

Supplementary Information

Peptide bond mimicry by (*E*)-alkene and (*Z*)-fluoroalkene peptide isosteres: synthesis and bioevaluation of α -helical anti-HIV peptide analogues

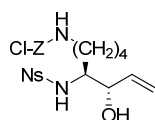
Shinya Oishi, Hirotaka Kamitani, Yasuyo Koderu, Kentaro Watanabe, Kazuya Kobayashi, Tetsuo Narumi, Kenji Tomita, Hiroaki Ohno, Takeshi Naito, Eiichi Kodama, Masao Matsuoka, and Nobutaka Fujii

General Information:

¹H NMR spectra were recorded using a JEOL AL-400 and JEOL ECA-500 spectrometer. Chemical shifts are reported in δ (ppm) relative to Me₄Si (in CDCl₃) as internal standard. ¹³C NMR spectra were recorded using a JEOL AL-400 and JEOL ECA-500, and referenced to the residual CHCl₃ signal. ¹⁹F NMR spectra were recorded using a JEOL AL-400 and JEOL ECA-500, and referenced to the residual CFCl₃ signal (δ_F 0.00 ppm). Exact mass (HRMS) spectra were recorded on a JMS-HX/HX 110A mass spectrometer. Optical rotations were measured with a JASCO P-1020 polarimeter. Infrared (IR) spectra were obtained on a JASCO FT/IR-4100 FT-IR spectrometer with JASCO ATR PRO410-S. Melting points (uncorrected) were measured by a hot stage melting point apparatus. For flash chromatography, Wakosil C-300, C-300E, and silica gel 60H (silica gel for thin-layer chromatography, Merck) were employed. For analytical HPLC, a Cosmosil 5C18-ARII column (4.6 x 250 mm, Nacalai Tesque, Inc., Kyoto, Japan) was employed with a linear gradient of CH₃CN containing 0.1% (v/v) TFA at a flow rate of 1 cm³ min⁻¹ on a Shimadzu LC-10ADvp (Shimadzu Corp., Ltd., Kyoto, Japan), and eluting products were detected by UV at 220 nm. Preparative HPLC was performed using a Cosmosil 5C18-ARII column (20 x 250 mm, Nacalai Tesque, Inc.) on a Shimadzu LC-6AD (Shimadzu corporation, Ltd.) in an isocratic mode of CH₃CN solution containing 0.1% (v/v) TFA at a flow rate of 10 cm³ min⁻¹. The purity of each peptide compound was more than 95%, as determined by HPLC analysis. Fmoc-protected amino acids and resins were purchased from Watanabe Chemical Industries, Ltd. (Hiroshima, Japan) or Merck Ltd. (Tokyo, Japan). All the other chemicals were purchased from either Nacalai Tesque, Inc. (Kyoto, Japan) or Sigma-Aldrich JAPAN (Tokyo, Japan).

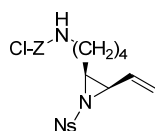
Synthetic procedures and characterization data of new compounds:

(3*S*,4*S*)-8-[*N*-(2-Chlorobenzyloxycarbonyl)amino]-4-[*N*-(2-nitrophenylsulfonyl)amino]oct-1-ene-3-ol (4).



To the allyl alcohol **3** (760 mg, 1.78 mmol) was added 4 N HCl/dioxane (3.0 cm³) at 0 °C, and the mixture was stirred for 2 h at room temperature. The resulting solution was concentrated under reduced pressure to give the deprotected amine, which was used for the next reaction without further purification. The residue was dissolved in CHCl₃ (1.7 cm³), and then 2,4,6-collidine (0.71 cm³, 5.34 mmol) and NsCl (592 mg, 2.67 mmol) was added to the solution at 0 °C. The mixture was stirred for 1.5 h at room temperature and washed with saturated NaHCO₃, brine, saturated citric acid, brine, saturated NaHCO₃ and brine. The organic layer was dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel with *n*-hexane-EtOAc (1:1) to give the title compound **4** (594 mg, 65%) as a colorless oil; $[\alpha]_D^{23} -32.3$ (*c* 1.00 in CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ 3364 (NHCO), 1702 (CO); δ_{H} (500 MHz; CDCl₃) 1.22-1.75 (6H, m), 2.30-2.35 (1H, m), 3.06-3.19 (2H, m), 3.43-3.49 (1H, m), 4.10 (1H, br s), 4.83-4.89 (1H, m), 4.89 (1H, d, *J* 10.3), 5.12-5.25 (3H, m), 5.60 (1H, ddd, *J* 16.0, 10.3 and 5.7), 5.70 (1H, d, *J* 8.0), 7.23-7.30 (2H, m), 7.35-7.44 (2H, m), 7.67-7.72 (2H, m), 7.81-7.85 (1H, m), 8.07-8.11 (1H, m); δ_{C} (100 MHz; CDCl₃) 22.5, 29.5, 31.8, 40.4, 59.1, 64.0, 73.6, 117.0, 125.2, 126.9, 129.4, 129.5, 129.8, 130.3, 132.7, 133.2, 133.6, 134.3, 135.4, 137.1, 147.6, 156.3; *m/z* (FAB) 512.1265 ([M+H]⁺, C₂₂H₂₇ClN₃O₇S requires 512.1258).

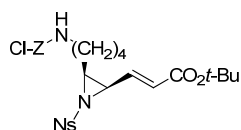
(3*R*,4*S*)-8-[*N*-(2-Chlorobenzyloxycarbonyl)amino]-3,4-[*N*-(2-nitrophenylsulfonyl)epiminoo]oct-1-ene (5**).**



To a solution of Ns-protected allyl alcohol **4** (5.10 g, 9.96 mmol) and PPh₃ (3.40 g, 13.0 mmol) in THF (100 cm³) was added dropwise DIAD in toluene solution (1.9 M, 6.8 cm³, 13.0 mmol) at 0 °C under Ar, and the mixture was stirred 4 h at room temperature. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane-EtOAc (2:1) gave the title compound **5** (4.13 g, 84%) as a colorless oil; $[\alpha]_D^{22} +3.24$ (*c* 1.00 in CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ 3391 (NHCO), 1720 (CO); δ_{H} (500 MHz; CDCl₃) 1.40-1.48 (2H, m), 1.50-1.64 (4H, m), 3.11-3.22 (3H, m), 3.60 (1H, t, *J* 6.9), 4.85 (1H, br s), 5.21 (2H, s), 5.37 (1H, d, *J* 10.3), 5.51 (1H, d, *J* 16.6), 5.58-5.68 (1H, m), 7.24-7.29 (2H, m), 7.36-7.44 (2H, m), 7.69-7.77 (3H, m), 8.18-8.22 (1H, m); δ_{C} (125 MHz; CDCl₃) 23.9, 26.4, 29.2, 40.7, 46.9, 47.8, 63.8, 122.1, 124.3, 126.9, 129.2, 129.3, 129.5 (2C), 129.7, 131.2, 132.1, 133.5, 134.3 (2C), 148.5, 156.1; *m/z* (FAB) 494.1151 ([M+H]⁺, C₂₂H₂₅ClN₃O₆S requires 494.1153).

tert-Butyl

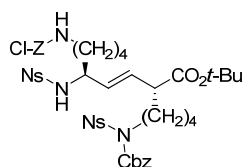
(4*R*,5*S*,2*E*)-9-[*N*-(2-chlorobenzoyloxycarbonyl)amino]-4,5-[*N*-(2-nitrophenylsulfonyl)epimino]non-2-enoate (**6**).



Ozone gas was bubbled through a solution of the aziridine **5** (164 mg, 0.33 mmol) in EtOAc (1.7 cm³) at -78 °C until a blue color persisted. Me₂S (0.49 cm³, 6.64 mmol) was added to the solution at -78 °C. After being stirred for 5 min at the same temperature, the reaction mixture was concentrated under reduced pressure to give the crude aldehyde, which was used for the next reaction without further purification. To a suspension of LiCl (35 mg, 0.83 mmol) in CH₃CN (1.4 cm³) were added (EtO)₂P(O)CH₂CO₂*t*-Bu (0.20 cm³, 0.83 mmol) and (*i*-Pr)₂NEt (0.15 cm³, 0.83 mmol) at 0 °C under Ar, and the reaction mixture was stirred for 1 h at the same temperature under Ar. The above aldehyde in CH₃CN (0.7 cm³) was added to the mixture at 0 °C, and the mixture was stirred for 3 h at room temperature. The reaction was quenched by saturated NH₄Cl and then diluted with excess diethyl ether. The organic layer was washed with brine and dried over MgSO₄. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane-EtOAc (2:1) gave the aziridinyl enoate **6** (91 mg, 46%) as a colorless oil; [α]_D²³ -14.7 (*c* 0.93 in CHCl₃); ν_{max}/cm⁻¹ 3402 (NHCO), 1710 (CO); δ_H (500 MHz; CDCl₃) 1.39-1.61 (15H, m), 3.10-3.28 (3H, m), 3.67 (1H, t, *J* 7.5), 5.04 (1H, br s), 5.20 (2H, s), 6.12 (1H, d, *J* 16.0), 6.57 (1H, dd, *J* 16.0 and 7.5), 7.20-7.47 (4H, m), 7.67-7.83 (3H, m), 8.16-8.23 (1H, m); δ_C (100 MHz; CDCl₃) 24.0, 26.7, 28.0 (3C), 29.1, 40.7, 46.0, 47.3, 63.9, 81.1, 124.4, 126.9, 129.0, 129.3, 129.5, 129.7, 131.4, 131.9, 132.3, 133.5, 134.3, 134.6, 137.1, 148.5, 156.1, 164.6; *m/z* (FAB) 592.1527 ([*M*-H]⁻, C₂₇H₃₁ClN₃O₈S requires 592.1520).

tert-Butyl

(2*R*,5*S*,3*E*)-2-{4-[*N*-(benzyloxycarbonyl)-*N*-(2-nitrophenylsulfonyl)amino]butyl}-9-[*N*-(2-chlorobenzoyloxycarbonyl)amino]-5-[*N*-(2-nitrophenylsulfonyl)amino]non-3-enoate (**8**).

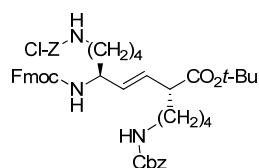


To a solution of the TBS ether **7** (735 mg, 0.94 mmol) in CH₃CN-CH₃OH (20:3, 11.5 cm³) at 0 °C was added aqueous H₂SiF₆ (3.28 M, 0.14 cm³, 0.47 mmol), and the mixture was stirred at 0 °C for 30 min. After quenched with saturated NaHCO₃ and diluted with diethyl ether, the organic layer was washed with brine and dried over MgSO₄ and the concentrated under reduced pressure to give the crude alcohol, which was used for the next reaction without

further purification. To a solution of the crude alcohol, PPh₃ (320 mg, 1.22 mmol) and CbzNHNs (411 mg, 1.22 mmol) in THF (18 cm³) was added dropwise DIAD in toluene solution (1.9 M, 0.64 cm³, 1.22 mmol) at 0 °C under Ar and the mixture was stirred 4 h at room temperature. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane-EtOAc (2:1 to 3:2) gave the title compound **8** (751 mg, 81%) as a colorless oil; $[\alpha]_D^{23} -71.5$ (*c* 1.00 in CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ 3346 (NHCO), 1723 (CO); δ_{H} (500 MHz; CDCl₃) 1.06-1.70 (21H, m), 2.63 (1H, dt, *J* 8.0 and 6.9), 3.10-3.23 (2H, m), 3.75-3.78 (2H, m), 3.86-3.98 (1H, m), 4.88 (1H, br s), 5.12 (2H, s), 5.21 (2H, s), 5.25 (1H, dd, *J* 15.5 and 7.5), 5.36 (1H, dd, *J* 15.5 and 8.6), 5.38 (1H, d, *J* 8.6), 7.20-7.27 (4H, m), 7.31-7.39 (4H, m), 7.41-7.46 (2H, m), 7.66 (1H, dt, *J* 7.4 and 1.1), 7.69-7.73 (3H, m), 7.83-7.87 (1H, m), 8.07-8.11 (2H, m); δ_{C} (125 MHz; CDCl₃) 22.5, 23.8, 28.0 (3C), 29.3, 29.6, 31.7, 35.6, 40.7, 47.9, 49.1, 56.7, 63.8, 69.4, 80.8, 124.3, 125.3, 126.9, 128.6 (2C), 128.7 (2C), 128.8, 129.2, 129.4, 129.7, 130.9 (2C), 131.2, 131.6, 132.7, 132.8, 133.4, 133.5, 134.1 (2C), 134.3, 134.4, 134.9, 147.7, 147.8, 151.6, 156.2, 172.6; *m/z* (FAB) 984.2545 ([M-H]⁻, C₄₅H₅₁ClN₅O₁₄S₂ requires 984.2562).

***tert*-Butyl (2*R*,5*S*,3*E*)-5-**

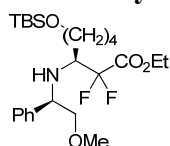
[*N*-(9-fluorenylmethoxycarbonyl)amino]-2-{4-[*N*-(benzyloxycarbonyl)amino]butyl}-9-[*N*-(2-chlorobenzyloxycarbonyl)amino]non-3-enoate (9**).**



To a solution of protected amine **8** (700 mg, 0.71 mmol) in DMF (7.0 cm³) were added K₂CO₃ (589 mg, 4.26 mmol) and PhSH (0.33 cm³, 3.20 mmol) at 0 °C, and the mixture was stirred for 3 h at room temperature. After dilution with EtOAc, and the organic layer was washed with water, brine and dried over Na₂SO₄. The solution was concentrated under reduced pressure to give the Ns-deprotected amine, which was used for the next reaction without further purification. To a solution of the crude amine were added Fmoc-OSu (287 mg, 0.85 mmol) and Et₃N (0.12 cm³, 0.85 mmol) at 0 °C, the mixture was stirred for 30 min at room temperature. The reaction was quenched by saturated NH₄Cl and then diluted with EtOAc. The organic layer was washed with brine and dried over MgSO₄. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane-EtOAc (2:1) gave the title compound **9** (498 mg, 84%) as a semisolid; $[\alpha]_D^{23} -17.6$ (*c* 0.73 in CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ 3332 (NHCO), 1704 (CO); δ_{H} (500 MHz; CDCl₃) 1.17-1.73 (21H, m), 2.74-2.88 (1H, m), 3.06-3.24 (4H, m), 4.02-4.16 (1H, m), 4.15-4.24 (1H, m), 4.32-4.50 (2H, m), 4.72-5.00 (2H, m), 5.00-5.27 (5H, m), 5.29-5.64 (2H, m), 7.21-7.42 (13H, m), 7.55-7.60 (2H, m), 7.75 (2H, d, *J* 7.5); δ_{C} (125 MHz; CDCl₃) 22.6, 24.1, 28.0 (3C), 29.4, 29.5, 31.8, 34.6,

40.7, 40.8, 47.2, 49.6, 52.5, 63.8, 66.5 (2C), 80.6, 119.9 (2C), 124.9 (2C), 125.0 (2C), 126.8 (2C), 127.0, 127.6 (2C), 128.0, 128.1, 128.5 (2C), 129.3, 129.4, 129.7, 132.6, 134.3, 136.6, 141.3, 143.9 (4C), 156.2 (2C), 156.4, 173.2; m/z (FAB) 838.3828 ($[M+H]^+$, $C_{48}H_{57}ClN_3O_8$ requires 838.3834).

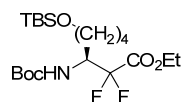
Ethyl (*S*)-7-(*tert*-butyldimethylsiloxy)-2,2-difluoro-3-{*N*-[(*S*)-2-methoxy-1-phenylethyl]amino}heptanoate (12**).**



To a solution of oxalyl chloride (2.4 cm³, 28.1 mmol) in CH₂Cl₂ (80 cm³) was added dropwise a solution of DMSO (1.8 cm³, 25.7 mmol) in CH₂Cl₂ (90 cm³) at -78 °C under argon. After 10 min, a solution of the alcohol **11** (5.1 g, 23.4 mmol) in CH₂Cl₂ (80 cm³) was added. After stirring for 15 min at -78 °C, Et₃N (16 cm³, 117 mmol) was added and the mixture was stirred for 1 h at -78 °C. The reaction was quenched by dilution with CH₂Cl₂ at room temperature and the mixture was extracted. The organic layer was washed with saturated NH₄Cl and brine, and dried over MgSO₄. Concentration under reduced pressure gave an aldehyde, which was used immediately in the next step without further purification. A solution of the above aldehyde and (*S*)-2-methoxy-1-phenylethylamine (3.65 g, 24.1 mmol) in THF (85 cm³) was stirred for 4 h at 0 °C under argon in the presence of activated molecular sieves 3Å. To the mixture were added a suspension of Wilkinson's catalyst (1.1 g, 1.17 mmol) in THF (70 cm³), BrCF₂CO₂Et (3.3 cm³, 25.7 mmol), and a solution of Et₂Zn in hexane (1.0 M, 94 cm³, 93.6 mmol). After being stirred for 1 h at 0 °C, the reaction was quenched with saturated NaHCO₃. The mixture was filtered and the filtrate was extracted with EtOAc. The extract was washed with saturated NaHCO₃ and brine, and dried over MgSO₄. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane-EtOAc (50:1) gave the title compound **12** (4.74 g, 43% yield) as a colorless oil: $[\alpha]_D^{23}$ -30.7 (*c* 1.29 in CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ 3354 (NH), 1769 (CO); δ_H (500 MHz; CDCl₃) 0.04 (6H, s), 0.89 (9H, s), 1.16-1.63 (9H, m), 2.05 (1H, br s), 2.91-3.03 (1H, m), 3.33-3.45 (2H, m), 3.35 (3H, s), 3.52 (2H, t, *J* 6.3), 4.26 (1H, dd, *J* 8.6 and 4.0), 4.29-4.37 (2H, m), 7.25-7.34 (5H, m); δ_C (100 MHz; CDCl₃) -5.3 (2C), 13.9, 18.3, 22.1, 25.9 (3C), 29.8, 32.5, 56.4 (t, *J* 22.3), 58.6, 59.7, 62.6, 62.8, 77.8, 117.7 (t, *J* 256.6), 127.7, 128.0 (2C), 128.4 (2C), 140.3, 164.2 (t, *J* 32.7); δ_F (375 MHz; CDCl₃) -112.5 (dd, *J* 256.6 and 12.4), -110.4 (dd, *J* 256.6 and 10.3); m/z (FAB) 474.2856 ($[M+H]^+$, $C_{24}H_{42}F_2NO_4Si$ requires 474.2851).

