Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Supporting Information

Development of Diketopiperazine-forming Dipeptidy Pro-Gly Spacer for Preparation of Antibody-Drug Conjugate

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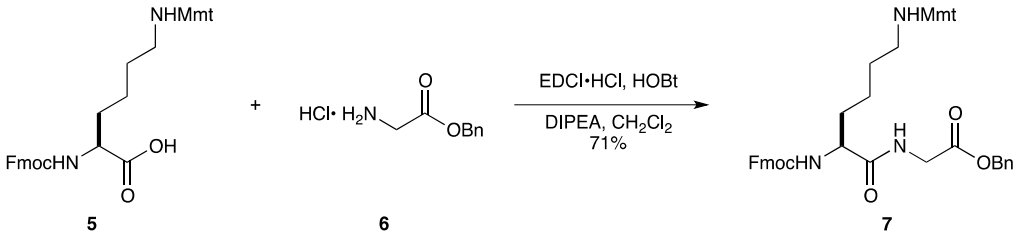
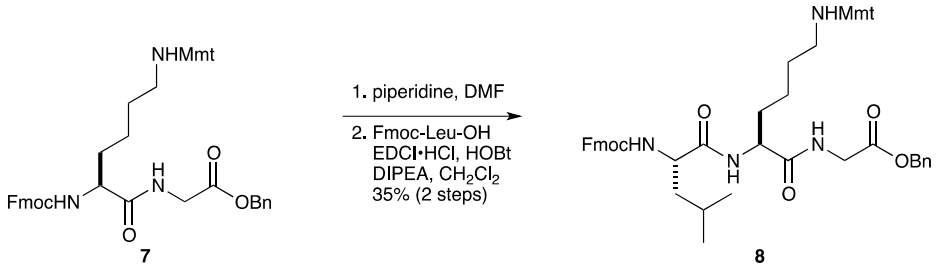
General Procedure

^{1}H and ^{13}C NMR spectra were recorded at ambient temperature (23~24 °C) in $CDCl_3$ using JEOL EX 400 MHz spectrometer. Chemical shifts are reported in ppm relative to internal tetramethylsilane (δ = 0.00 ppm) for ^{1}H and $CDCl_3$ (δ = 77.00 ppm) for ^{13}C NMR spectra. Optical rotations were measured with a JASCO DIP-310 polarimeter. Melting points (not corrected) were measured with a YANACO micro melting point apparatus. Silica gel 60N (spherical, neutral, Kanto Chemical Co., Inc, Tokyo) was used for flash column (40-100 μm) and open column (100-200 μm) chromatography. Silica gel 60 F_{254} (E. Merck) was used for analytical and preparative thin-layer chromatography.



To a stirred solution of Fmoc-Lys(Mmt)-OH **5** (5.00 g, 7.80 mmol) and H-Gly-OBn•HCl **6** (1.89 g, 9.36 mmol) in CH_2Cl_2 (40 mL) were added HOBt (1.27 g, 9.36 mmol), EDCI•HCl (1.80 g, 9.36 mmol) and DIPEA (8.2 mL, 46.8 mmol) at 0 °C. After stirring the mixture at r.t. for 18 h, the reaction was quenched with sat. NH_4Cl and extracted with $CHCl_3$. The extracted layer was washed with sat. $NaHCO_3$ and brine. The extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (Hexane/EtOAc 3/2 to 2/3, Et_3N 2%) to afford Fmoc-Lys(Mmt)-Gly-OBn **7** (4.38 g, 71%) as colorless amorphous.

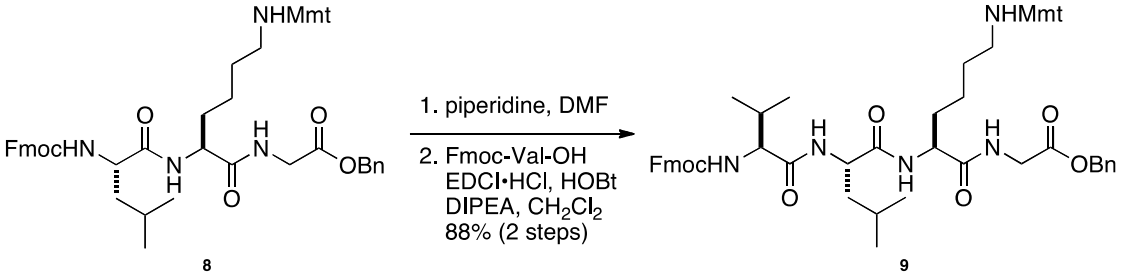
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.2 Hz, 2H), 7.15-7.65 (m, 23H), 6.83 (d, J = 8.8 Hz, 2H), 6.52 (br, 1H), 5.31 (br, 1H), 5.16 (brs, 2H), 4.40-4.50 (m, 2H), 4.15-4.30 (m, 2H), 4.08 (brs, 2H), 3.79 (s, 3H), 2.16 (br, 2H), 1.84 (br, 1H), 1.25-1.75 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.6, 169.2, 157.6, 155.9, 146.2, 143.5, 141.1, 138.2, 134.9, 129.6, 128.5, 128.4, 128.2, 127.6, 127.6, 126.9, 126.0, 124.9, 119.9, 119.8, 113.0, 70.3, 67.3, 67.0, 55.2, 54.8, 47.2, 43.4, 41.4, 32.6, 30.6, 23.3; HRMS (ESI-TOFMS) calcd for $[C_{50}H_{49}N_3O_6+Na]^+$ 810.3519, found 810.3523; $[\alpha]^{20}_D$ –7.2 (*c* 0.68, $CHCl_3$).



To a stirred solution of Fmoc-Lys(Mmt)-Gly-OBn **7** (4.28 g, 5.43 mmol) in DMF (10 mL) was added piperidine (2.2 mL, 21.7 mmol) at r.t. After stirring the mixture at r.t. for 10 min, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/AcOEt 9/1 to $CHCl_3$/MeOH 9/1, Et_3N 2%) to afford crude H-Lys(Mmt)-Gly-OBn as a DMF solution. To a stirred solution of the crude amine in CH_2Cl_2 (30 mL) were added Fmoc-Leu-OH (2.50 g, 7.06 mmol), HOBt (954 mg, 7.06 mmol), EDCI•HCl (1.36 g, 7.06 mmol) and DIPEA (2.8 mL, 16.3 mmol) at 0 °C. After stirring the mixture at r.t. for 17 h, the reaction was quenched with sat. NH_4Cl. The mixture was extracted with $CHCl_3$. The organic layer was washed with sat. $NaHCO_3$ and brine. The extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (Hexane/EtOAc 3/2 to 2/3, Et_3N 2%) to afford Fmoc-Leu-Lys(Mmt)-Gly-OBn **8** (1.73 g, 35%, 2 steps) as colorless amorphous.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.6 Hz, 2H), 7.60-7.10 (m, 23H), 6.78 (d, J = 8.8 Hz, 2H), 6.77 (br, 1H), 6.55 (br, 1H), 5.25 (brd, 1H), 5.10 (brs, 2H), 4.35-4.50 (m, 2H), 4.25-4.35 (m, 1H), 4.17 (t, J = 6.8 Hz, 2H), 4.04 (d, J = 3.6 Hz, 2H), 3.74 (s, 3H), 2.10 (br, 2H), 1.75-1.95 (m, 1H), 1.25-1.70 (m, 8H), 0.85-1.00 (m, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.0, 171.2, 169.2, 157.5, 156.1, 146.2, 143.6, 143.4, 141.1, 134.9, 129.6, 128.5, 128.4, 128.2, 127.6, 126.9, 126.0, 124.9, 119.9, 112.9, 70.3, 67.3, 67.1, 55.2, 53.8, 53.0, 47.2, 43.4, 41.3, 32.1, 30.6, 24.8, 23.3, 23.1, 21.9; HRMS (ESI-TOFMS) calcd for $[C_{56}H_{60}N_4O_7+Na]^+$ 923.4360, found 923.4371;

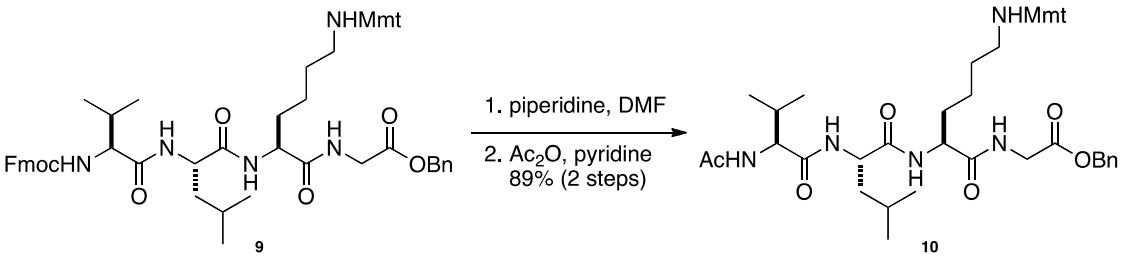
$[\alpha]^{20}_{D}$ –20.5 (*c* 0.56, $CHCl_3$).



