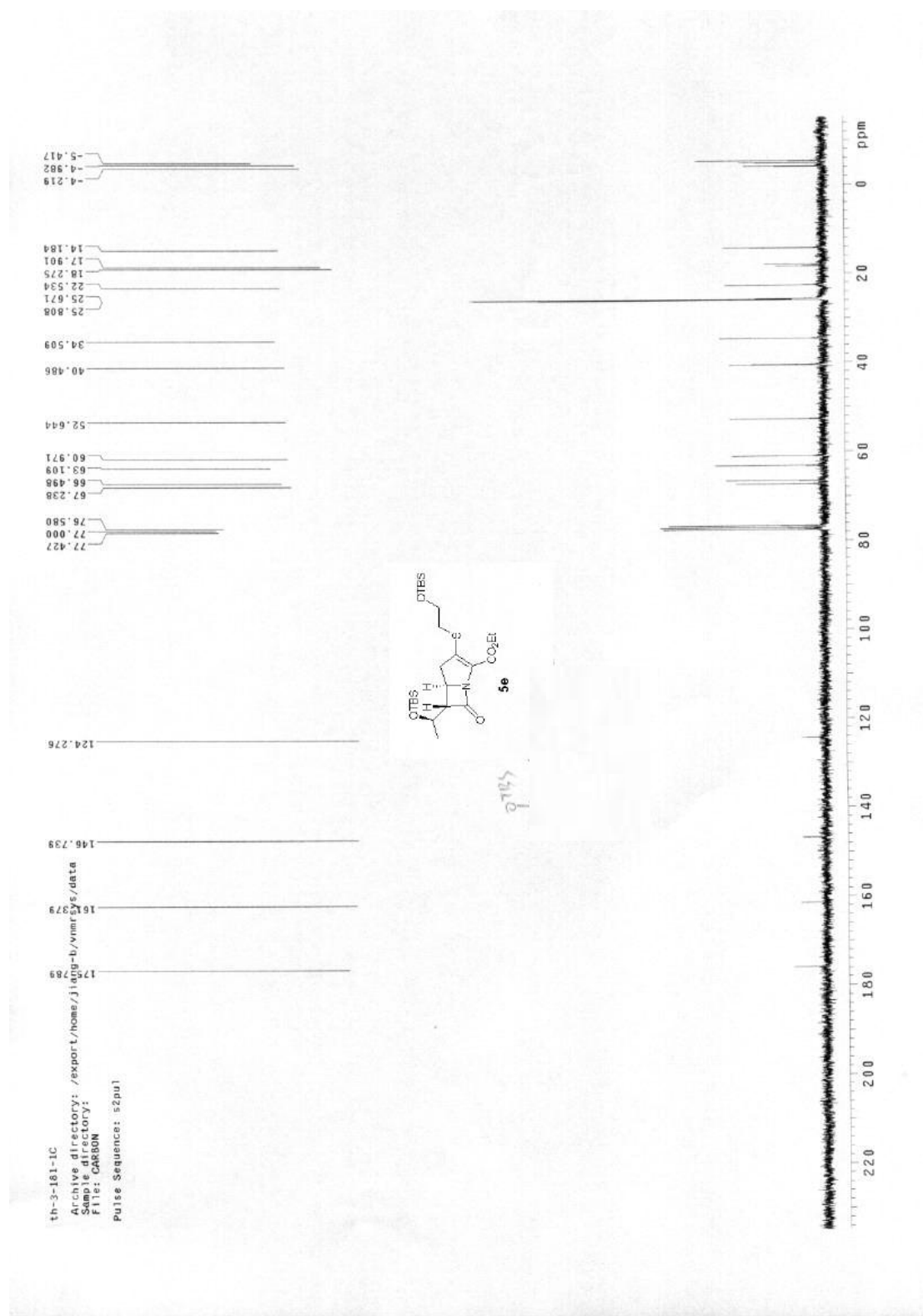


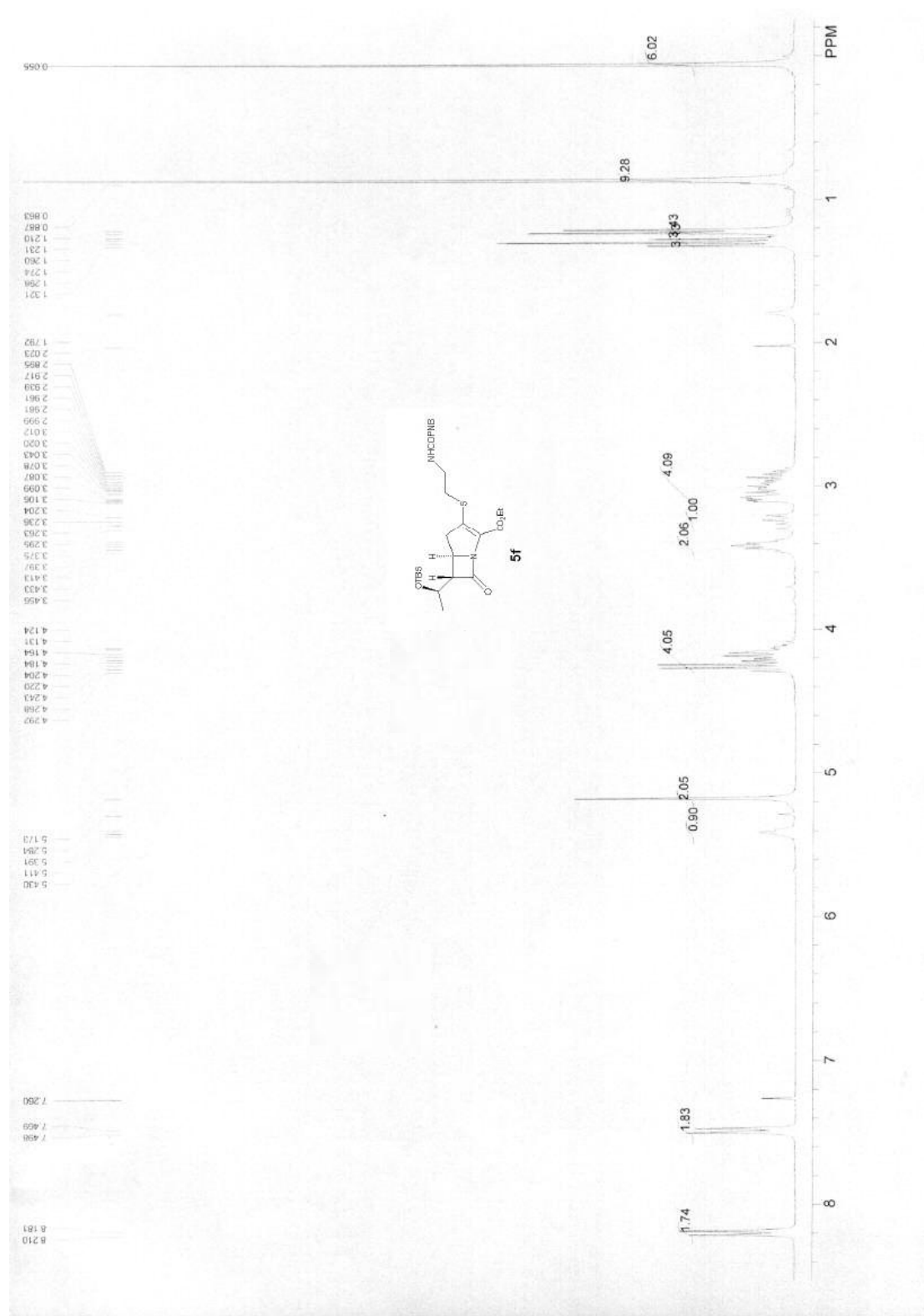












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