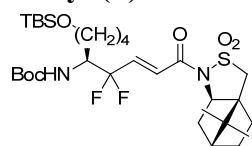
Ethyl

(*S*)-3-[*N*-(*tert*-butoxycarbonyl)amino]-7-(*tert*-butyldimethylsiloxy)-2,2-difluoroheptanoate (13**).**



To a solution of the ester **12** (2.77 g, 5.85 mmol) in EtOH (57 cm³) was added 20% palladium hydroxide on carbon (822 mg, 1.17 mmol) and (Boc)₂O (2.55 g, 11.7 mmol). The suspension was stirred over night under H₂ (balloon) at room temperature. The mixture was filtered through a pad of Celite. Concentration of the filtrate under reduced pressure followed by flash chromatography over silica gel with *n*-hexane-EtOAc (19:1) gave the title compound **13** (2.25 g, 87 % yield) as a colorless oil; $[\alpha]_D^{22}$ -14.4 (*c* 1.40 in CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ 3361 (NHCO), 1769 (CO), 1714 (CO); δ_{H} (500 MHz; CDCl₃) 0.04 (6H, s), 0.89 (9H, s), 1.31-1.80 (18H, m), 3.55-3.66 (2H, m), 4.19-4.38 (3H, m), 4.55 (1H, d, *J* 10.3); δ_{C} (100 MHz; CDCl₃) -5.4 (2C), 13.8, 18.3, 21.8, 25.9 (3C), 27.4, 28.2 (3C), 32.2, 52.7 (dd, *J* 27.3 and 24.0), 62.7, 63.0, 80.1, 114.5 (t, *J* 254.9), 155.1, 163.4 (t, *J* 32.3); δ_{F} (375 MHz; CDCl₃) -120.0 (dd, *J* 256.6 and 18.6), -113.6 (dd, *J* 256.6 and 6.2); *m/z* (FAB) 440.2640 ([M+H]⁺, C₂₀H₄₀F₂NO₅Si requires 440.2644).

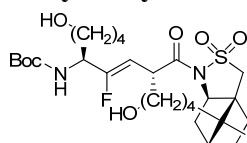
(5*S*,2*E*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-9-(*tert*-butyldimethylsiloxy)-4,4-difluoronon-2-enoyl (*S*)-sultam (14**).**



To a solution of the ester **13** (500 mg, 1.14 mmol) in CH₂Cl₂ (12 cm³) at -78 °C under argon was added dropwise a solution of DIBAL-H in toluene (0.99 M, 1.85 cm³, 1.82 mmol), and the mixture was stirred for 2 h at -78 °C. The reaction was quenched with aqueous 0.5 N Rochelle salt and extracted with Et₂O. The extract was washed with brine and dried over MgSO₄. Concentration under reduced pressure gave the aldehyde as an oil, which was used immediately in the next step without purification. To a stirred solution of (*S*)-*N*-(diethoxyphosphonoacetyl)camphorsultam (583 mg, 1.48 mmol) in CH₃CN (15 cm³) at 0 °C under argon were added LiCl (63 mg, 1.48 mmol) and *i*-Pr₂NEt (0.254 cm³, 1.48 mmol). After stirring for 30 min, a solution of the above aldehyde in CH₃CN (5.0 cm³) was added to the mixture at 0 °C, and the mixture was stirred for 2 h at room temperature. The reaction was quenched with saturated NH₄Cl and extracted with Et₂O. The extract was washed with brine and dried over MgSO₄. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane-EtOAc (6:1) gave the title compound **14** (633 mg, 87% yield) as a colorless solid. (Found: C, 56.65; H, 8.34; N, 4.28. C₃₀H₅₂F₂N₂O₆SSi requires C, 56.75; H, 8.26; N, 4.41%); mp 48-49 °C; $[\alpha]_D^{23}$ -60.6 (*c* 1.20 in CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ 3347 (NHCO), 1716 (CO); δ_{H} (500 MHz; CDCl₃) 0.04 (6H, s), 0.88 (9H, s), 0.98 (3H, s), 1.17 (3H, s), 1.33-1.60 (16H, m), 1.69-1.81 (1H, m), 1.84-2.00 (3H, m), 2.08-2.17 (2H, m),

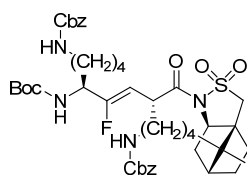
3.45 (1H, d, *J* 13.8), 3.53 (1H, d, *J* 13.8), 3.56-3.66 (2H, m), 3.94 (1H, t, *J* 6.3), 3.97-4.09 (1H, m), 4.53 (1H, d, *J* 10.3), 6.86 (1H, dd, *J* 24.1 and 15.5), 6.92 (1H, dd, *J* 61.3 and 15.5); δ_C (100 MHz; CDCl₃) -5.4 (2C), 18.3, 19.8, 20.8, 21.9, 25.9 (3C), 26.4, 28.1, 28.2 (3C), 32.2, 32.8, 38.3, 44.7, 47.8, 48.6, 53.0, 54.5 (t, *J* 27.3), 62.7, 65.1, 79.9, 119.6 (t, *J* 246.6), 125.4 (t, *J* 7.4), 137.9 (t, *J* 26.5), 155.4, 162.2; δ_F (375 MHz; CDCl₃) -110.4 (dt, *J* 248.3 and 12.4), -108.6 (dt, *J* 248.3 and 10.3).

(2*R*,5*S*,3*Z*)-5-[*N*-(*tert*-Butoxycarbonyl)amino]-4-fluoro-2-(4-hydroxybutyl)-9-hydroxynon-3-enoyl (*S*)-sultam (17**).**



To a solution of *N*-enoyl sultam **15** (3.74g, 4.67 mmol) in EtOH (150 cm³) was added 4.2% palladium-activated carbon ethylenediamine complex (1.18 g, 0.467 mmol), and the reaction mixture was stirred for 12 h under H₂ (balloon) at room temperature. The mixture was filtered through a pad of Celite. Concentration of the filtrate under reduced pressure gave the reduced sultam **16**, which was used for the next reaction without further purification. To a solution of the reduced sultam **16** in CH₃CN/H₂O (20/3, 46 cm³) at 0 °C was added aqueous H₂SiF₆ (3.28 M, 1.3 cm³, 4.40 mmol), and the mixture was stirred at room temperature for 1 h. After quenched with saturated NaHCO₃ and diluted with EtOAc, the organic layer was washed with brine and dried over MgSO₄. Concentration under reduced pressure followed by flash chromatography over silica gel with *n*-hexane-EtOAc (1:1 to 1:4) gave the corresponding diol **17** (2.09 g, 78% yield) as a colorless amorphous.; $[\alpha]_D^{23}$ -80.4 (*c* 0.80 in CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ 3379 (NHCO), 1692 (CO); δ_H (500 MHz; CDCl₃) 0.97 (3H, s), 1.15 (3H, s), 1.30-1.69 (21H, m), 1.79-2.14 (7H, m), 3.44 (1H, d, *J* 13.8), 3.51 (1H, d, *J* 13.8), 3.59 (2H, t, *J* 6.9), 3.60 (2H, t, *J* 6.9), 3.88 (1H, t, *J* 6.3), 4.05-4.25 (2H, m), 4.84 (1H, d, *J* 8.0), 4.96 (1H, dd, *J* 36.7 and 9.2); δ_C (125 MHz; CDCl₃) 19.8, 20.7, 21.7, 22.8, 26.4, 28.3 (3C), 31.7, 31.9, 32.0, 32.7, 33.5, 38.3, 41.0, 44.5, 47.7, 48.3, 51.8 (d, *J* 26.4), 53.0, 62.3 (2C), 65.1, 79.7, 104.1 (d, *J* 10.8), 155.0, 158.3 (d, *J* 262.7), 173.1; δ_F (470 MHz; CDCl₃) -120.8 - -121.0 (m); *m/z* (FAB) 575.3179 ([M+H]⁺, C₂₈H₄₈FN₂O₇S requires 575.3166).

(2*R*,5*S*,3*Z*)-2-{4-[*N*-(Benzyloxycarbonyl)amino]butyl}-9-[*N*-(benzyloxycarbonyl)amino]-5-[*N*-(*tert*-butoxycarbonyl)amino]-4-fluoronon-3-enoyl (*S*)-sultam (18**).**



To a solution of diol **17** (860 mg, 1.50 mmol) in CH₂Cl₂ (10 cm³) were added TsCl (1.14 g,

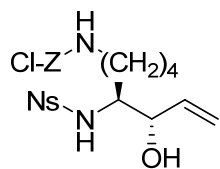
5.99 mmol) and Et₃N (1.0 cm³, 7.48 mmol) were added at 0 °C, and the resulting mixture was stirred for 5 h at room temperature. The reaction was quenched by saturated NH₄Cl, and the organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was dissolved in DMF (5.0 cm³), and then NaN₃ (973 mg, 15.0 mmol) was added to the solution. The reaction mixture was stirred for 14 h at room temperature and then diluted with Et₂O. The organic layer was washed with H₂O, brine and dried over MgSO₄, and then concentrated under reduced pressure. The residue was dissolved in *n*-hexane-EtOAc (3:1), and the solution was filtered on silica gel bed. The filtrate was concentrated under reduced pressure. The residue was dissolved in THF/H₂O (2/1, 11 cm³), and PPh₃ (1.29 g, 4.91 mmol) was added to the solution. The mixture was stirred for 24 h at room temperature. The resulting solution was concentrated under reduced pressure. The residue was dissolved in DMF (5.0 cm³), and then Z-OSu (860 mg, 3.45 mmol) and Et₃N (0.69 cm³, 4.91 mmol) were added to the solution at 0 °C. The resulting mixture was stirred for 5 h at room temperature. The reaction was quenched by saturated NH₄Cl and then diluted with EtOAc. The organic layer was washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel with *n*-hexane-EtOAc (3:2) to give the title compound **18** (822 mg, 65% yield) as a semisolid. $[\alpha]_D^{27} -60.0$ (*c* 1.00 in CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ 3362 (NHCO), 1702 (CO); δ_{H} (500 MHz; CDCl₃) 0.89 (3H, s), 1.09 (3H, s), 1.20-2.06 (28H, m), 3.02-3.32 (6H, m), 3.78-3.86 (1H, m), 4.02-4.18 (2H, m), 4.79 (1H, br s), 4.88 (1H, br s), 4.92 (1H, dd, *J* 36.1 and 8.6), 5.04-5.22 (5H, m), 7.29-7.41 (10H, m); δ_{C} (125 MHz; CDCl₃) 20.0, 20.9, 23.0, 24.0, 26.5, 28.5 (3C), 29.4, 29.9, 31.8, 32.8, 33.7, 38.5, 40.8, 40.9, 41.1, 44.7, 47.9, 48.4, 52.1 (d, *J* 26.4), 53.0, 65.3, 66.7 (2C), 79.9, 104.8 (d, *J* 13.2), 128.2 (2C), 128.3 (2C), 128.4 (2C), 128.7 (4C), 136.8, 136.9, 155.1, 156.5, 156.7, 158.4 (d, *J* 262.7), 173.2; δ_{F} (470 MHz; CDCl₃) -121.8 - -123.1 (m); *m/z* (FAB) 841.4224 ([M+H]⁺, C₄₄H₆₂FN₄O₉S requires 841.4222).

Peptides 20E-23E.

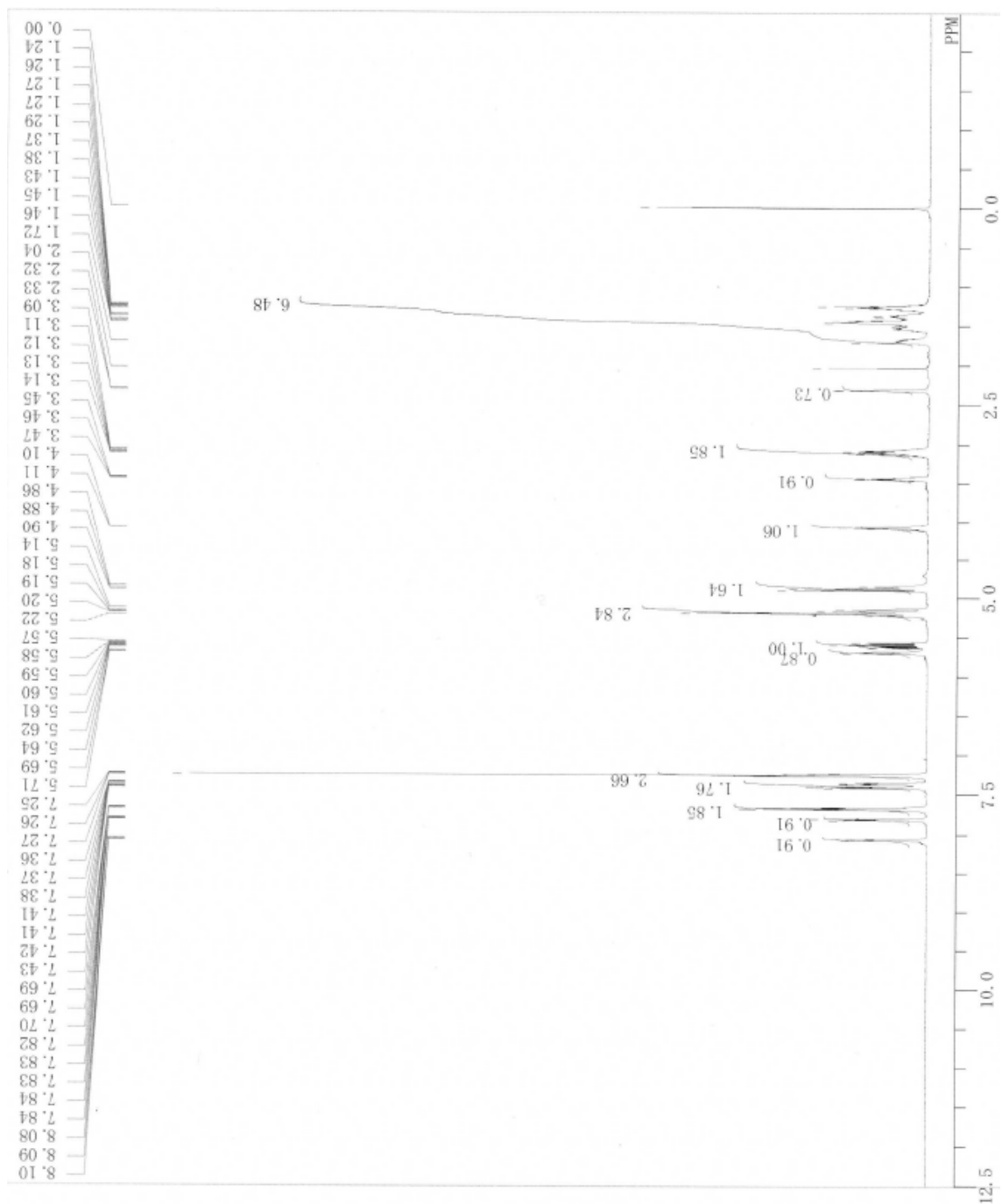
EADI was employed in Fmoc-based SPPS. The peptides were yielded as TFA salts (**20E**: 13 mg, **21E**: 5 mg, **22E**: 4 mg, **23E**: 5 mg); TOF-MS (MALDI), MW calcd for ([M+H]⁺) 3763.22, found: 3763.97 (**20E**), 3763.43 (**21E**), 3762.95 (**22E**), 3762.95 (**23E**).

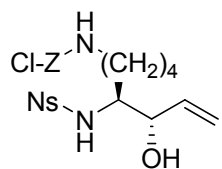
Peptides 20F-23F

FADI was employed in Fmoc-based SPPS. The peptides were yielded as TFA salts (**20F**: 33 mg, **21F**: 12 mg, **22F**: 6 mg, **23F**: 21 mg); TOF-MS (MALDI), MW calcd for ([M+H]⁺) 3781.21, found: 3781.62 (**20F**), 3781.08 (**21F**), 3781.98 (**22F**), 3781.32 (**23F**).