8 9

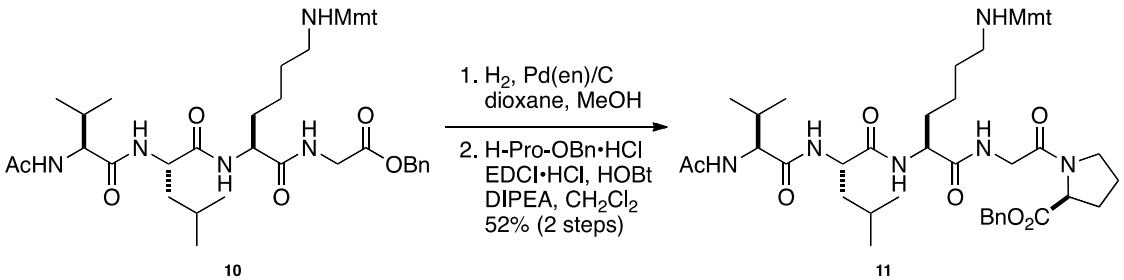
To a stirred solution of Fmoc-Leu-Lys(Mmt)-Gly-OBn **8** (1.63 g, 1.81 mmol) in DMF (5 mL) was added piperidine (0.7 mL, 7.24 mmol) at r.t. After stirring the mixture at r.t. for 10 min, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/AcOEt 9/1 to $CHCl_3$/MeOH 9/1, Et_3N 2%) to afford crude H-Leu-Lys(Mmt)-Gly-OBn as a DMF solution. To a stirred solution of the crude amine in CH_2Cl_2 (10 mL) were added Fmoc-Val-OH (800 mg, 2.35 mmol), HOBt (318 mg, 2.35 mmol), EDCI•HCl (450 mg, 2.35 mmol) and DIPEA (950 □L, 5.43 mmol) at 0 °C. After stirring the mixture at r.t. for 14 h, the reaction was quenched with sat. NH_4Cl and extracted with $CHCl_3$. The organic layer was washed with sat. $NaHCO_3$ and brine. The extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH 98/2, Et_3N 2%) to afford Fmoc-Val-Leu-Lys(Mmt)-Gly-OBn **9** (1.59 g, 88%, 2 steps) as colorless amorphous.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.6 Hz, 2H), 7.05-7.55 (m, 23H), 6.74 (d, *J* = 8.8 Hz, 2H), 5.82 (br, 1H), 4.92 (brs, 2H), 4.72 (br, 1H), 4.62 (br, 1H), 4.31 (q, *J* = 8.0 Hz, 2H), 4.21 (t, *J* = 10.0 Hz, 1H), 4.03-4.21 (m, 3H), 3.85 (dd, *J* = 5.6, 18.4 Hz, 1H), 3.69 (s, 3H), 2.04 (brt, 2H), 1.20-2.00 (m, 10H), 0.70-0.90 (m, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.6, 171.5, 170.9, 169.0, 157.5, 156.3, 146.3, 143.6, 143.5, 141.0, 138.2, 135.0, 130.0, 128.4, 128.2, 128.0, 127.6, 126.9, 125.9, 125.0, 124.9, 119.8, 112.9, 70.3, 67.1, 66.9, 60.1, 55.1, 52.8, 51.6, 47.1, 43.5, 42.1, 41.3, 33.2, 31.9, 30.9, 24.9, 23.5, 23.0, 22.3, 19.0, 18.6; HRMS (ESI-TOFMS) calcd for $[C_{61}H_{70}N_5O_8+H]^+$ 1000.5224, found 1000.5234; $[\alpha]^{20}_{D}$ –24.5 (*c* 0.73, $CHCl_3$).



To a stirred solution of Fmoc-Val-Leu-Lys(Mmt)-Gly-OBn **9** (1.50 g, 1.50 mmol) in DMF (5 mL) was added piperidine (0.6 mL, 6.00 mmol) at r.t. After stirring the mixture at r.t. for 10 min, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/AcOEt 9/1 to $CHCl_3$/MeOH 9/1, Et_3N 2%) to afford crude H-Val-Leu-Lys(Mmt)-Gly-OBn as a DMF solution. To a stirred solution of the crude amine in pyridine (5 mL) was added acetic anhydride (1.4 mL, 15.0 mmol). After stirring the mixture at r.t. for 30 min, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH 95/5, Et_3N 2%) to afford Ac-Val-Leu-Lys(Mmt)-Gly-OBn **10** (1.10 g, 89%, 2 steps) as colorless amorphous.

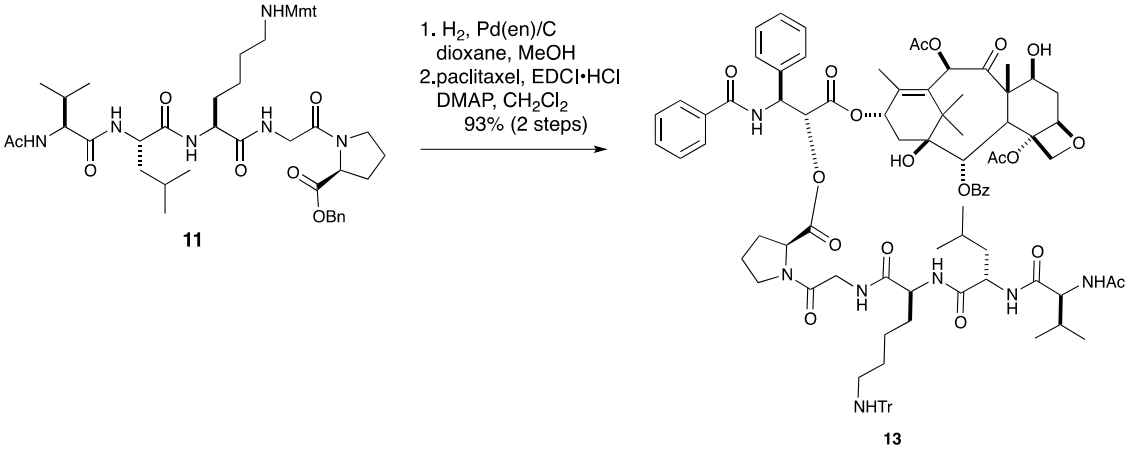
^{1}H-NMR (400 MHz, CD_3OD) δ 7.10-7.42 (m, 17H), 6.78 (d, J = 9.2 Hz, 2H), 5.05 (s, 2H), 4.39 (dd, J = 6.4, 8.4 Hz, 1H), 4.28 (dd, J = 6.0, 8.0 Hz, 1H), 4.08 (d, J = 7.6 Hz, 1H), 4.04 (d, J = 17.6 Hz, 1H), 3.85 (d, J = 17.6 Hz, 1H), 3.72 (s, 3H), 2.10 (br, 2H), 1.95 (s, 3H), 1.25-2.00 (m, 10H), 0.80-0.95 (m, 12H); ^{13}C-NMR (100 MHz, CD_3OD) δ 174.2, 174.0, 173.6, 173.1, 170.5, 159.1, 147.7, 139.4, 136.9, 130.9, 129.6, 129.3, 129.1, 128.5, 127.0, 113.8, 71.7, 67.8, 60.5, 55.6, 54.6, 53.0, 53.0, 44.9, 42.0, 41.5, 33.4, 31.8, 31.7, 31.4, 25.8, 24.8, 23.5, 22.5, 22.4, 22.0, 19.9, 18.9; HRMS (ESI-TOFMS) calcd for $[C_{48}H_{61}N_5O_7+Na]^+$ 842.4469, found 842.4468; $[\alpha]^{20}_D$ –25.6 (*c* 0.66, $CHCl_3$).