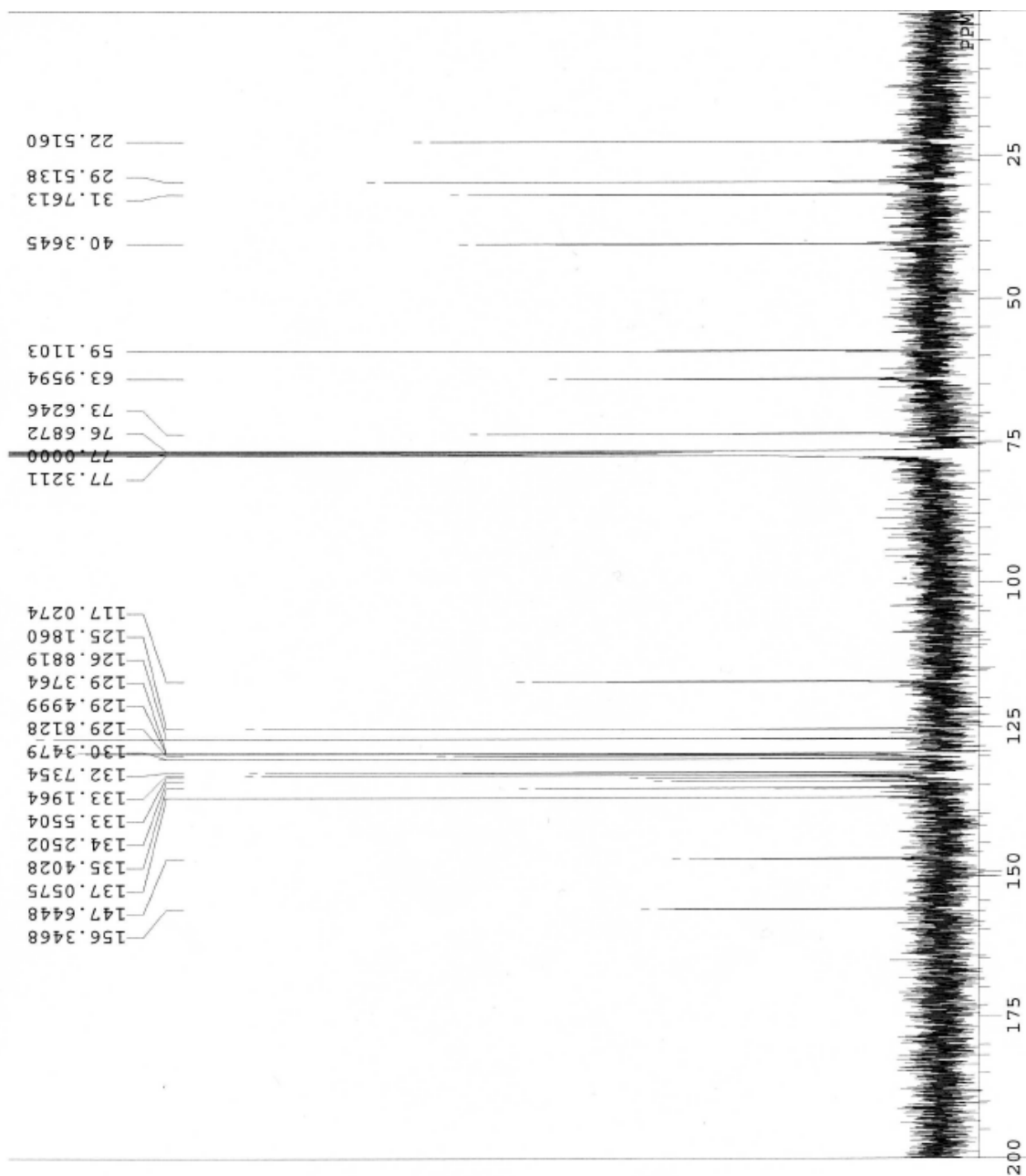


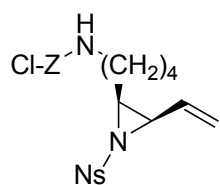
4 (500 MHz, CDCl₃)



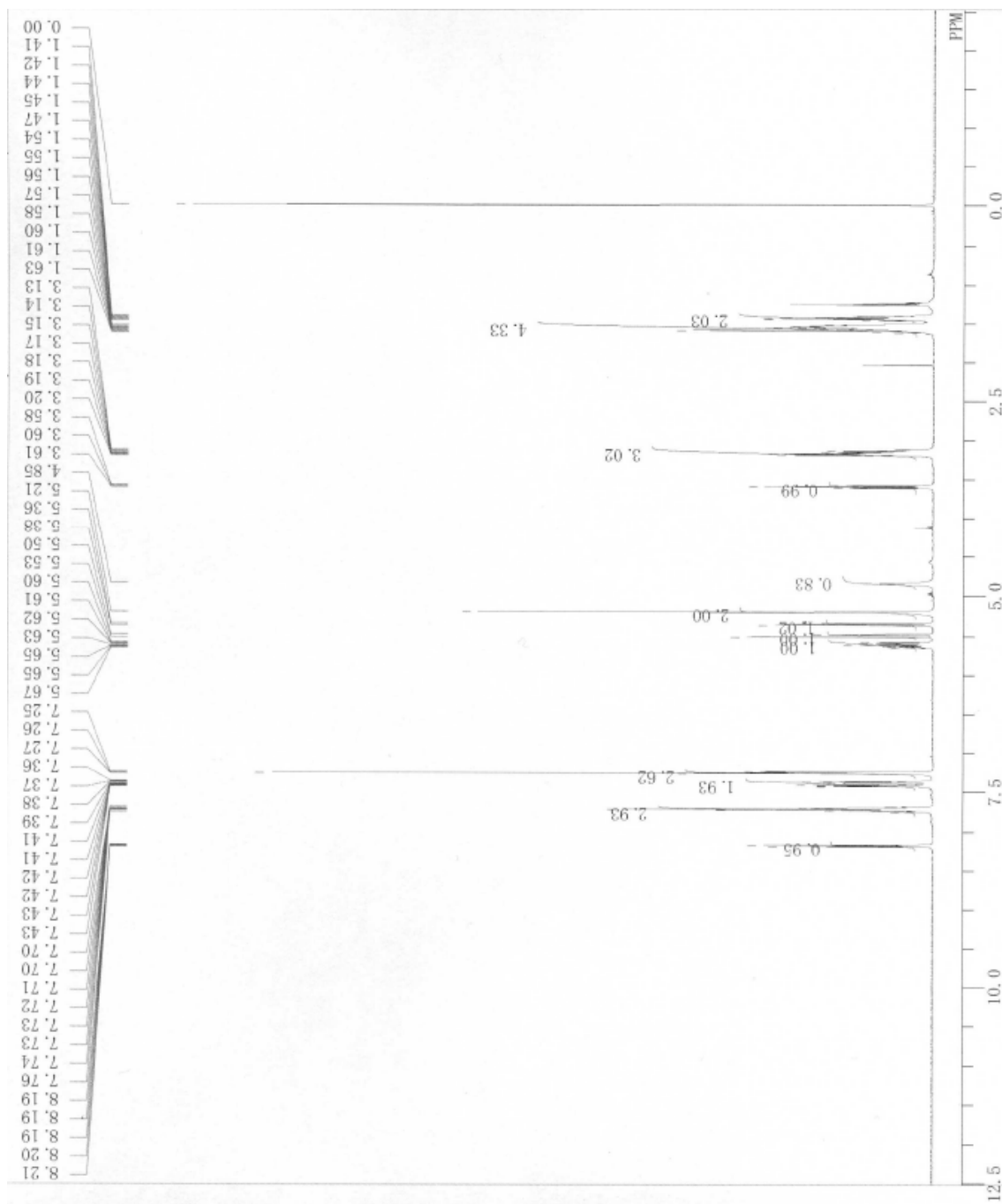


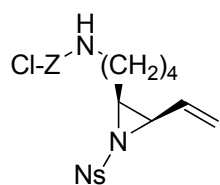
4 (100 MHz, CDCl₃)



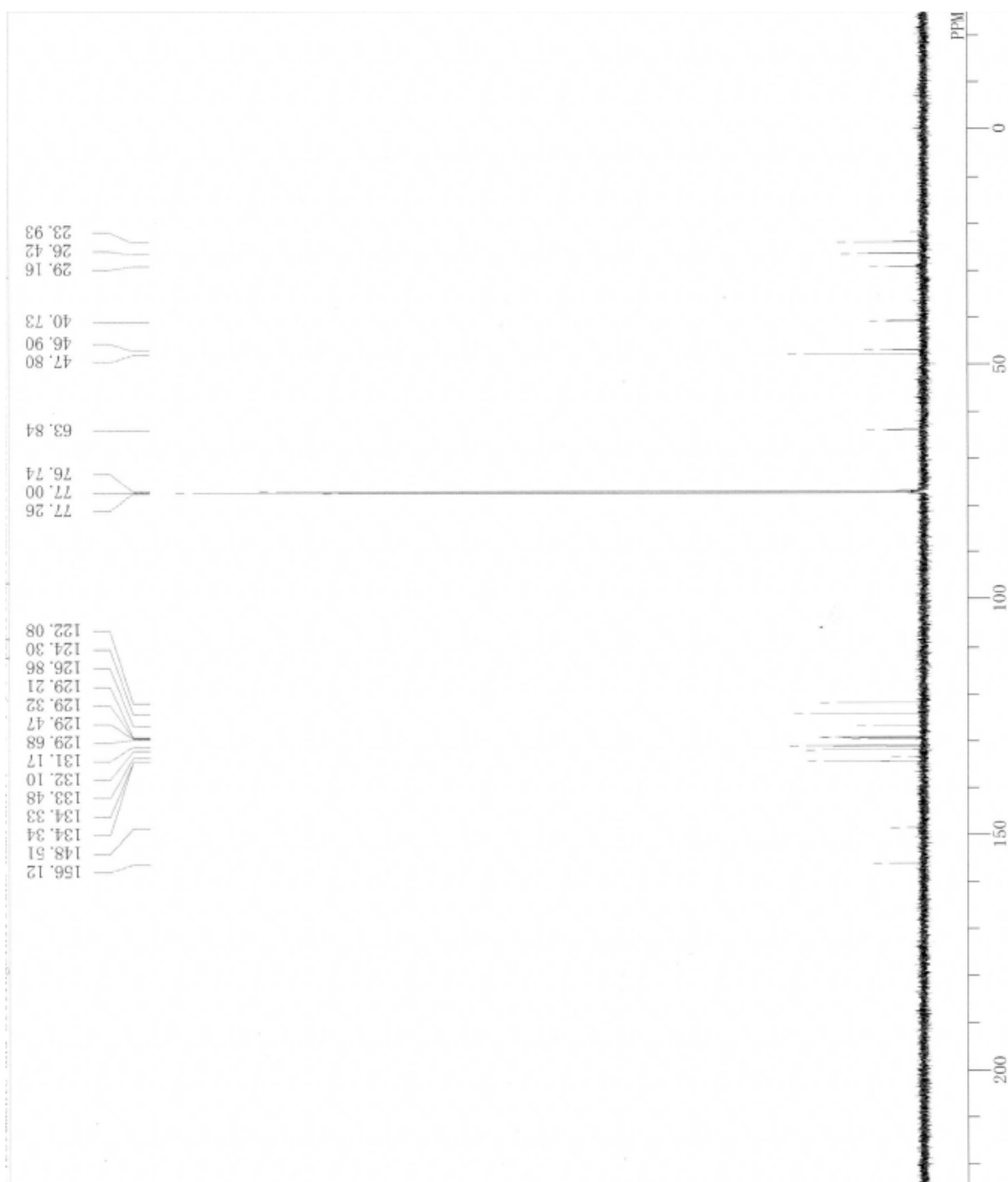


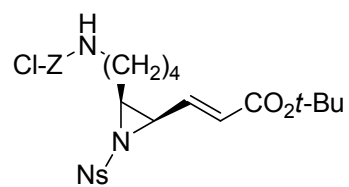
5 (500 MHz, CDCl₃)



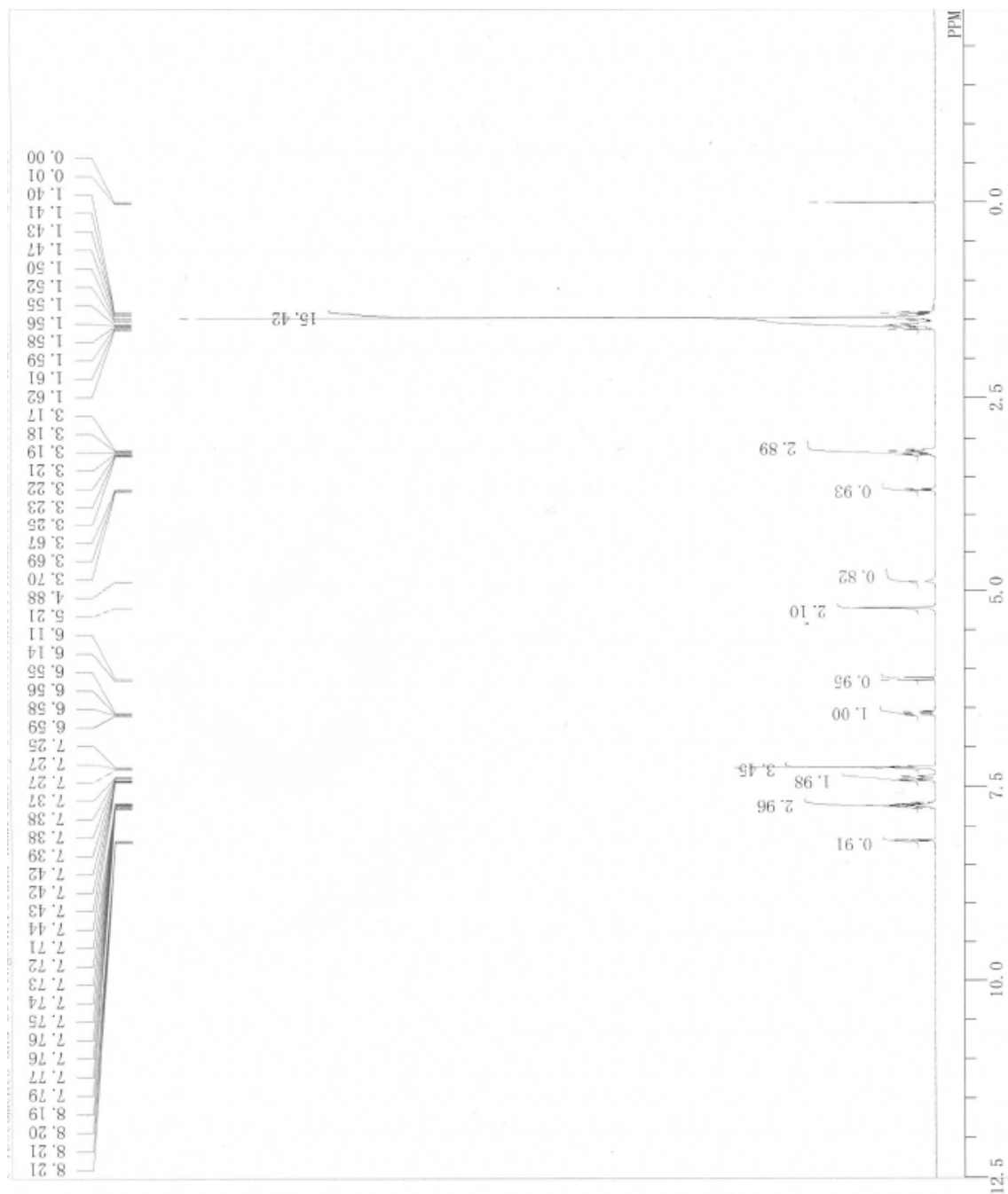


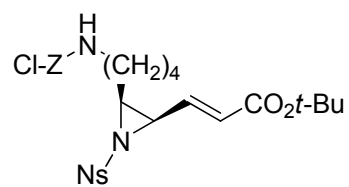
5 (125 MHz, CDCl₃)



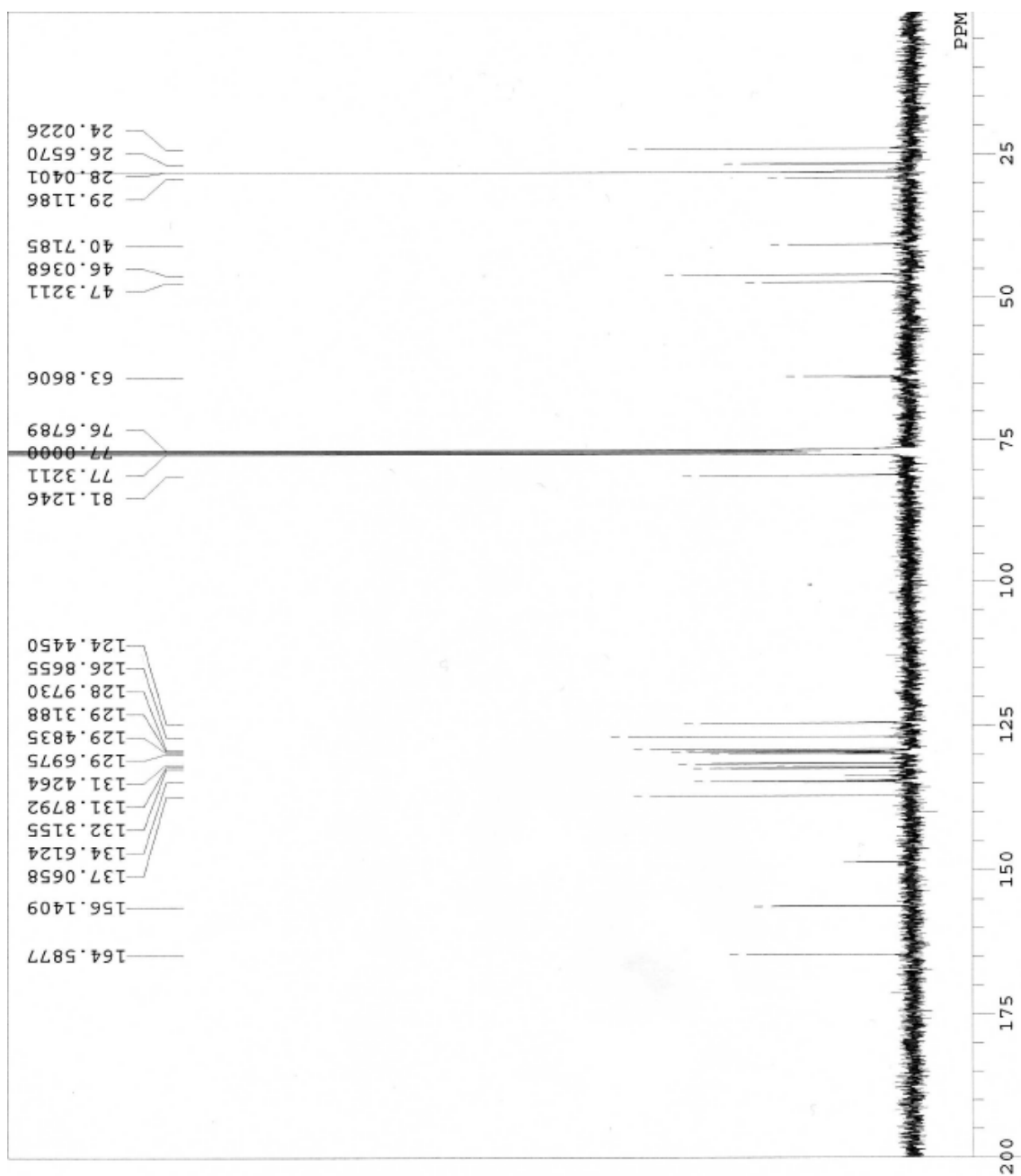


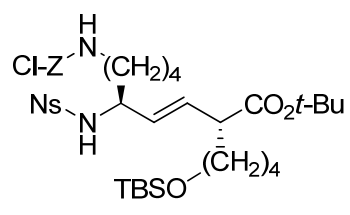
6 (500 MHz, CDCl₃)



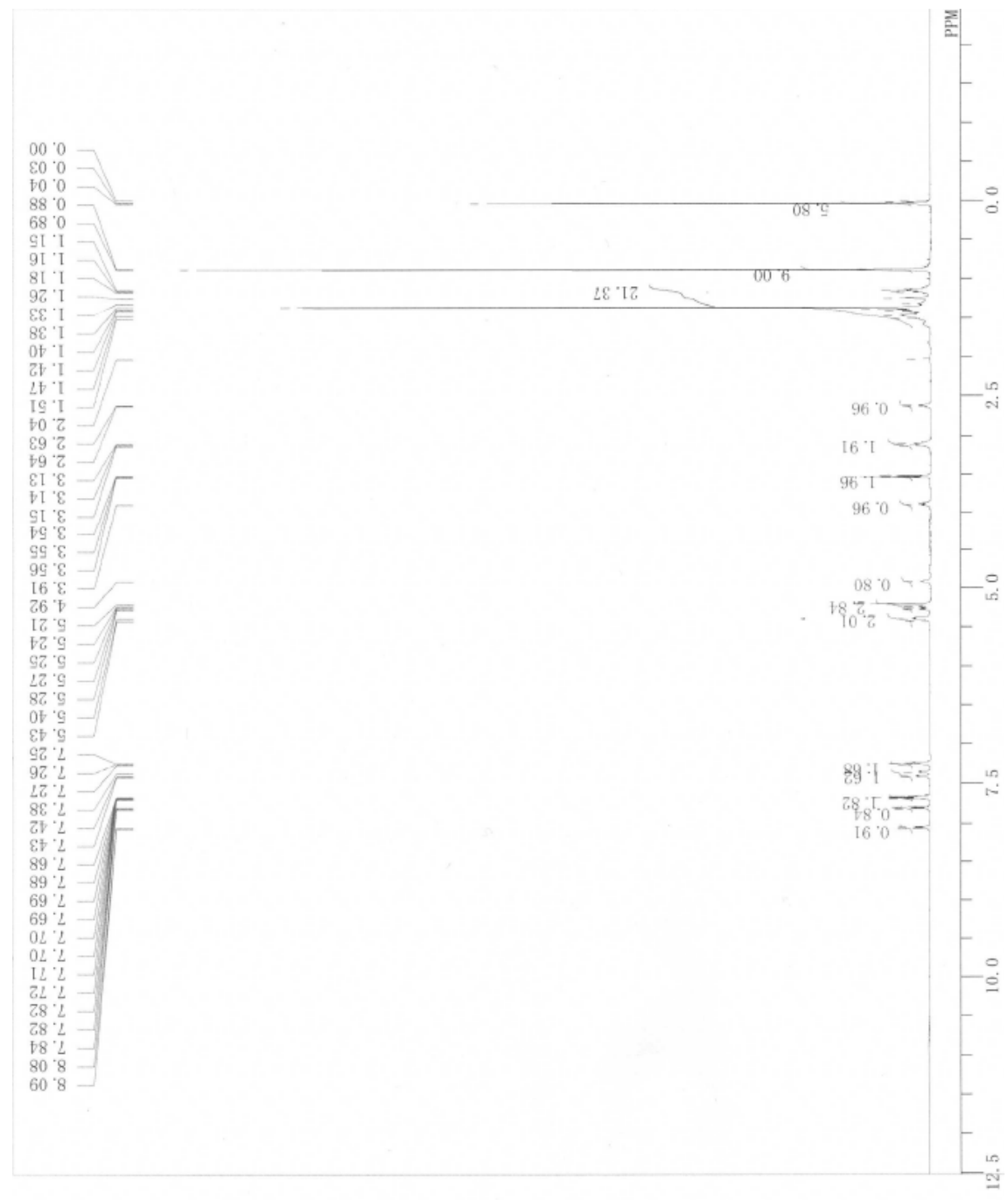


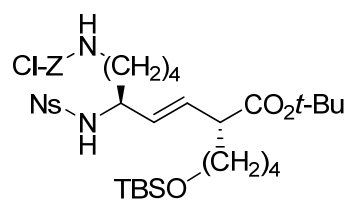
6 (100 MHz, CDCl₃)



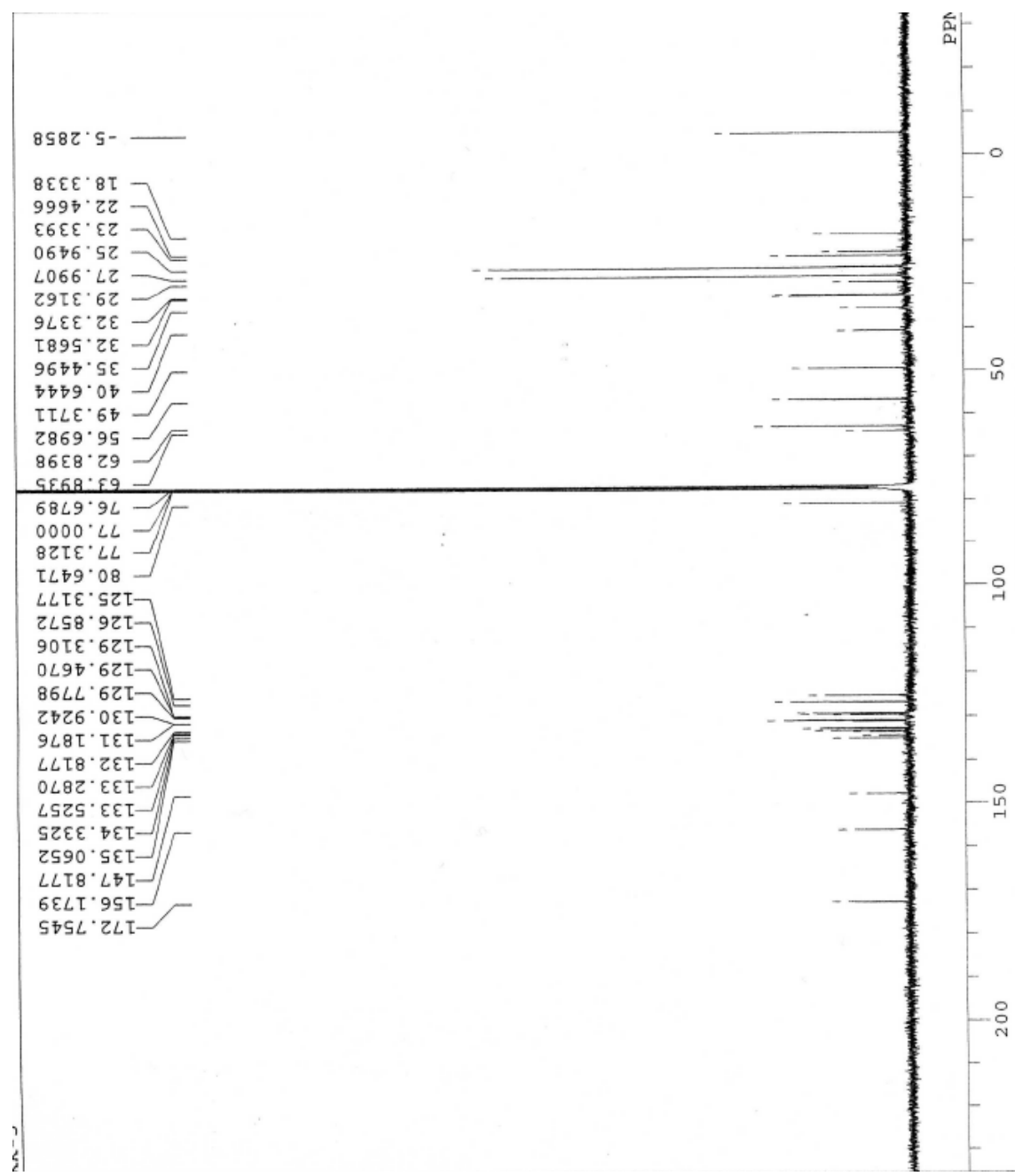


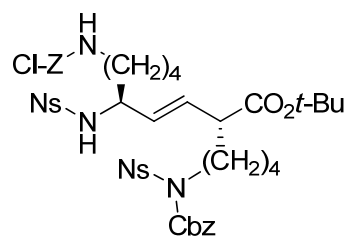
7 (500 MHz, CDCl₃)



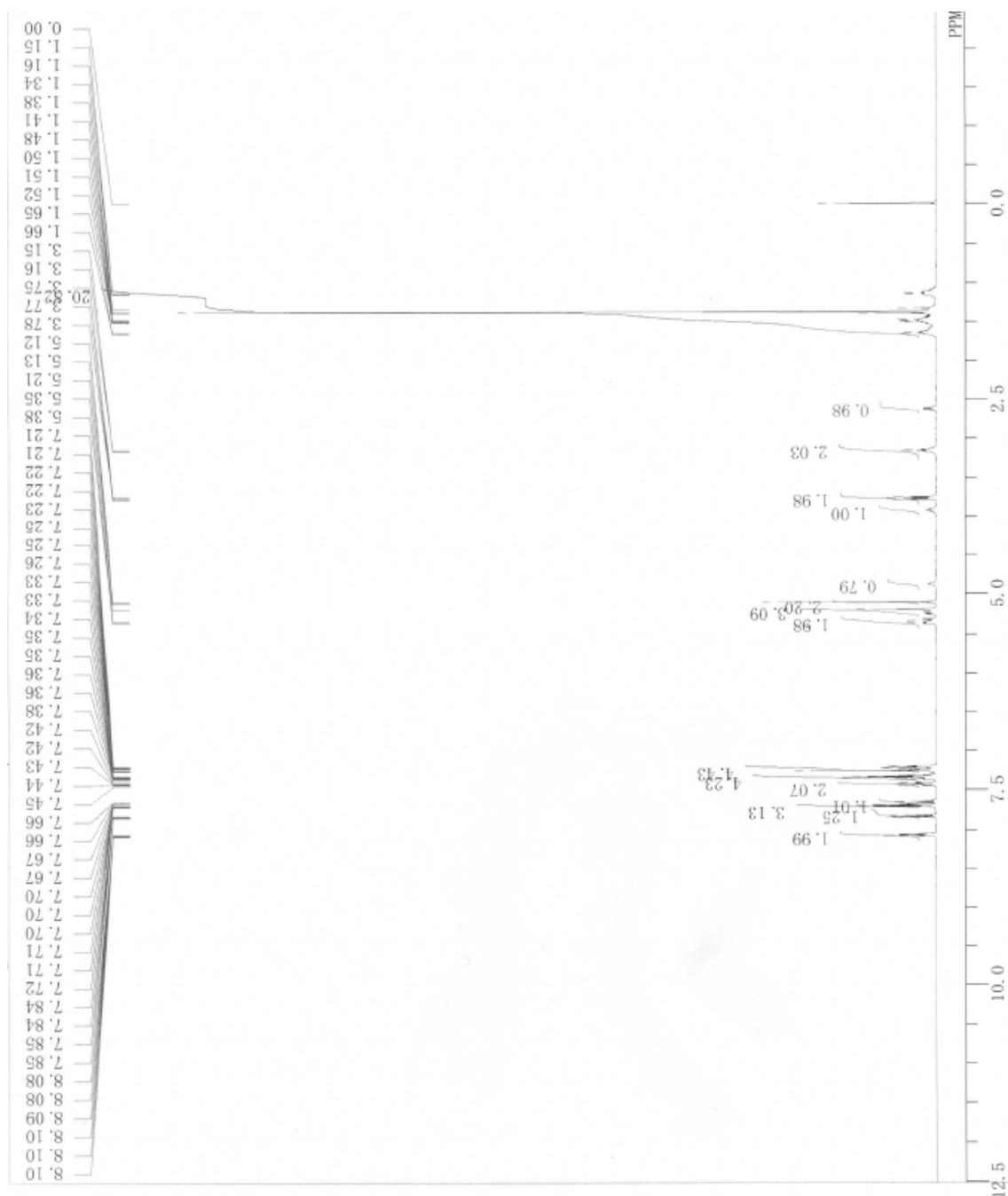


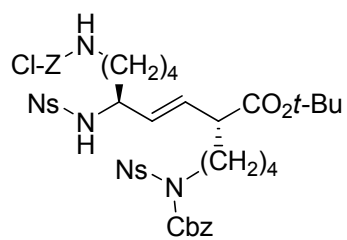
7 (100 MHz, CDCl₃)



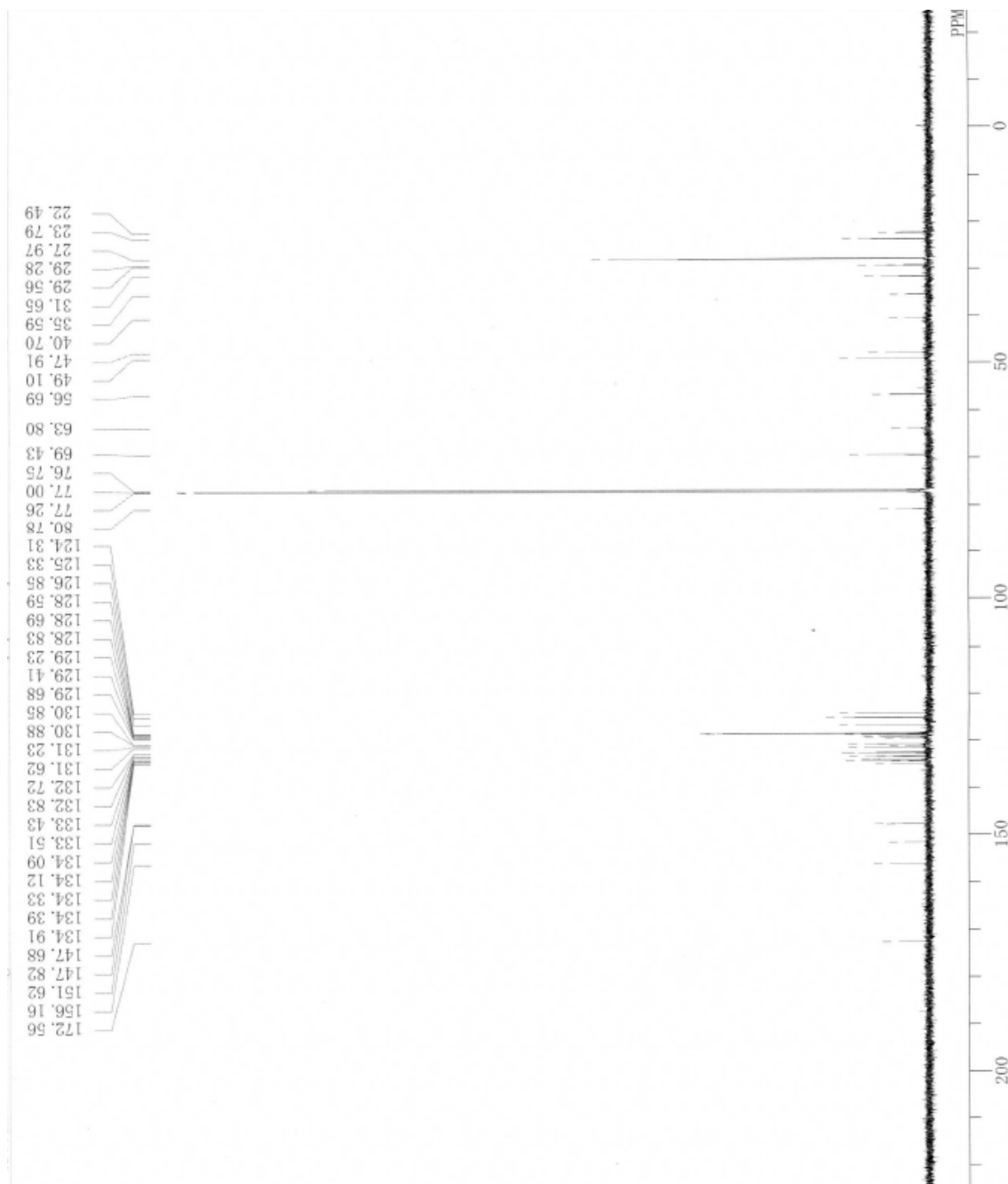


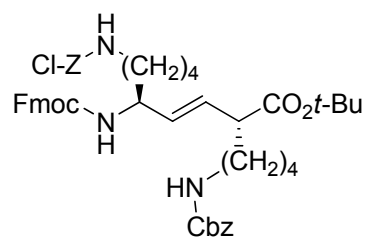
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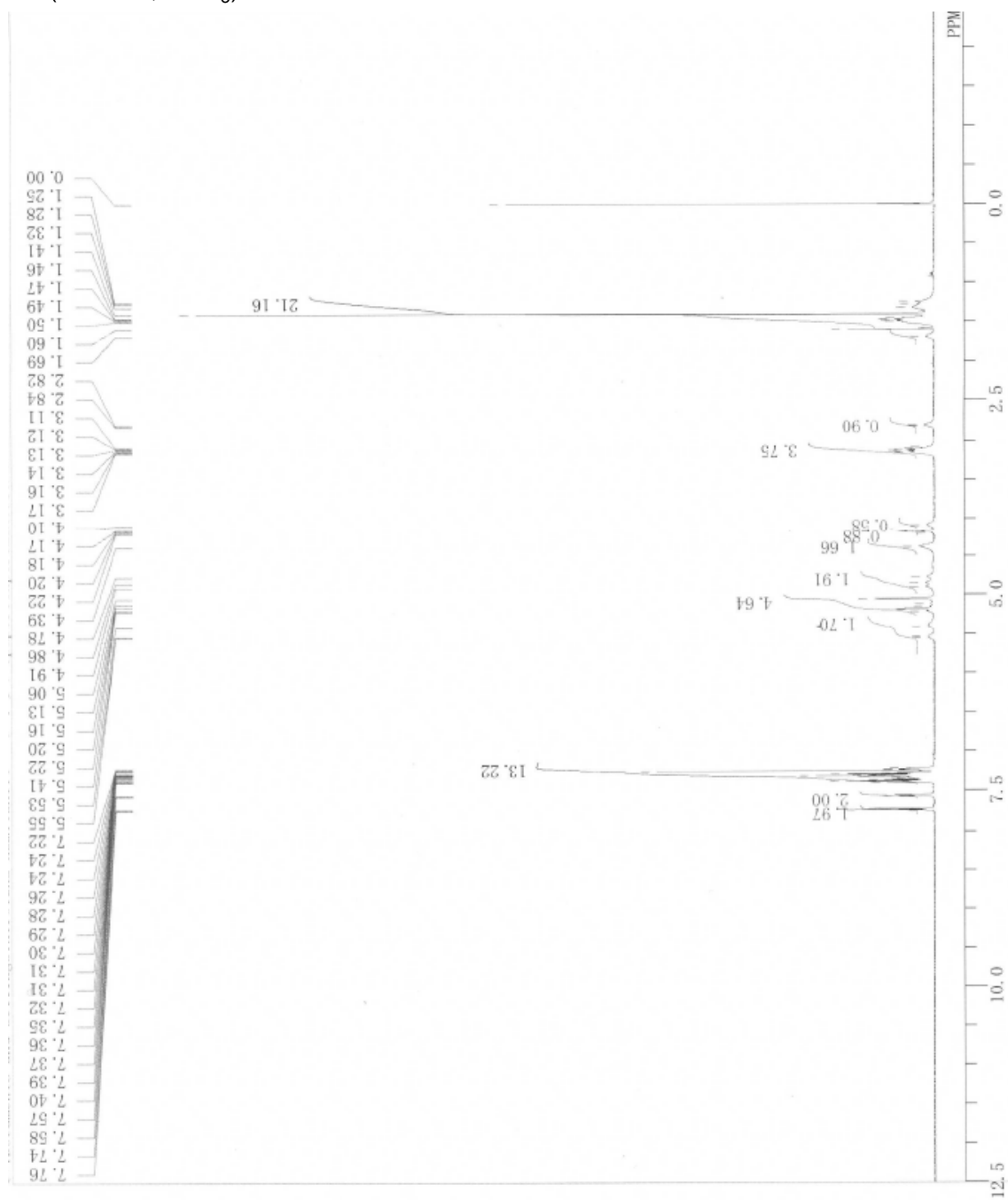