A suspension of Ac-Val-Leu-Lys(Mmt)-Gly-OBn **10** (200 mg, 0.204 mmol) and Pd-ethylenediamine complex (4.6%, 37.0 mg) in dioxane (1.8 mL) and MeOH (0.8 mL) was stirred under H_2 atmosphere for 2.5 h. The reaction mixture was filtered and concentrated *in vacuo*. The residue was purified with by silica gel column chromatography ($CHCl_3$/AcOEt 1/1

to $CHCl_3$/MeOH 4/1, Et_3N 2%) to afford crude Ac-Val-Leu-Lys(Mmt)-Gly-OH. To a stirred solution of Ac-Val-Leu-Lys(Mmt)-Gly-OH, H-Pro-OBn•HCl (394 mg, 1.63 mmol) and HOBt (66.1 mg, 0.489 mmol) in CH_2Cl_2 (1 mL) was added EDCI•HCl (93.7 mg, 0.489 mmol) and DIPEA (570 □L, 3.26 mmol) at 0 °C. After stirring the mixture at r.t. for 14 h, the reaction mixture was directly purified by gel filtration chromatography (LH-20, $CHCl_3$/MeOH 1/1) and silica gel column chromatography ($CHCl_3$/MeOH 98/2 to 4/1, Et_3N 2%) to afford Ac-Val-Leu-Lys(Mmt)-Gly-Pro-OBn **11** (117 mg, 52%, 2 steps) as colorless amorphous.

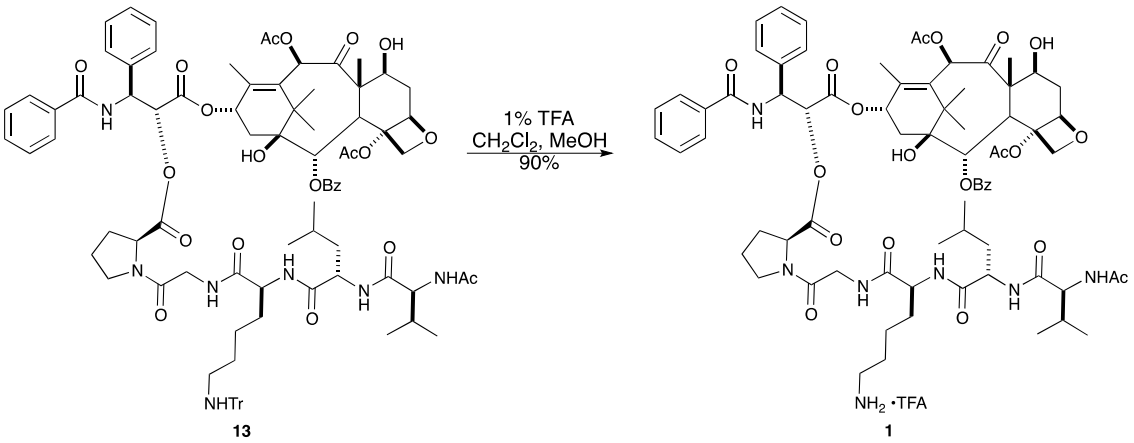
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.05-7.50 (m, 17H), 6.75 (d, J = 8.8 Hz, 2H), 5.23 (br, 1H), 5.16 (d, J = 12.0 Hz, 1H), 5.04 (d, J = 12.0 Hz, 1H), 5.04 (br, 1H), 4.78 (br, 1H), 4.53 (d, J = 6.0 Hz, 2H), 3.92 (d, J = 17.6 Hz, 1H), 3.71 (s, 3H), 3.45-3.75 (m, 2H), 1.94 (s, 3H), 1.09-2.26 (m, 15H), 0.70-0.95 (m, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.0, 171.5, 171.2, 170.8, 169.6, 166.7, 157.4, 146.2, 138.3, 135.3, 129.5, 128.4, 128.3, 128.2, 127.9, 127.5, 125.8, 112.8, 70.2, 66.8, 58.8, 57.7, 55.1, 52.1, 51.1, 46.5, 46.1, 43.6, 43.0, 42.3, 34.7, 32.4, 31.3, 29.1, 24.9, 24.6, 23.5, 23.0, 19.1; HRMS (ESI-TOFMS) calcd for $[C_{53}H_{68}N_6O_8+Na]^+$ 939.4996, found 939.5002; $[\alpha]^{20}_D$ –53.9 (*c* 0.53, $CHCl_3$).



A suspension of Ac-Val-Leu-Lys(Mmt)-Gly-Pro-OBn **11** (100 mg, 0.204 mmol) and Pd-ethylenediamine complex (4.6%, 16.5 mg) in dioxane (0.8 mL) and MeOH (0.35 mL) was stirred under H_2 atmosphere for 8 h. The reaction mixture was filtered and concentrated *in vacuo*. The residue was purified with by silica gel column chromatography ($CHCl_3$/MeOH 98/2 to 4/1, Et_3N 2%) to afford crude Ac-Val-Leu-Lys(Mmt)-Gly-Pro-OH. To a stirred solution of Ac-Val-Leu-Lys(Mmt)-Gly-Pro-OH and paclitaxel **12** (25.3 mg, 0.0296 mmol) in CH_2Cl_2 (1 mL) was added EDCI•HCl (11.4 mg, 0.0592 mmol) and DMAP (7.2 mg, 0.0592 mmol) at 0 °C. After stirring the mixture at r.t. for 14 h, the reaction mixture was directly purified by gel

filtration chromatography (LH-20, $CHCl_3$/MeOH 1/1) and silica gel column chromatography ($CHCl_3$/MeOH 9/1) to afford Ac-Val-Leu-Lys(Mmt)-Gly-Pro-paclitaxel **13** (42.3 mg, 86% based on paclitaxel) as colorless amorphous.

^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.16 (d, J = 8.4 Hz, 1H), 7.10-8.05 (m, 27H), 6.82 (d, J = 8.4 Hz, 2H), 6.28 (s, 1H), 5.88 (app. t, J = 8.0 Hz, 1H), 5.63 (t, J = 8.0 Hz, 1H), 5.41 (brd, 1H), 5.30 (d, J = 7.2 Hz, 1H), 4.90 (brq, 2H), 4.38 (brd, 1H), 4.29 (t, J = 7.6 Hz, 1H), 3.85-4.50 (m, 4H), 3.70 (s, 3H), 3.45-3.60 (m, 2H), 2.31 (s, 3H), 2.08 (s, 3H), 1.83 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.90-2.50 (m, 24H), 0.70-0.90 (m, 12H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 201.9, 171.4, 171.0, 170.6, 169.3, 169.0, 168.4, 168.3, 166.4, 166.1, 164.9, 156.9, 146.3, 139.1, 137.9, 136.6, 133.8, 133.1, 131.4, 129.7, 129.3, 128.5, 128.1, 127.4, 127.2, 125.6, 112.7, 83.4, 80.2, 79.1, 79.0, 76.6, 75.2, 74.7, 74.4, 70.7, 70.3, 69.7, 57.8, 57.3, 54.9, 53.6, 52.4, 50.8, 46.1, 45.5, 43.4, 43.0, 40.5, 36.6, 34.4, 32.3, 30.3, 30.1, 29.1, 26.3, 24.1, 23.4, 23.0, 22.6, 22.5, 21.6, 21.4, 20.7, 19.2, 18.2, 14.0, 13.9, 9.9, 9.8; HRMS (ESI-TOFMS) calcd for $[C_{93}H_{112}N_7O_{21}+H]^+$ 1662.7911, found 1662.7932; $[\alpha]^{20}{}_D$ –48.7 (*c* 0.58, $CHCl_3$).