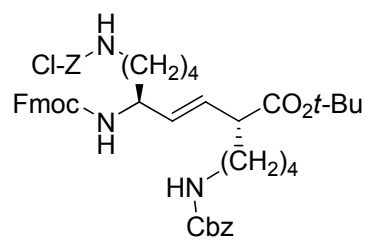
8 (125 MHz, CDCl₃)



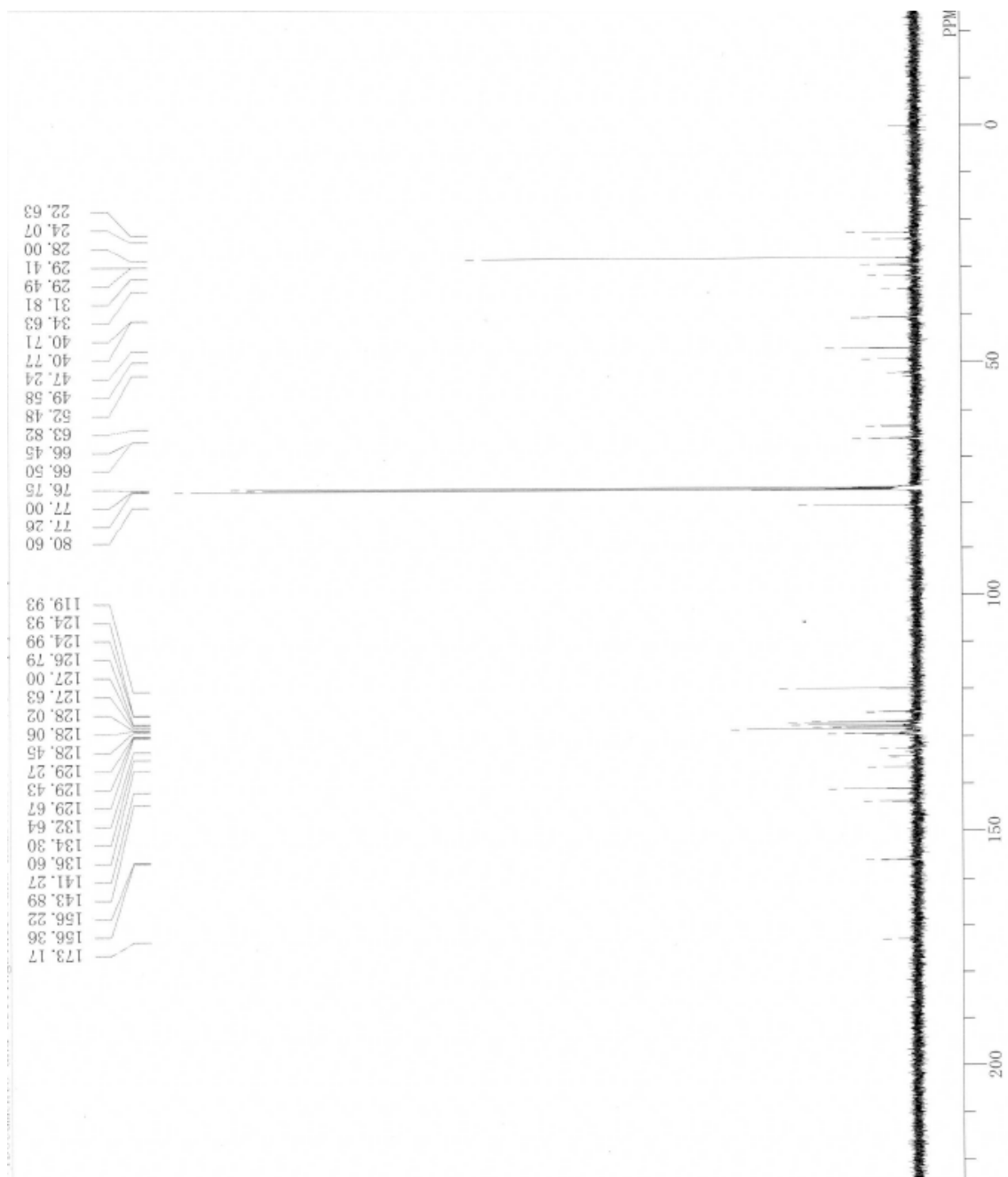


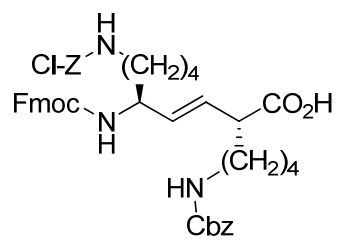
9 (500 MHz, CDCl₃)



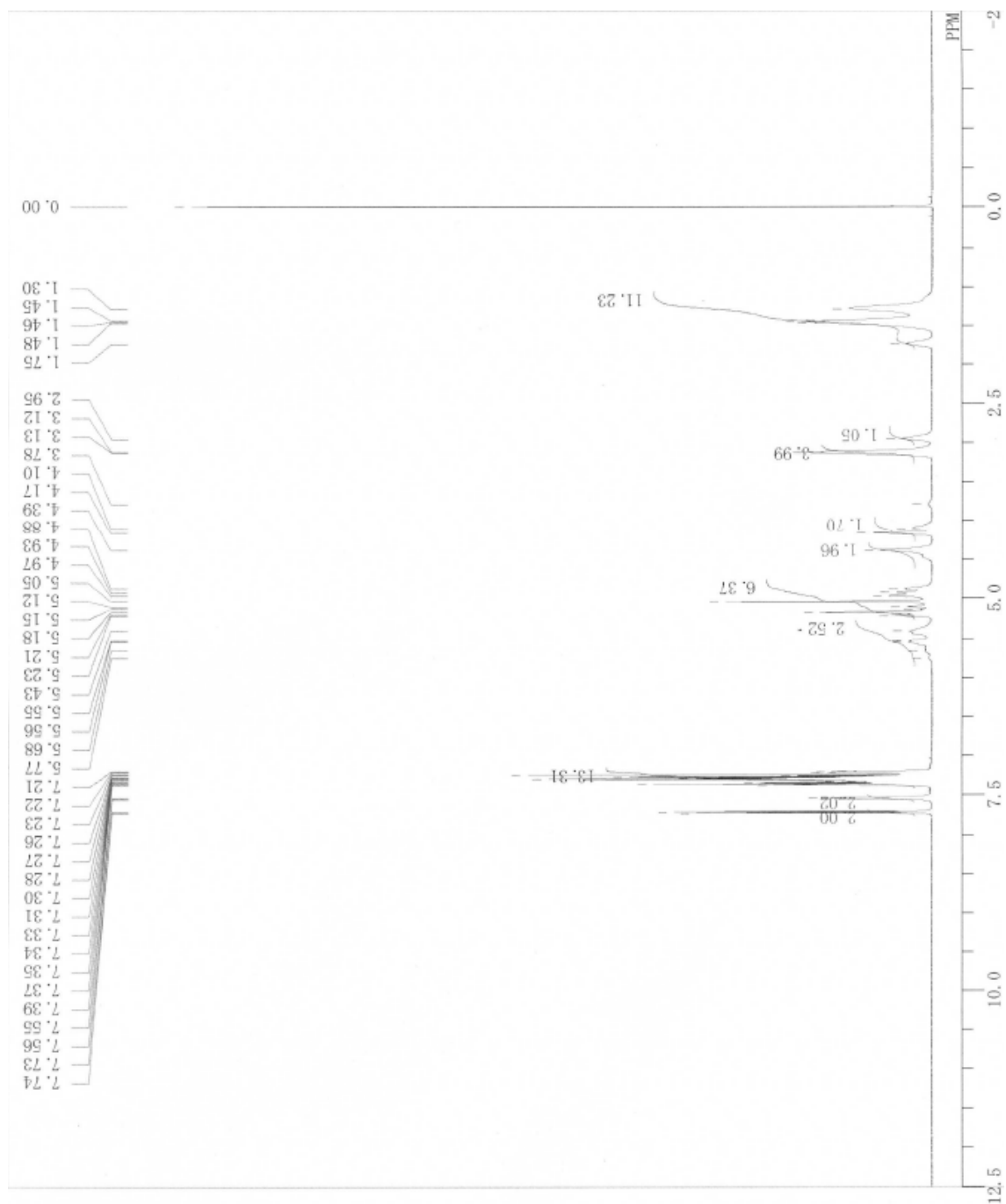


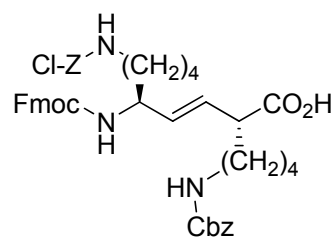
9 (125 MHz, CDCl₃)



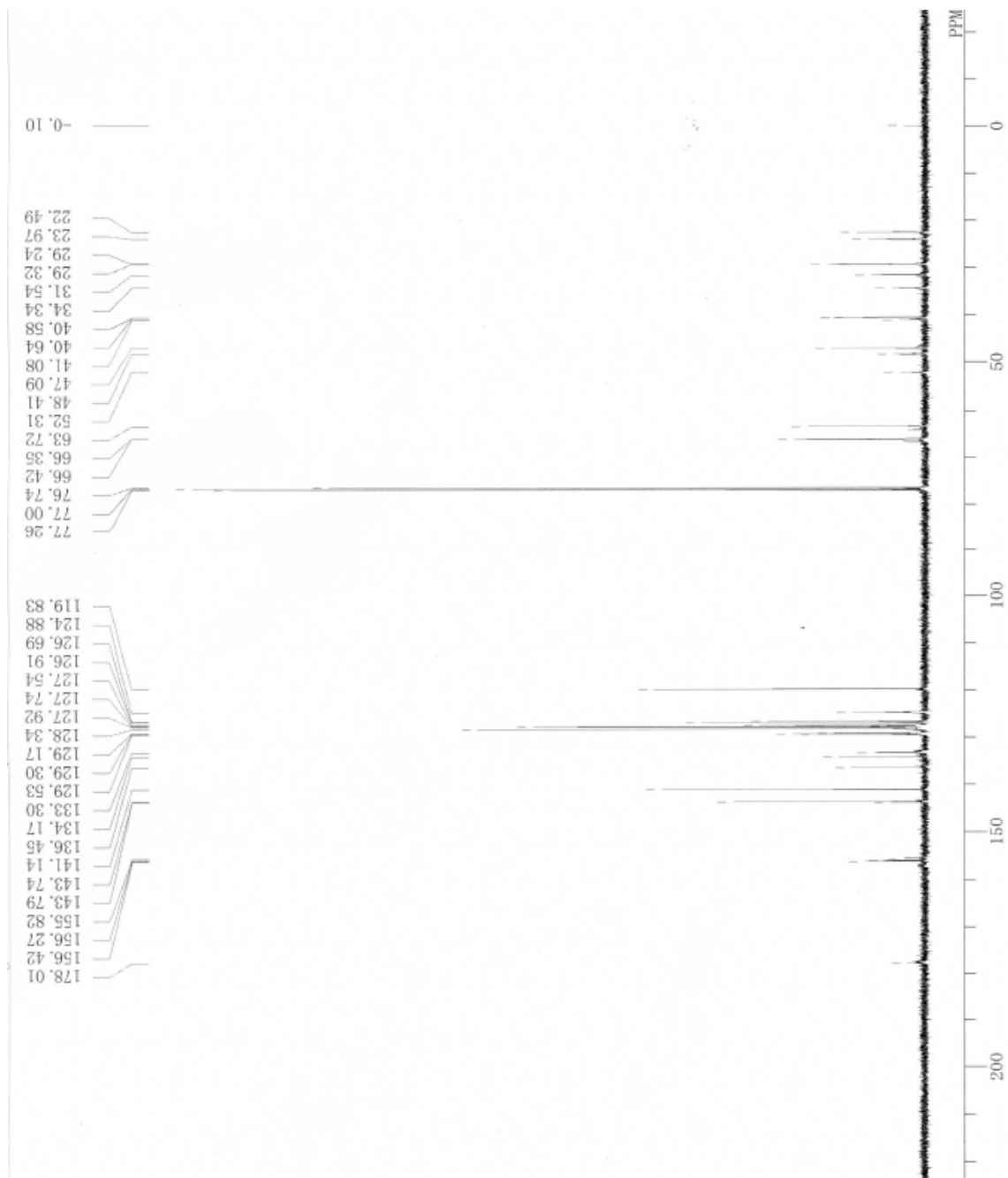


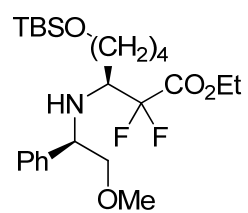
10 (500 MHz, CDCl₃)



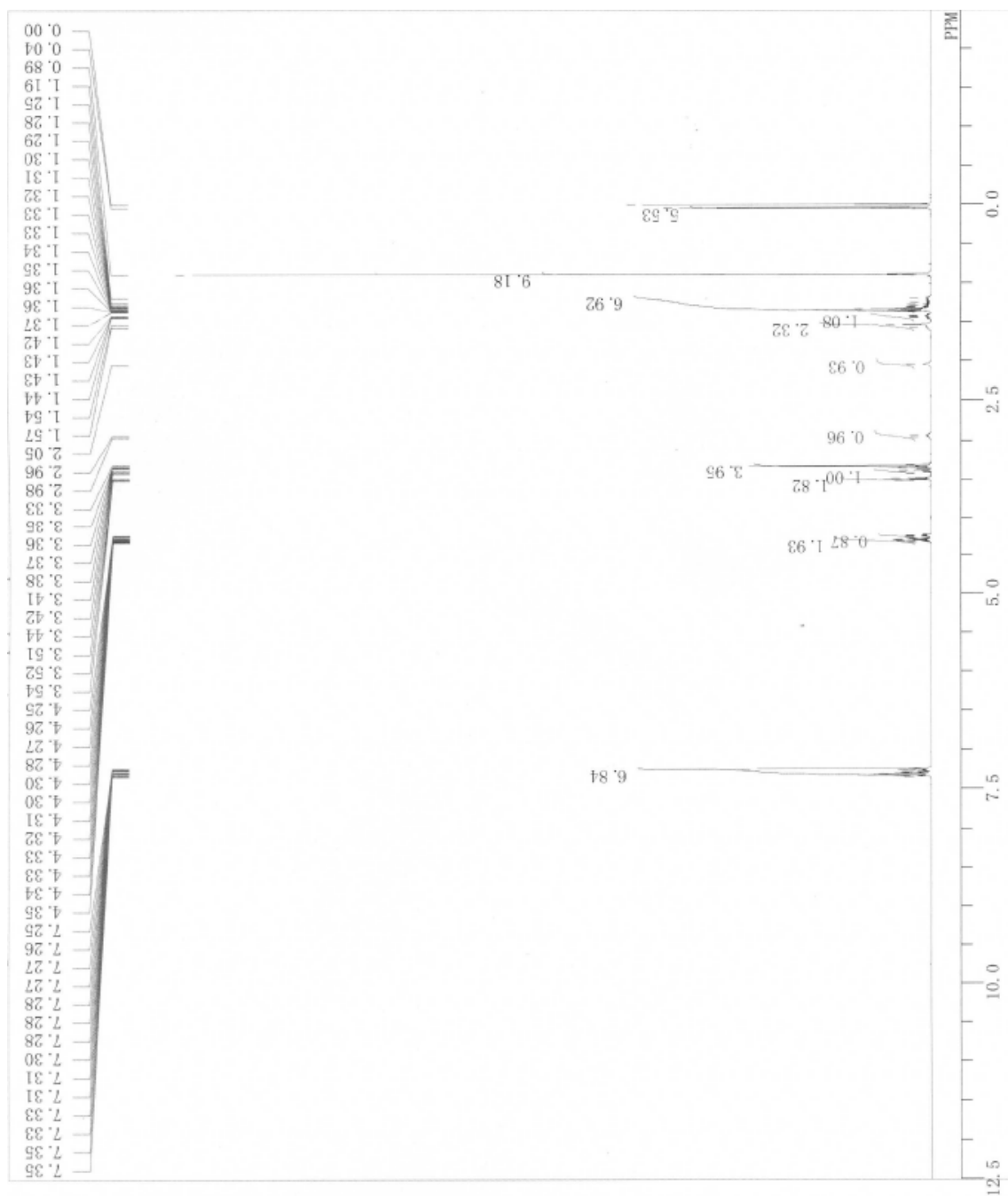


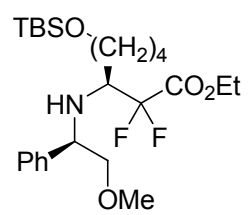
10 (125 MHz, CDCl₃)



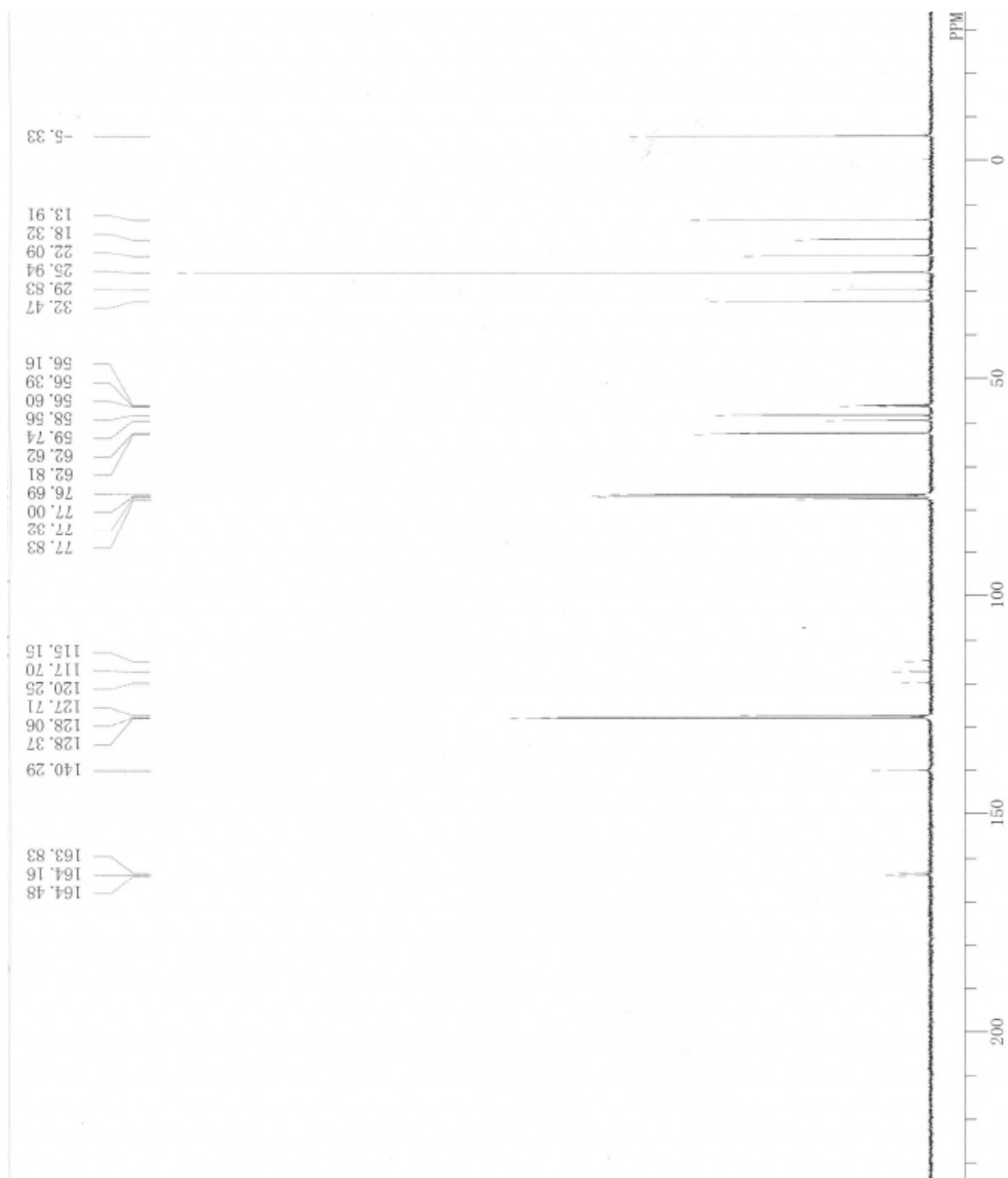


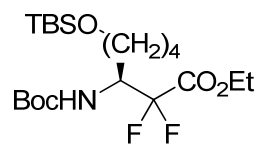
12 (500 MHz, CDCl₃)



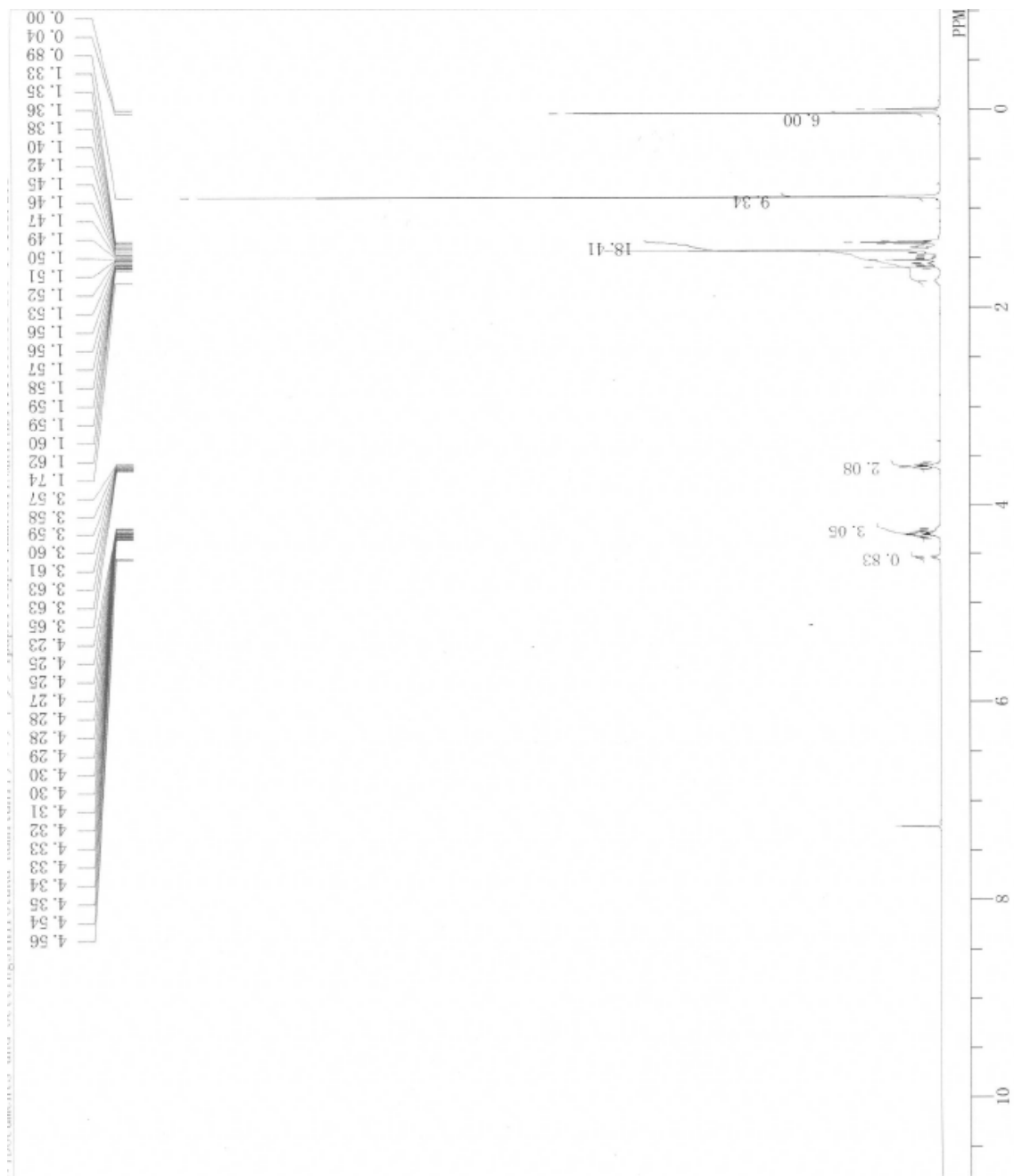


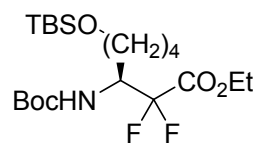
12 (100 MHz, CDCl₃)



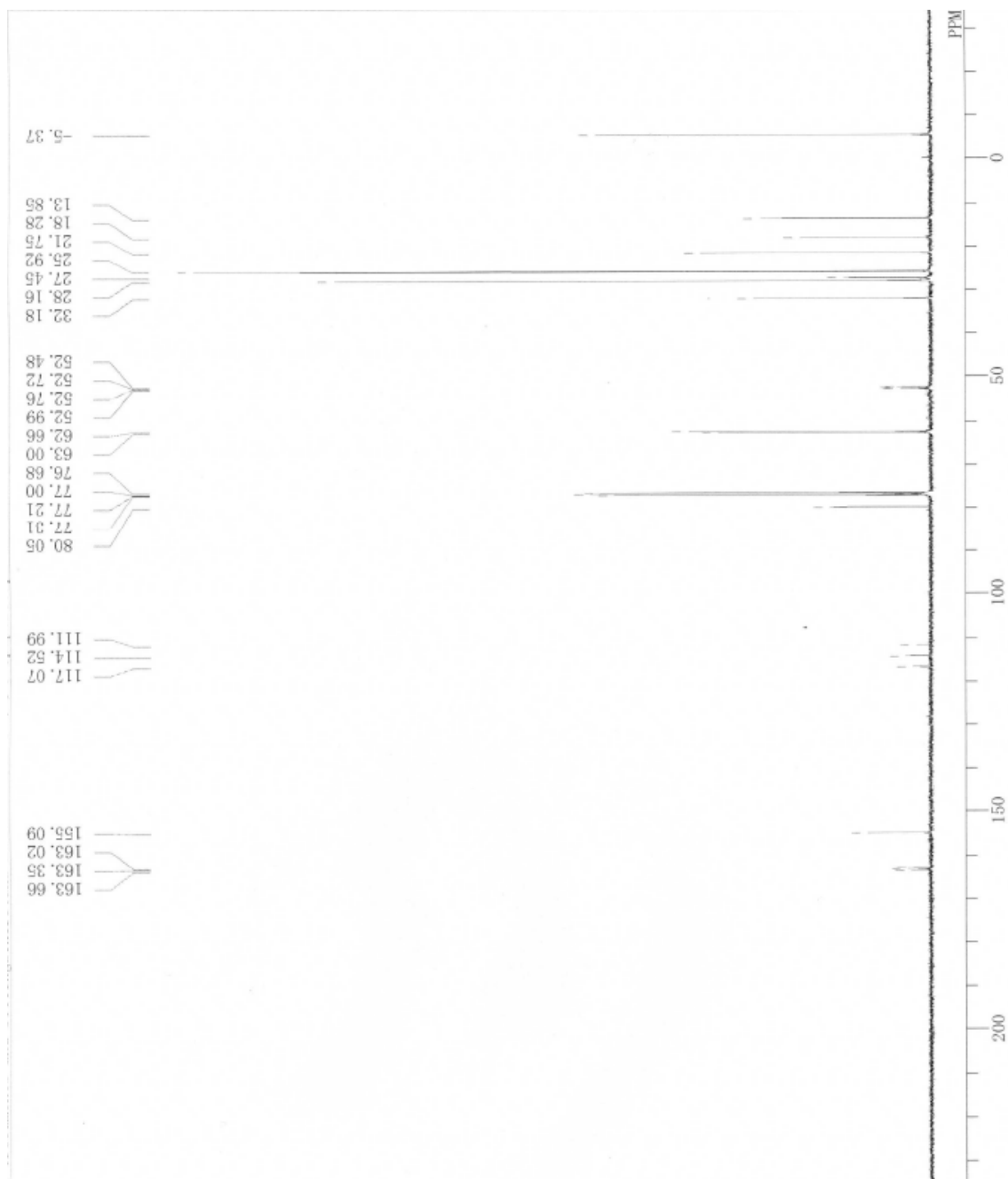


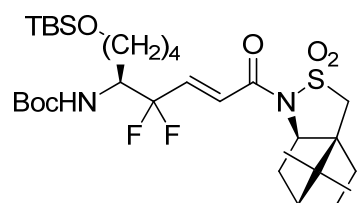
13 (500 MHz, CDCl₃)



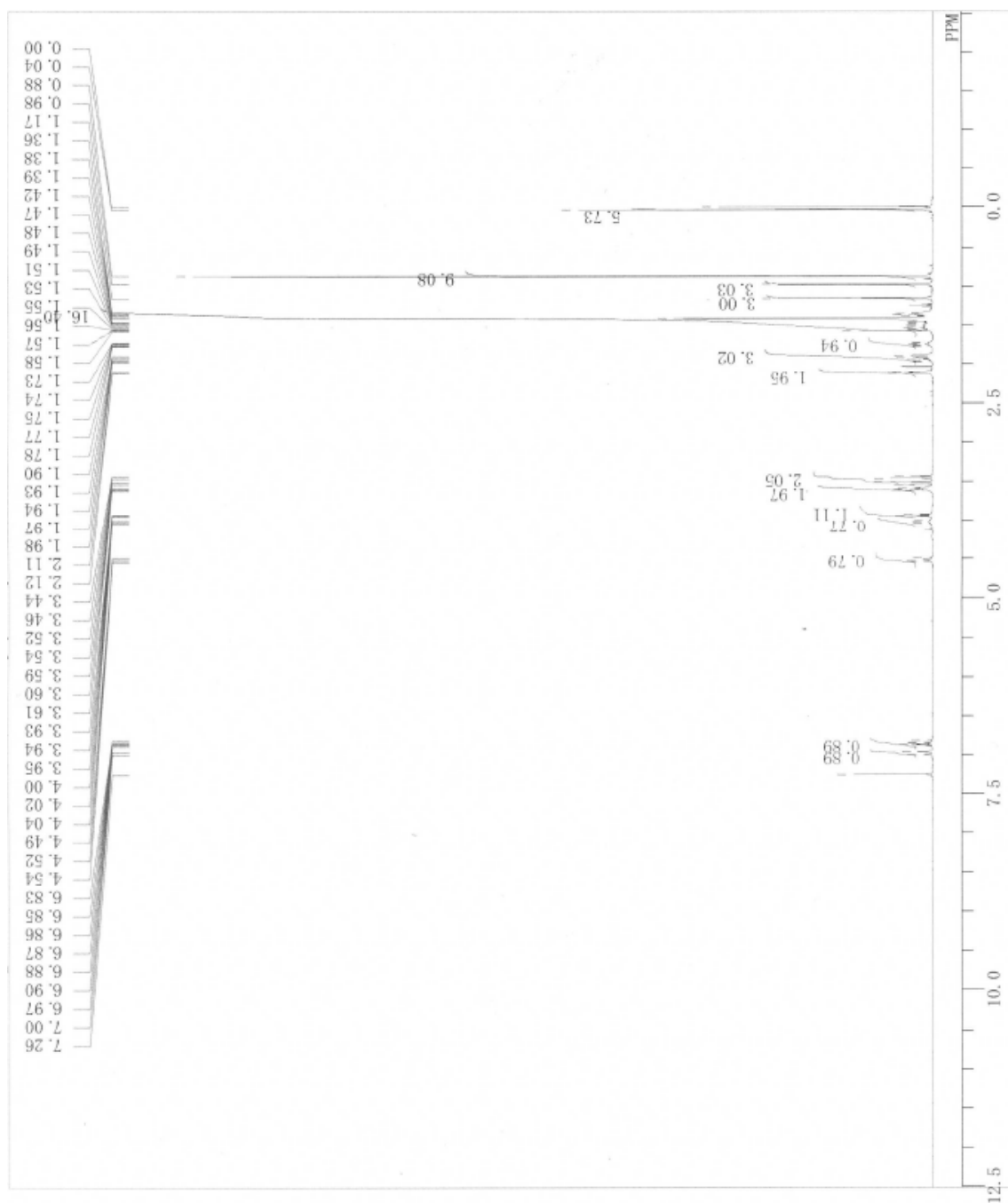


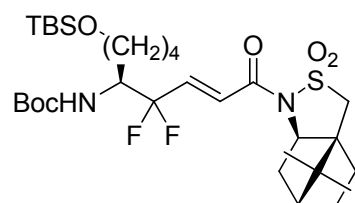
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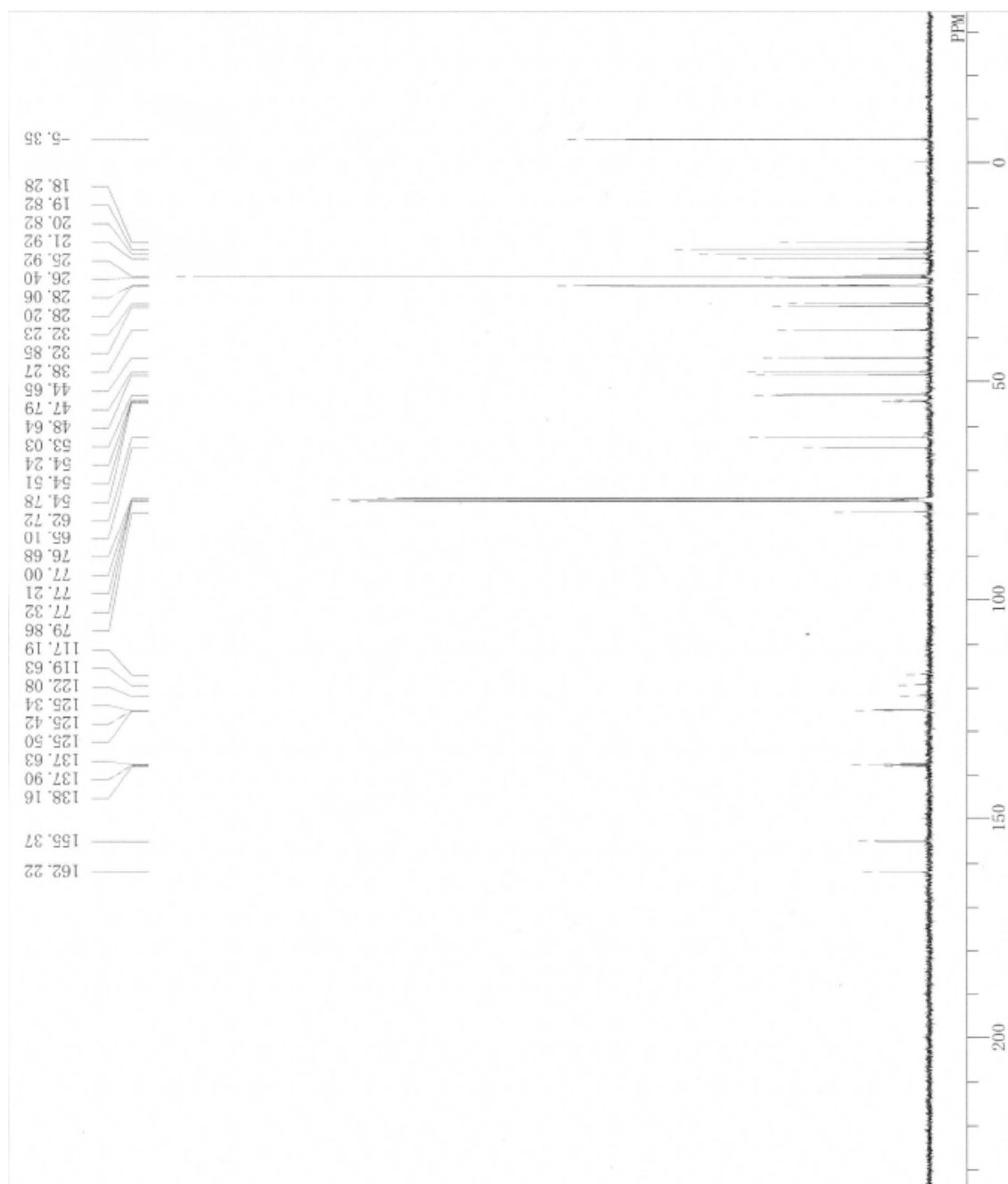


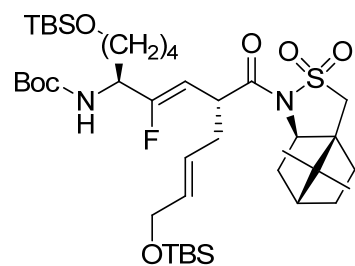
14 (500 MHz, CDCl₃)