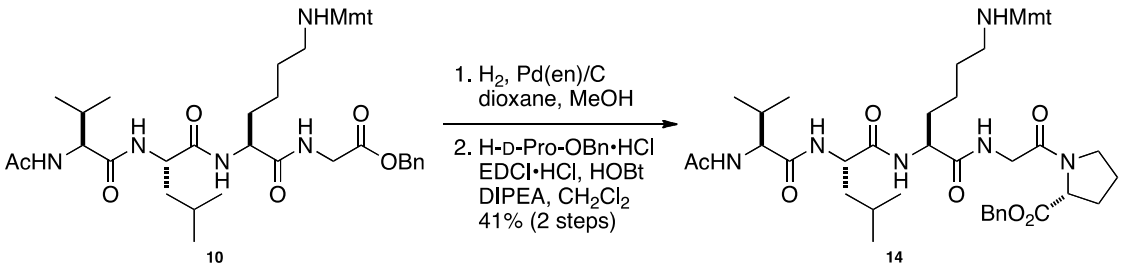


13 **1**

To a stirred solution of Ac-Val-Leu-Lys(Mmt)-Gly-Pro-paclitaxel **13** (19.6 mg, 0.0118 mmol) in 1% TFA containing CH_2Cl_2 (0.9 mL) was added MeOH (7 μL) at r.t. After stirring the mixture at r.t. for 10 min, the reaction mixture was directly purified by gel filtration chromatography (LH-20, $CHCl_3$/MeOH 1/1) to afford Ac-Val-Leu-Lys-Gly-Pro-paclitaxel •TFA (16.0 mg, 90%) as colorless solids **1**.

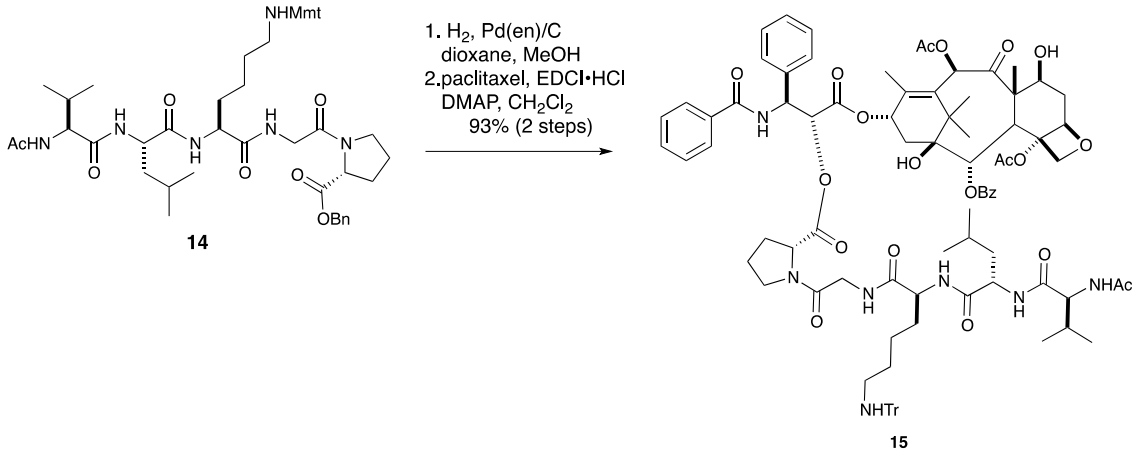
^{1}H-NMR (400 MHz, CD_3OD) δ 8.13 (d, J = 7.2 Hz, 2H), 7.25-7.95 (m, 13H), 6.43 (s, 1H), 6.06 (brt, 1H), 5.86 (d, J = 7.2 Hz, 1H), 5.62 (d, J = 8.0 Hz, 1H), 5.50 (d, J = 6.8 Hz, 1H), 4.99 (d, J = 8.8 Hz, 1H), 4.58 (q, J = 4.4 Hz, 1H), 4.23-4.40 (m, 3H), 4.05-4.20 (m, 4H), 3.79 (d, J = 7.2 Hz, 1H), 3.50-3.70 (m, 2H), 2.91 (t, J = 7.2 Hz, 2H), 2.40 (s, 3H), 2.17 (s, 3H), 2.00 (s, 3H),

1.87 (s, 3H), 1.65 (s, 3H), 1.12 (s, 3H), 1.11 (s, 3H), 1.05-2.50 (m, 18H), 0.80-1.00 (m, 12H); ^{13}C-NMR (100 MHz, CD_3OD) δ 204.7, 174.3, 173.8, 173.4, 173.2, 172.4, 171.3, 171.1, 170.0, 169.7, 168.6, 167.3, 142.1, 137.7, 135.2, 134.6, 134.4, 132.8, 131.2, 131.1, 131.0, 129.9, 129.5, 128.6, 128.4, 85.8, 82.2, 79.4, 79.3, 78.9, 77.4, 76.8, 76.2, 72.9, 72.3, 60.8, 60.2, 59.2, 55.3, 54.0, 53.2, 47.9, 47.3, 44.6, 42.6, 41.5, 40.6, 37.5, 36.4, 32.1, 31.6, 30.8, 30.5, 30.0, 27.9, 27.0, 25.9, 25.7, 23.6, 23.4, 22.6, 22.0, 21.0, 19.8, 18.9, 15.2, 10.6; HRMS (ESI-TOFMS) calcd for $[C_{73}H_{96}N_7O_{20}+H]^+$ 1390.6710, found 1390.6724; $[\alpha]^{20}_D$ –55.6 (*c* 0.80, MeOH).



A suspension of Ac-Val-Leu-Lys(Mmt)-Gly-OBn **10** (200 mg, 0.204 mmol) and Pd-ethylenediamine complex (4.6%, 37.0 mg) in dioxane (1.8 mL) and MeOH (0.8 mL) was stirred under H_2 atmosphere for 2.5 h. The reaction mixture was filtered and concentrated *in vacuo*. The residue was purified with by silica gel column chromatography ($CHCl_3$/AcOEt 1/1 to $CHCl_3$/MeOH 4/1, Et_3N 2%) to afford crude Ac-Val-Leu-Lys(Mmt)-Gly-OH. To a stirred solution of Ac-Val-Leu-Lys(Mmt)-Gly-OH, H-D-Pro-OBn•HCl (348 mg, 1.44 mmol) and HOBt (58.4 mg, 0.432 mmol) in CH_2Cl_2 (0.9 mL) was added EDCI•HCl (82.8 mg, 0.432 mmol) and DIPEA (0.5 mL, 2.88 mmol) at 0 °C. After stirring the mixture at r.t. for 13 h, the reaction mixture was directly purified by gel filtration chromatography (LH-20, $CHCl_3$/MeOH 1/1) and silica gel column chromatography ($CHCl_3$/MeOH 98/2 to 95/5, Et_3N 2%) to afford Ac-Val-Leu-Lys(Mmt)-Gly-D-Pro-OBn **14** (92.9 mg, 41%, 2 steps) as colorless amorphous.
^{1}H-NMR (400 MHz, CD_3OD) δ 7.05-7.50 (m, 17H), 6.76 (d, *J* = 8.8 Hz, 2H), 5.08 (s, 2H), 4.35-4.60 (m, 3H), 4.20 (d, *J* = 7.6 Hz, 1H), 4.04 (d, *J* = 12.0 Hz, 1H), 3.98 (d, *J* = 12.0 Hz, 1H), 3.70 (s, 3H), 3.35-3.65 (m, 2H), 1.95 (s, 3H), 1.20-2.20 (m, 14H), 0.80-0.95 (m, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.0, 171.9, 171.6, 171.5, 171.3, 171.2, 170.8, 169.7, 169.7, 167.1, 166.7, 157.4, 146.2, 138.3, 135.3, 135.0, 129.4, 128.4, 128.3, 128.3, 128.1, 127.8, 127.5, 125.8, 112.8, 76.7, 70.2, 67.1, 66.7, 58.9, 58.5, 58.2, 57.7, 55.0, 52.2, 51.1, 50.6, 46.4, 46.2, 43.6, 42.8, 42.3, 34.5, 32.3, 31.2, 29.7, 29.1, 24.8, 24.6, 23.5, 23.1, 22.9, 22.8, 22.2, 18.9, 18.5; HRMS (ESI-TOFMS) $[C_{53}H_{68}N_6O_8+Na]^+$ 939.4996, found 939.4998; $[\alpha]^{20}_D$ +12.9 (*c* 0.77,