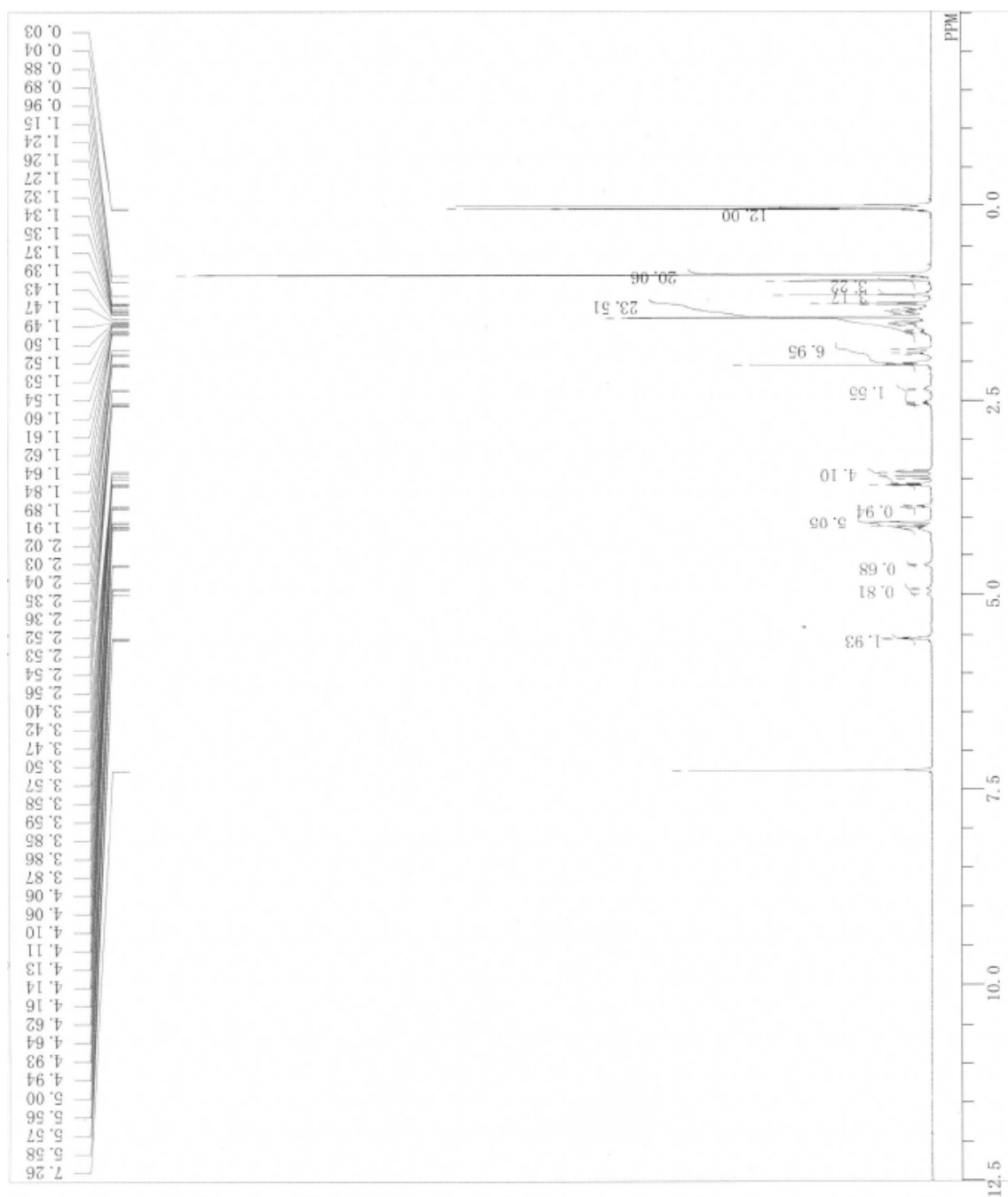


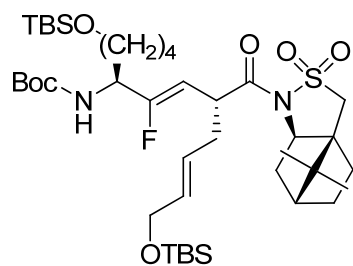
14 (100 MHz, CDCl₃)



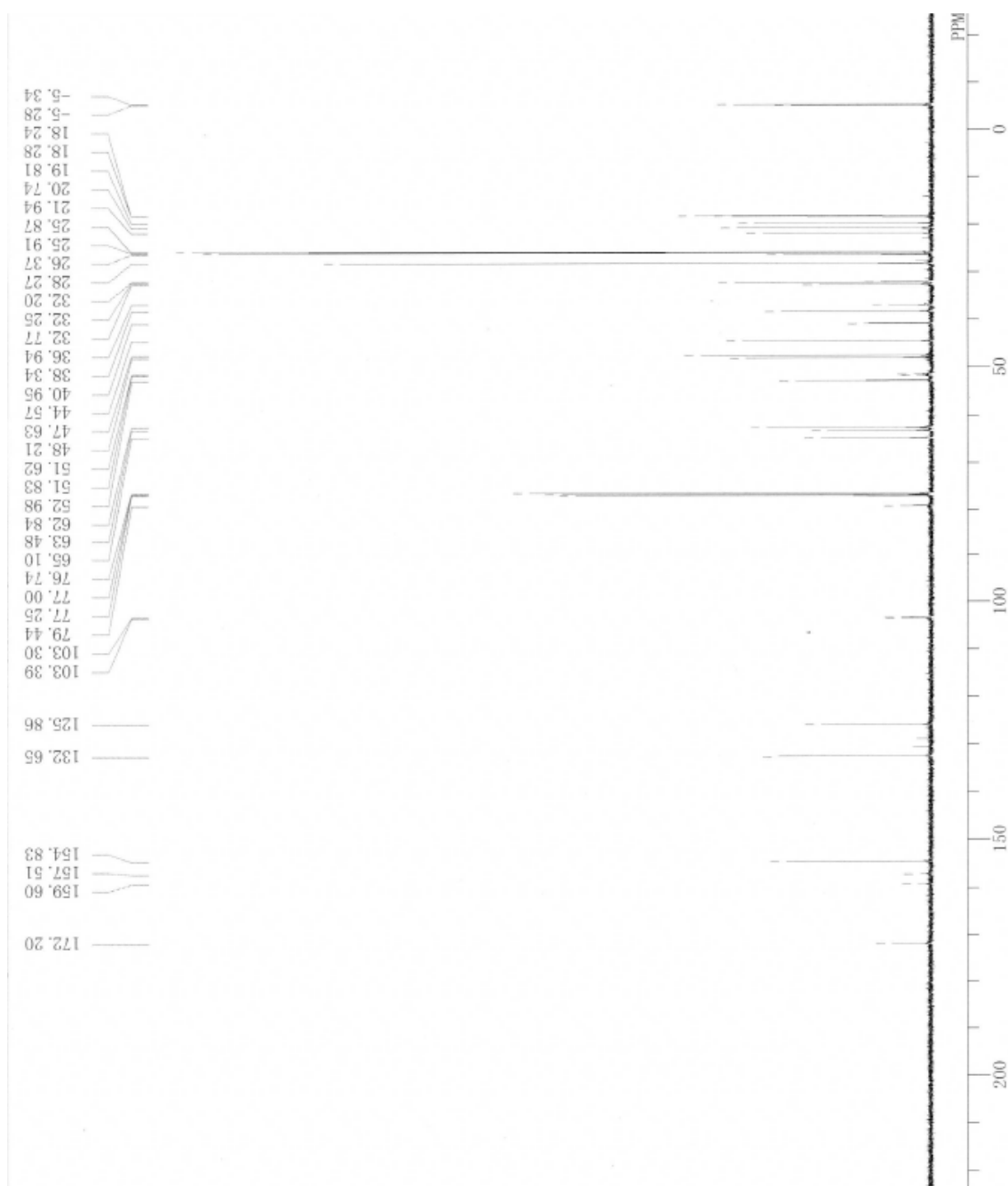


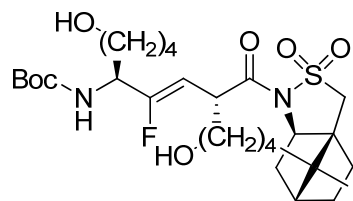
15 (500 MHz, $CDCl_3$)



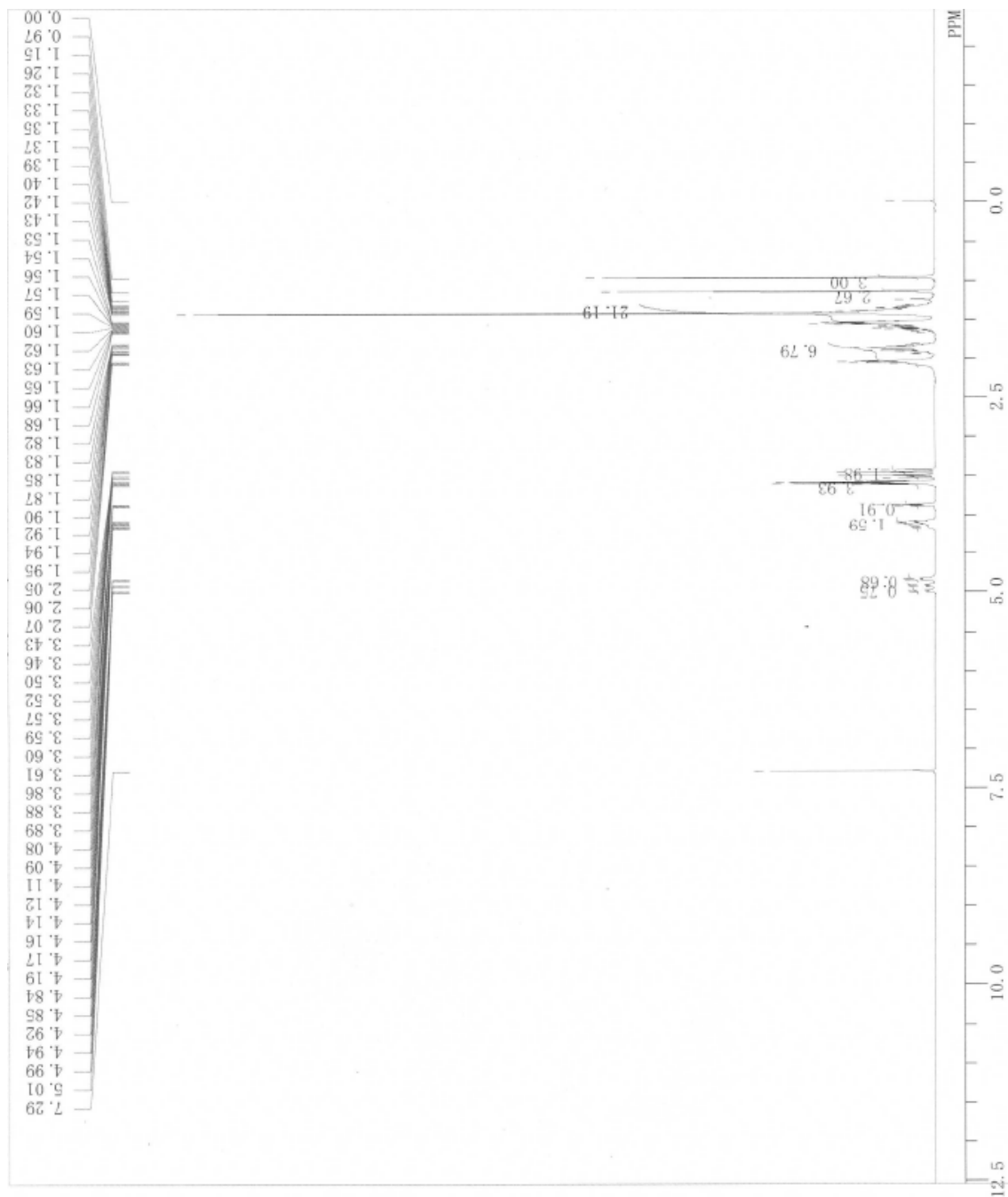


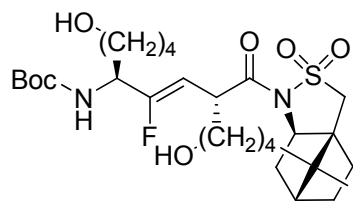
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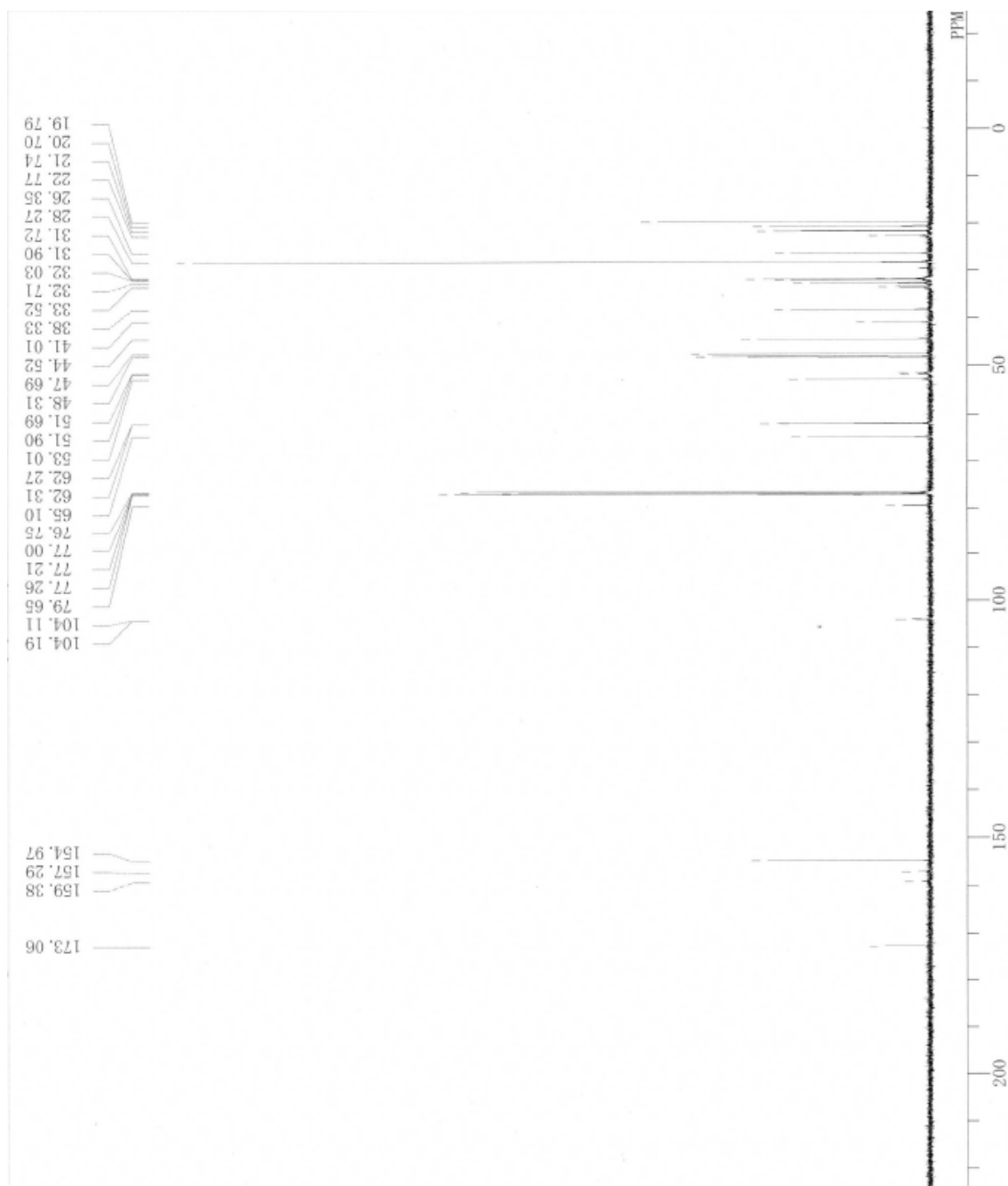


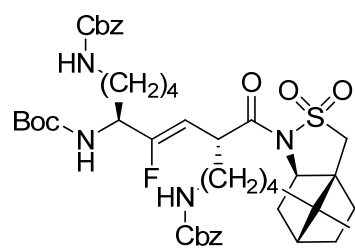
17 (500 MHz, CDCl₃)



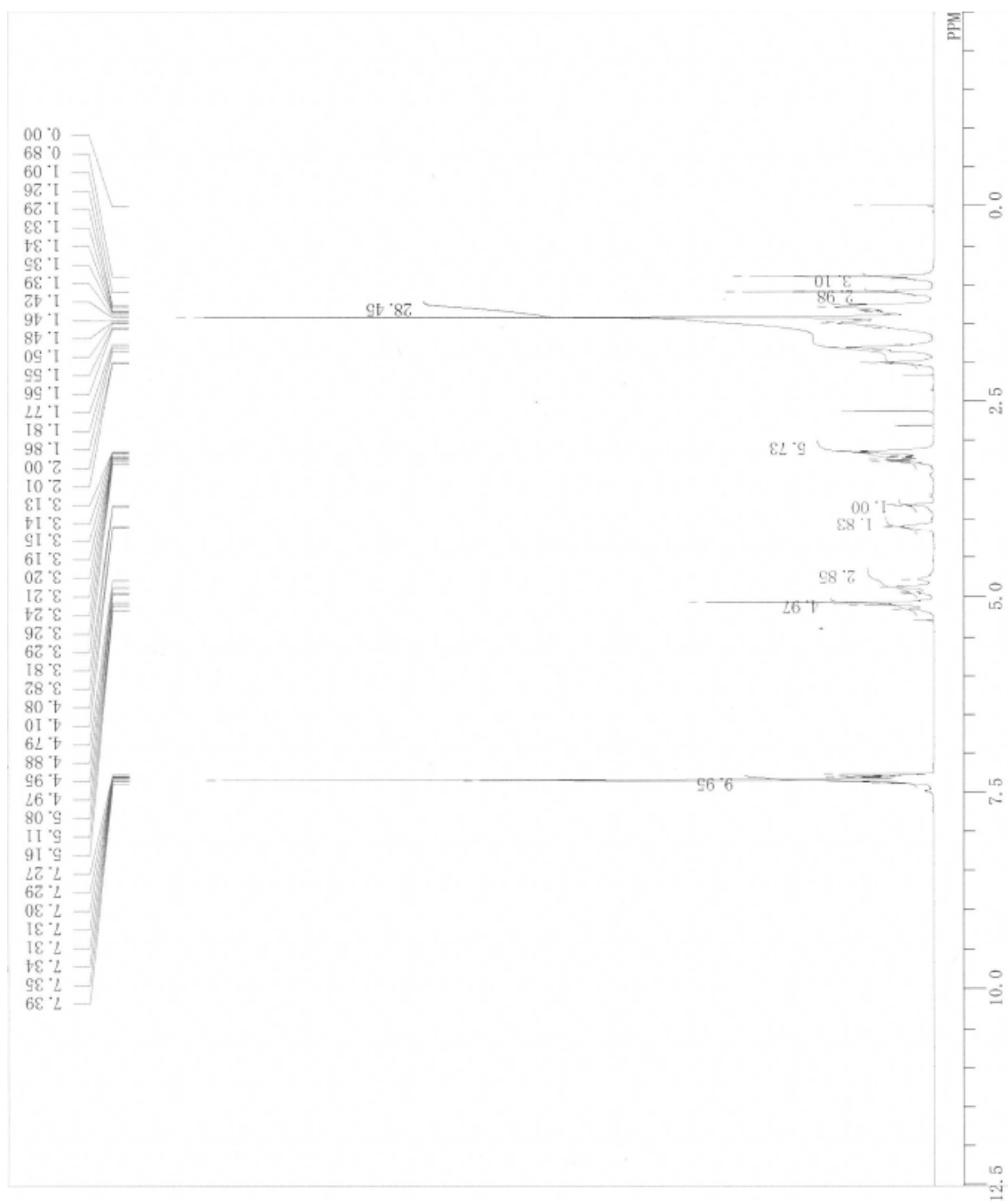


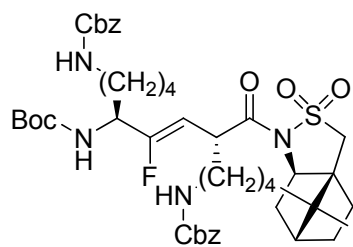
17 (125 MHz, CDCl₃)