$CHCl_3$).

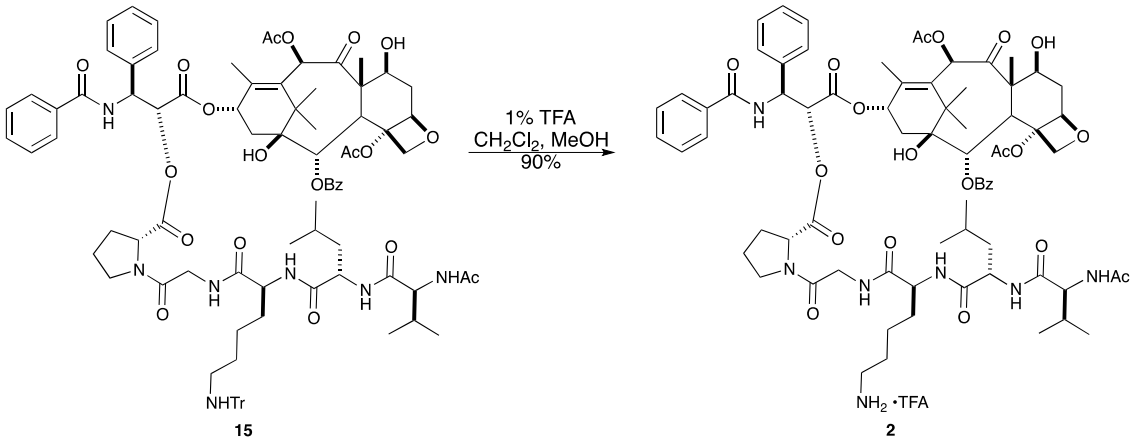


14 **15**

A suspension of Ac-Val-Leu-Lys(Mmt)-Gly-D-Pro-OBn **14** (90.2 mg, 0.0983 mmol) and Pd-ethylenediamine complex (4.6%, 14.9 mg) in dioxane (0.75 mL) and MeOH (0.3 mL) was stirred under H_2 atmosphere for 7 h. The reaction mixture was filtered and concentrated *in vacuo*. The residue was purified with by silica gel column chromatography ($CHCl_3$/AcOEt 1/1 to 4/1, Et_3N 2%) to afford crude Ac-Val-Leu-Lys(Mmt)-Gly-D-Pro-OH. To a stirred solution of Ac-Val-Leu-Lys(Mmt)-Gly-Pro-OH and paclitaxel **12** (25.0 mg, 0.0293 mmol) in CH_2Cl_2 (1 mL) was added EDCI•HCl (11.2 mg, 0.0585 mmol) and DMAP (7.1 mg, 0.0585 mmol) at 0 °C. After stirring the mixture at r.t. for 14 h, the reaction mixture was directly purified by gel filtration chromatography (LH-20, $CHCl_3$/MeOH 1/1) and silica gel column chromatography ($CHCl_3$/MeOH 9/1) to afford Ac-Val-Leu-Lys(Mmt)-Gly-D-Pro-paclitaxel **15** (145.4 mg, 93% based on paclitaxel) as colorless amorphous.

^{1}H-NMR (400 MHz, CD_3OD) δ 8.10 (d, J = 7.2 Hz, 2H), 7.82 (d, J = 7.6 Hz, 2H), 7.05-7.70 (m, 23H), 6.80 (d, J = 7.6 Hz, 2H), 6.43 (brs, 1H), 5.95-6.15 (m, 1H), 5.96 (d, J = 6.4 Hz, 1H), 5.62 (d, J = 6.0 Hz, 1H), 5.46 (d, J = 6.8 Hz, 1H), 4.94 (d, J = 10.0 Hz, 1H), 4.58 (brd, 1H), 4.44 (app.t, J = 7.6 Hz, 1H), 4.38 (dd, J = 5.6, 8.0 Hz, 1H), 4.31 (dd, J = 6.8, 10.4 Hz, 1H), 4.13-4.25 (m, 2H), 4.12 (d, J = 7.6 Hz, 1H), 4.11 (brs, 2H), 3.77 (d, J = 7.2 Hz, 1H), 3.73 (s, 3H), 3.45-3.65 (m, 2H), 2.29 (s, 3H), 2.14 (s, 3H), 1.96 (s, 3H), 1.88 (s, 3H), 1.63 (s, 3H), 1.18 (s, 3H), 1.11 (s, 3H), 1.05-2.50 (m, 18H), 0.80-0.95 (m, 12H); ^{13}C-NMR (100 MHz, CD_3OD) δ 204.7, 174.1, 173.9, 173.5, 173.1, 172.6, 171.3, 171.1, 170.9, 170.1, 170.1, 169.0, 167.3, 159.1, 147.6, 142.0, 141.8, 139.3, 138.0, 135.2, 134.9, 134.7, 134.4, 132.7, 131.2, 131.0, 130.9, 130.0, 129.6, 129.4, 128.5, 128.4, 128.4, 127.0, 113.9, 85.7, 85.7, 82.2, 82.1, 79.5, 79.3, 78.9, 77.3, 76.7, 76.1, 73.0, 72.2, 71.7, 60.4, 60.0, 59.9, 59.2, 55.7, 55.3, 54.7, 53.0, 53.0, 47.9, 47.4, 44.9,

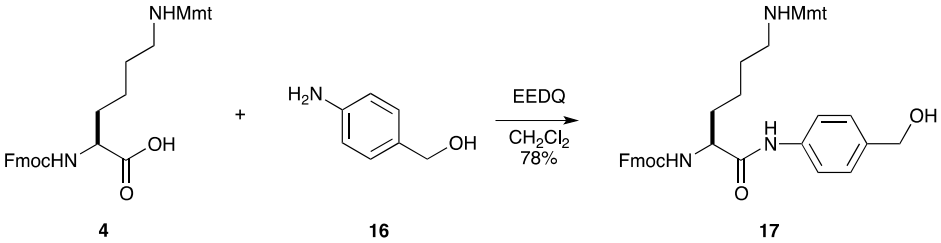
44.6, 42.7, 41.6, 37.5, 36.3, 33.4, 31.8, 31.7, 31.4, 30.8, 29.8, 27.0, 25.9, 25.7, 24.9, 23.6, 23.4, 23.3, 22.6, 22.5, 22.1, 20.9, 20.8, 19.9, 19.0, 15.1, 15.0, 10.6, 10.5; HRMS (ESI-TOFMS) calcd for $[C_{93}H_{112}N_7O_{21}+H]^+$ 1662.7911, found 1662.7933; $[\alpha]^{20}{}_D$ –19.9 (*c* 0.75, $CHCl_3$).



15 **2**

To a stirred solution of Ac-Val-Leu-Lys(Mmt)-Gly-D-Pro-paclitaxel **15** (29.6 mg, 0.0178 mmol) in 1% TFA containing CH_2Cl_2 (0.5 mL) was added MeOH (10 μL) at r.t. After stirring the mixture at r.t. for 4 h, the reaction mixture was directly purified by gel filtration chromatography (LH-20, $CHCl_3$/MeOH 1/1) to afford Ac-Val-Leu-Lys-Gly-D-Pro-paclitaxel•TFA **2** (19.0 mg, 71%) as colorless solids.

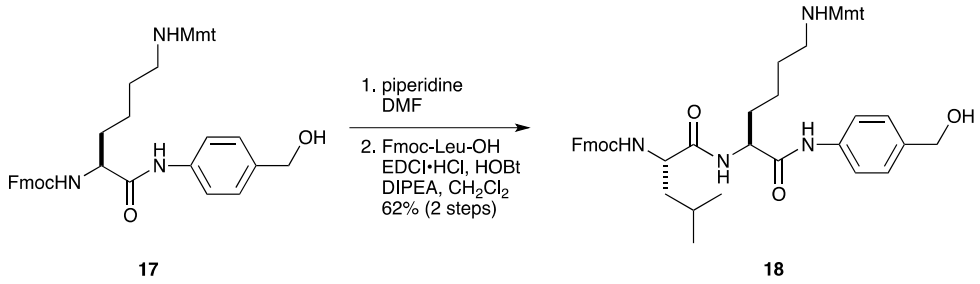
^{1}H-NMR (400 MHz, CD_3OD) δ 8.10 (d, *J* = 7.6 Hz, 2H), 7.35-7.88 (m, 12H), 7.10-7.35 (m, 1H), 6.43 (s, 1H), 6.04 (t, *J* = 7.2 Hz, 1H), 5.93 (d, *J* = 6.0 Hz, 1H), 5.62 (d, *J* = 7.2 Hz, 1H), 5.46 (d, *J* = 6.4 Hz, 1H), 4.97 (d, *J* = 8.8 Hz, 1H), 4.50-4.70 (m, 1H), 4.35-4.45 (m, 2H), 4.30 (dd, *J* = 6.4, 10.8 Hz, 1H), 4.17 (brs, 2H), 4.07 (brs, 2H), 3.78 (d, *J* = 7.2 Hz, 1H), 3.40-3.70 (m, 2H), 2.91 (t, *J* = 7.6 Hz, 2H), 2.33 (s, 3H), 2.16 (s, 3H), 2.00 (s, 3H), 1.89 (s, 3H), 1.64 (s, 3H), 1.13 (s, 3H), 1.12 (s, 3H), 1.06-2.52 (m, 18H), 0.83-1.05 (m, 12H); ^{13}C-NMR (100 MHz, CD_3OD) δ 204.7, 174.4, 174.3, 173.9, 173.9, 173.8, 173.7, 173.3, 172.5, 172.4, 171.3, 171.2, 171.0, 170.2, 170.0, 169.7, 169.2, 169.0, 167.3, 141.9, 141.7, 138.0, 135.3, 134.9, 134.8, 134.4, 132.8, 131.2, 131.0, 130.9, 130.0, 129.5, 129.4, 128.5, 128.4, 119.5, 116.6, 85.8, 82.2, 78.9, 77.4, 76.7, 76.1, 73.0, 72.3, 72.3, 61.0, 60.9, 60.0, 59.9, 59.2, 55.1, 54.1, 54.0, 53.3, 53.2, 47.9, 47.4, 44.6, 42.7, 41.3, 40.6, 37.5, 36.3, 32.4, 31.6, 31.5, 30.8, 29.9, 28.0, 27.0, 26.9, 25.9, 25.9, 25.6, 23.6, 23.4, 23.3, 22.6, 22.5, 22.4, 21.9, 20.9, 20.8, 19.8, 19.0, 15.1, 15.0, 10.6, 10.5; HRMS (ESI-TOFMS) calcd for $[C_{73}H_{96}N_7O_{20}+H]^+$ 1390.6710, found 1390.6719; $[\alpha]^{20}{}_D$ –24.8 (*c* 0.95, MeOH).



4 **16** **17**

To a stirred suspension of Fmoc-Lys(Mmt)-OH **4** (10.0 g, 15.6 mmol) and *p*-aminobenzyl alcohol **16** (9.61 g, 78.0 mmol) in CH_2Cl_2 (50 mL) was added EEDQ (7.72 g, 31.2 mmol) at r.t. After stirring the mixture at r.t. for 21 h, the reaction was quenched with sat. NH_4Cl and extracted with $CHCl_3$. The organic layer was washed with sat. $NaHCO_3$ and brine. The extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH 98/2 to 95/5, Et_3N 2%) and gel filtration chromatography (LH-20, $CHCl_3$/MeOH 1/1) to afford Fmoc-Lys(Mmt)-aminobenzyl alcohol **17** (9.02 g, 78%) as pale yellow amorphous.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.68 (brd, 1H), 7.72 (d, J = 3.2, 7.6 Hz, 2H), 7.10-7.55 (m, 22H), 6.76 (d, J = 8.8 Hz, 2H), 5.82 (br, 1H), 4.54 (s, 2H), 4.25-4.45 (m, 3H), 4.13 (app. t, J = 6.8 Hz, 1H), 3.73 (s, 3H), 2.14 (t, J = 6.8 Hz, 1H), 1.87 (br, 1H), 1.70 (br, 1H), 1.27-1.60 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.7, 157.5, 156.3, 146.0, 143.4, 141.1, 137.9, 136.9, 136.7, 129.6, 128.3, 127.6, 127.0, 126.0, 124.8, 119.9, 113.0, 70.5, 67.2, 64.9, 55.7, 55.2, 47.1, 43.4, 32.4, 30.5, 23.5; HRMS (ESI-TOFMS) calcd for $[C_{48}H_{47}N_3O_5+Na]^+$ 768.3413, found 768.3418; $[\alpha]^{20}_D$ –20.7 (*c* 0.94, $CHCl_3$).

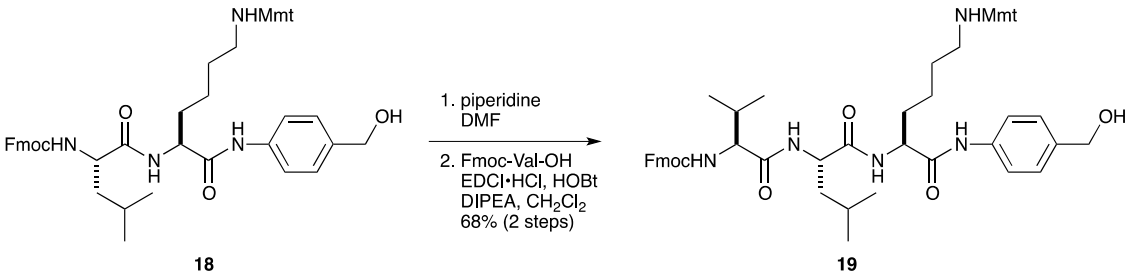


17 **18**

To a stirred solution of Fmoc-Lys(Mmt)-aminobenzyl alcohol **17** (4.64 g, 6.22 mmol) in DMF (15 mL) was added piperidine (2.5 mL, 24.9 mmol) at r.t. After stirring the mixture at r.t. for 5 min, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/AcOEt 9/1 to $CHCl_3$/MeOH 9/1, Et_3N 2%) to afford crude H-Lys(Mmt)-aminobenzyl alcohol as a DMF solution. To a stirred solution of the crude amine in CH_2Cl_2 (30 mL) were added Fmoc-Leu-OH (2.42 g, 6.84 mmol), HOBt (924 mg, 6.84 mmol),

EDCI•HCl (1.31 g, 6.84 mmol) and DIPEA (3.6 mL, 20.5 mmol) at 0 °C. After stirring the mixture at r.t. for 18 h, the reaction was quenched with sat. NH_4Cl. The mixture was extracted with $CHCl_3$. The organic layer was washed with sat. $NaHCO_3$ and brine. The extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH 98/2, Et_3N 2%) to afford Fmoc-Leu-Lys(Mmt)-aminobenzyl alcohol **18** (3.32 g, 62%, 2 steps) as pale yellow amorphous.