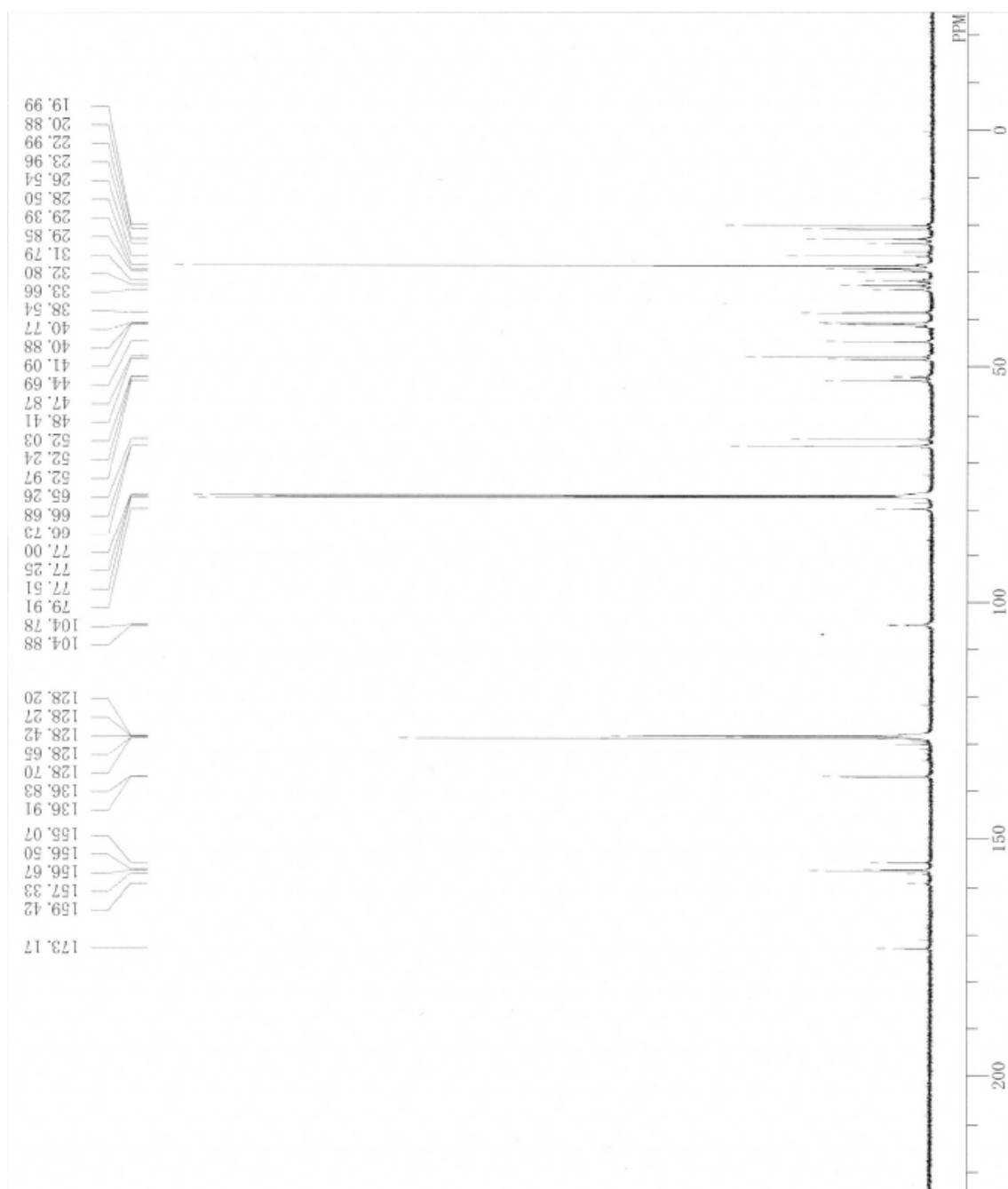


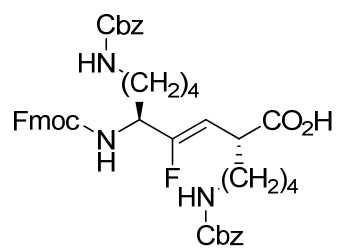
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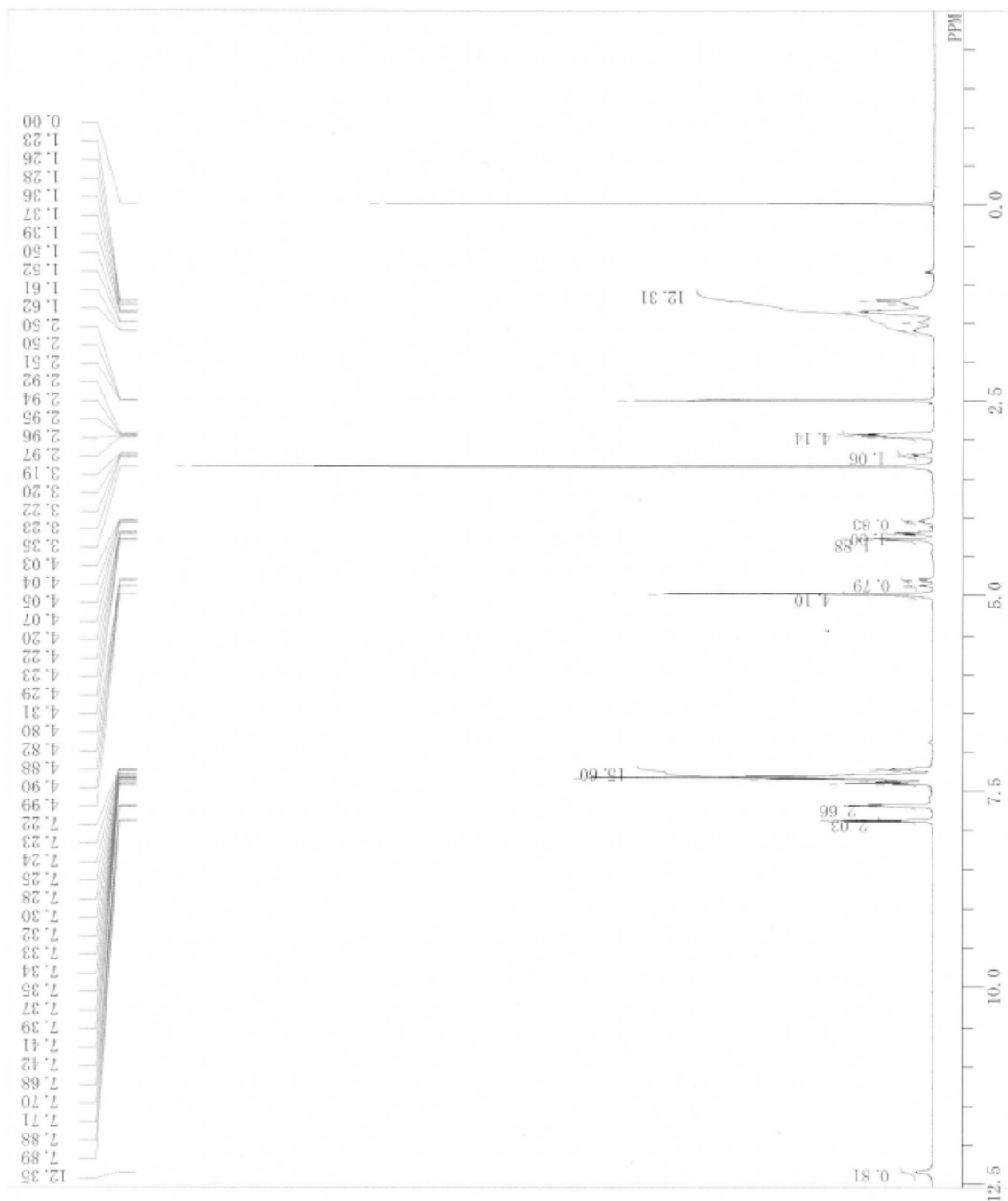


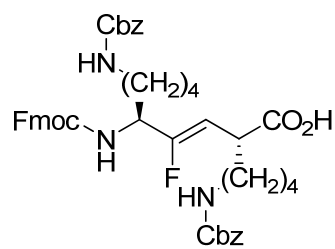
18 (125 MHz, CDCl₃)



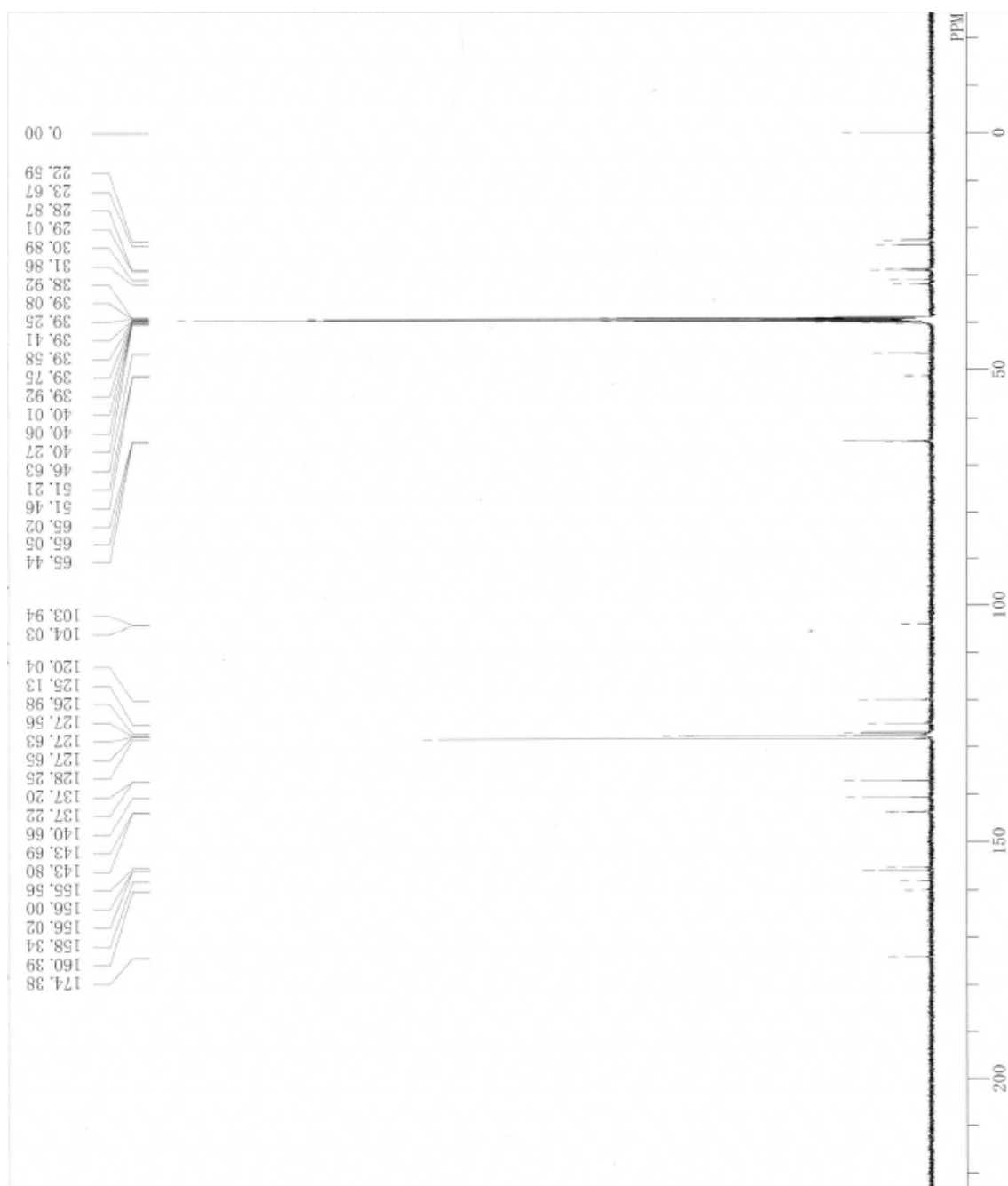


19 (500 MHz, DMSO-d₆)





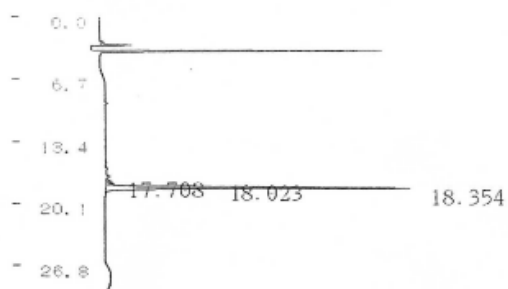
19 (125 MHz, DMSO-*d*₆)



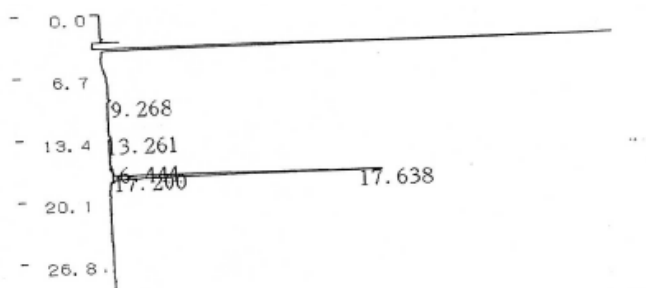
HPLC charts of SC29EK derivatives

Linear gradient of 0.1% TFA in CH₃CN (25-50% over 25 min) in 0.1% TFA aq.

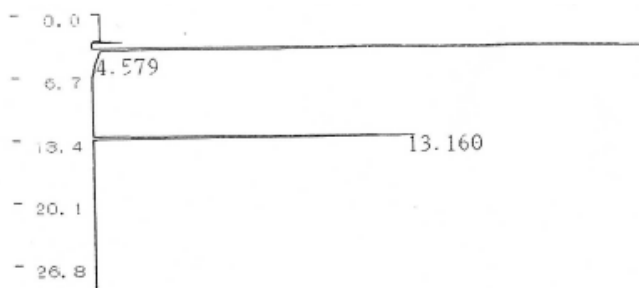
20E



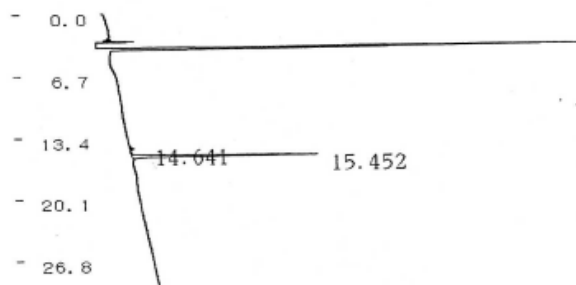
21E



22E

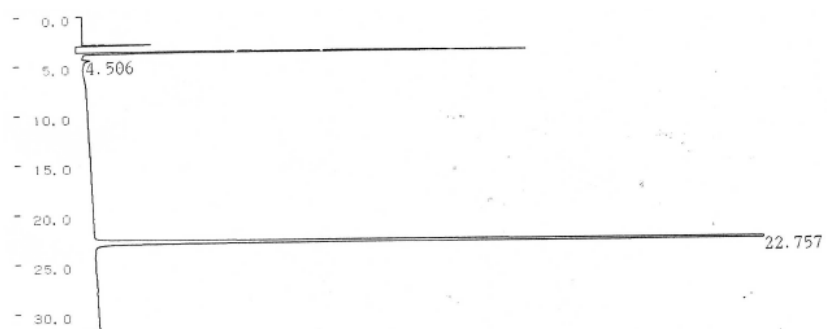


23E

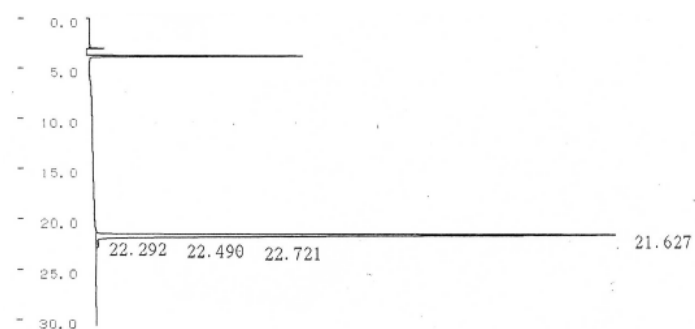


Linear gradient of 0.1% TFA in CH₃CN (20-50% over 30 min) in 0.1% TFA aq.

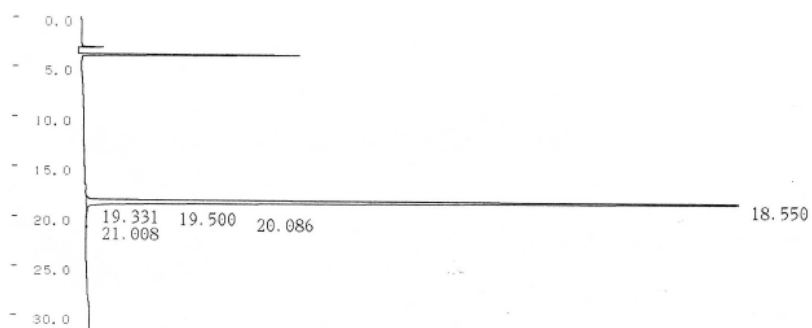
20F



21F



22F



23F