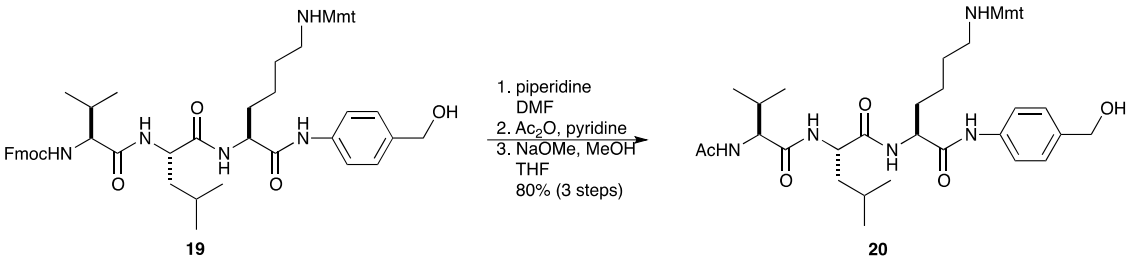
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.66 (br, 1H), 7.74 (d, J = 6.8 Hz, 2H), 7.10-7.60 (m, 22H), 6.94 (br, 1H), 6.76 (d, J = 8.8 Hz, 2H), 5.47 (br, 1H), 4.59 (s, 2H), 4.55 (br, 1H), 4.42 (app. q, J = 6.8 Hz, 1H), 4.37 (app. q, J = 6.4 Hz, 1H), 4.33 (br, 1H), 4.14 (t, J = 6.4 Hz, 1H), 3.75 (s, 3H), 2.12 (br, 2H), 1.95 (br, 1H), 1.30-1.70 (m, 8H), 0.80-1.00 (m, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.5, 169.4, 157.5, 156.2, 146.1, 143.3, 141.1, 136.9, 136.8, 129.6, 128.3, 127.6, 126.9, 126.0, 124.7, 120.0, 119.9, 112.9, 70.3, 66.9, 64.8, 58.4, 55.2, 54.0, 47.1, 43.4, 41.3, 31.8, 30.5, 24.8, 23.6, 23.0, 21.9; HRMS (ESI-TOFMS) calcd for $[C_{54}H_{59}N_4O_6+H]^+$ 859.4435, found 859.4423; $[\alpha]^{20}_D$ –29.1 (*c* 1.45, $CHCl_3$).



To a stirred solution of Fmoc-Leu-Lys(Mmt)-aminobenzyl alcohol **18** (3.20 g, 3.73 mmol) in DMF (10 mL) was added piperidine (1.5 mL, 14.9 mmol) at r.t. After stirring the mixture at r.t. for 10 min, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/AcOEt 9/1 to $CHCl_3$/MeOH 9/1, Et_3N 2%) to afford crude H-Leu-Lys(Mmt)-Gly-OBn as a DMF solution. To a stirred solution of the crude amine in CH_2Cl_2 (15 mL) were added Fmoc-Val-OH (1.39 g, 4.10 mmol), HOBt (554 mg, 4.10 mmol), EDCI•HCl (785 mg, 4.10 mmol) and DIPEA (2.0 mL, 4.10 mmol) at 0 °C. After stirring the mixture at r.t. for 20 h, the reaction was quenched with sat. NH_4Cl. The mixture was extracted with $CHCl_3$. The organic layer was washed with sat. $NaHCO_3$ and brine. The extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH 98/2, Et_3N 2%) to afford

Fmoc-Val-Leu-Lys(Mmt)-aminobenzyl alcohol **19** (2.43 g, 68%, 2 steps) as colorless amorphous.

^{1}H-NMR (400 MHz, CD_3OD) δ 7.76 (d, J = 6.8 Hz, 2H), 7.64 (d, J = 7.2 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.14-7.45 (m, 17H), 7.13 (d, J = 6.8 Hz, 2H), 6.76 (d, J = 8.8 Hz, 2H), 4.58 (br, 1H), 4.54 (s, 2H), 4.25-4.50 (m, 4H), 4.17 (t, J = 7.2 Hz, 1H), 3.87 (d, J = 6.8 Hz, 2H), 3.72 (s, 3H), 1.95-2.20 (m, 3H), 1.20-1.90 (m, 9H), 0.80-0.95 (m, 12H); ^{13}C-NMR (100 MHz, CD_3OD): δ 174.2, 174.1, 172.1, 159.1, 158.5, 147.6, 145.0, 142.3, 139.2, 138.5, 138.3, 130.8, 129.5, 128.6, 128.5, 128.4, 128.0, 127.0, 126.0, 121.1, 120.8, 113.8, 79.4, 71.6, 68.1, 64.8, 62.5, 58.3, 55.6, 55.5, 53.2, 44.8, 41.5, 33.3, 31.8, 31.3, 25.9, 25.0; HRMS (ESI-TOFMS) calcd for $[C_{59}H_{68}N_5O_7+H]^+$ 958.5119, found 958.5114; $[\alpha]^{20}_D$ –46.7 (*c* 0.68, $CHCl_3$).

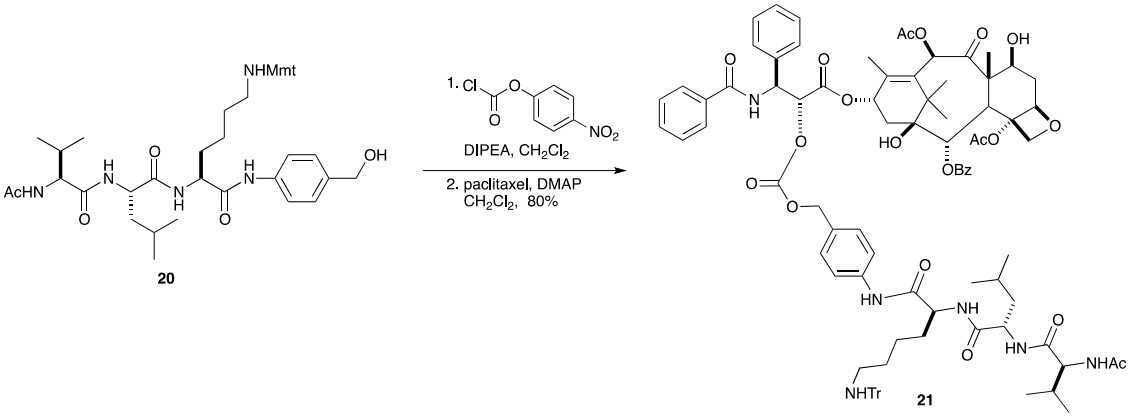


19 **20**

To a stirred solution of Fmoc-Val-Leu-Lys(Mmt)-aminobenzyl alcohol **19** (200 mg, 0.209 mmol) in DMF (1 mL) was added piperidine (90 μL, 0.835 mmol) at r.t. After stirring the mixture at r.t. for 10 min, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/AcOEt 9/1 to $CHCl_3$/MeOH 9/1, Et_3N 2%) to afford crude H-Val-Leu-Lys(Mmt)-aminobenzyl alcohol as a DMF solution. To a stirred solution of the crude amine in pyridine (5 mL) was added acetic anhydride (0.2 mL, 2.09 mmol). After stirring the mixture at r.t. for 30 min, the mixture was concentrated *in vacuo*. To a stirred solution of the residue in THF (1 mL) and MeOH (1 mL) was added NaOMe (3.0 mg). After stirring the mixture at r.t. for 80 min, the mixture was directly purified by silica gel column chromatography ($CHCl_3$/MeOH 98/2 to $CHCl_3$/MeOH 9/1, Et_3N 2%) to afford Ac-Val-Leu-Lys(Mmt)-aminobenzyl alcohol **20** (134 mg, 80%, 3 steps) as colorless amorphous.

^{1}H-NMR (400 MHz, CD_3OD) δ 7.53 (d, J = 8.4 Hz, 2H), 7.05-7.40 (m, 14H), 6.77 (d, J = 8.8 Hz, 2H), 4.54 (s, 2H), 4.49 (t, J = 7.2 Hz, 1H), 4.44 (dd, J = 5.6, 8.4 Hz, 1H), 4.16 (d, J = 7.6 Hz, 2H), 3.71 (s, 3H), 2.11 (t, J = 6.8 Hz, 1H), 1.96 (s, 3H), 1.24-2.05 (m, 10H), 0.80-0.95 (m, 12H); ^{13}C-NMR (100 MHz, CD_3OD) δ 174.2, 173.5, 173.1, 172.1, 159.1, 147.6, 139.3, 138.5, 138.4, 130.8, 129.5, 128.5, 127.0, 121.1, 113.8, 71.6, 64.9, 60.5, 55.6, 55.4, 53.1, 44.8, 41.7, 33.5, 31.9, 31.3, 25.9, 25.0, 23.5, 22.6, 22.1, 19.9, 19.0; HRMS (ESI-TOFMS) calcd for

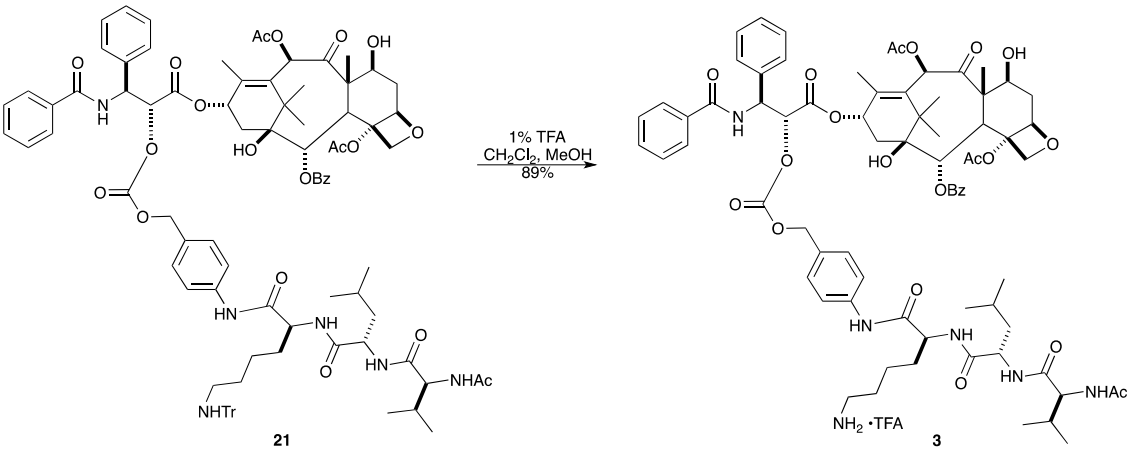
$[C_{46}H_{60}N_5O_6+H]^+$ 778.4544, found 778.4551; $[\alpha]^{20}_D$ –42.9 (*c* 0.63, MeOH).



To a stirred suspension of Ac-Val-Leu-Lys(Mmt)-aminobenzyl alcohol **20** (183 mg, 0.235 mmol) in CH_2Cl_2 (1 mL) was added DIPEA (120 □L, 0.705 mmol) and *p*-nitrophenyl chloroformate (57.0 mg, 0.282 mmol) at 0 °C. After stirring the mixture at r.t. for 3.5 h, The reaction was quenched with sat. $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ and extracted organic layers were washed with brine. After drying the extract over Na_2SO_4, and concentration, the crude was purified by silica gel column chromatography ($CHCl_3$:MeOH 20:1-9:1) to give Ac-Val-Leu-Lys(Mmt)-aminobenzyl-PNP (147 mg). Then, To a solution of Ac-Val-Leu-Lys(Mmt)-aminobenzyl-PNP (147 mg, 0.156 mmol) and paclitaxel **11** (80.0 mg, 0.0937 mmol), DMAP (20.0 mg, 0.164 mmol) was added at 4 °C. After 2 h, the reaction mixture was directly purified by gel filtration chromatography (LH-20, $CHCl_3$/MeOH 1/1) and recycle gel filtration HPLC ($CHCl_3$, 3.5 mL/min) to afford Ac-Val-Leu-Lys(Mmt)-aminobenzyl-paclitaxel **21** (124 mg, 80% based on paclitaxel) as a colorless amorphous.

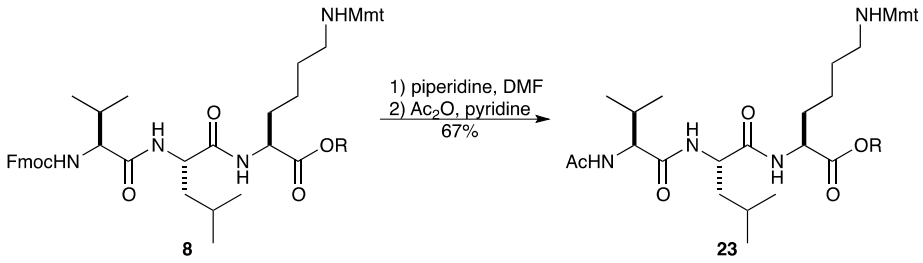
^{1}H-NMR (400 MHz, CD_3OD) δ 8.10 (d, *J* = 7.2 Hz, 2H), 7.74 (d, *J* = 7.2 Hz, 2H), 7.05-7.68 (m, 27H), 6.77 (d, *J* = 9.2 Hz, 2H), 6.44 (s, 1H), 6.07 (t, *J* = 8.8 Hz, 1H), 5.84 (d, *J* = 6.0 Hz, 1H), 5.63 (d, *J* = 7.2 Hz, 1H), 5.48 (d, *J* = 6.0 Hz, 1H), 5.08-5.20 (m, 2H), 4.97 (d, *J* = 10.0 Hz, 1H), 4.40-4.50 (m, 2H), 4.34 (dd, *J* = 6.4, 10.8 Hz, 1H), 4.10-4.20 (m, 3H), 3.81 (d, *J* = 7.2 Hz, 1H), 3.69 (s, 3H), 2.39 (s, 3H), 2.13 (s, 3H), 1.96 (s, 3H), 1.90 (s, 3H), 1.65 (s, 3H), 1.13 (s, 3H), 1.11 (s, 3H), 1.05-2.55 (m, 16H), 0.80-0.95 (m, 12H); ^{13}C-NMR (100 MHz, CD_3OD) δ 204.7, 174.1, 173.5, 173.1, 172.1, 171.3, 171.0, 170.1, 169.8, 167.3, 159.3, 155.4, 141.9, 139.7, 137.8, 135.1, 134.7, 134.4, 132.7, 131.9, 131.1, 130.9, 130.1, 129.8, 129.5, 129.3, 128.6, 128.4, 127.3, 121.1, 114.0, 85.8, 82.1, 79.4, 79.3, 79.3, 78.9, 78.5, 78.4, 77.4, 76.7, 76.2, 76.1, 73.1, 72.3, 72.2, 71.1, 60.5, 59.1, 55.7, 55.3, 53.0, 47.8, 45.0, 44.6, 41.7, 37.5, 36.4, 33.3, 31.8, 27.0, 25.9,

24.9, 23.5, 23.4, 23.3, 22.6, 22.5, 22.2, 21.0, 20.9, 19.9, 19.1, 15.1, 15.1, 10.6, 10.6; HRMS (ESI-TOFMS) calcd for $[C_{94}H_{109}N_6O_{21}+H]^+$ 1657.7646, found 1657.7651; $[\alpha]^{20}_D$ –43.8 (*c* 0.50, $CHCl_3$).



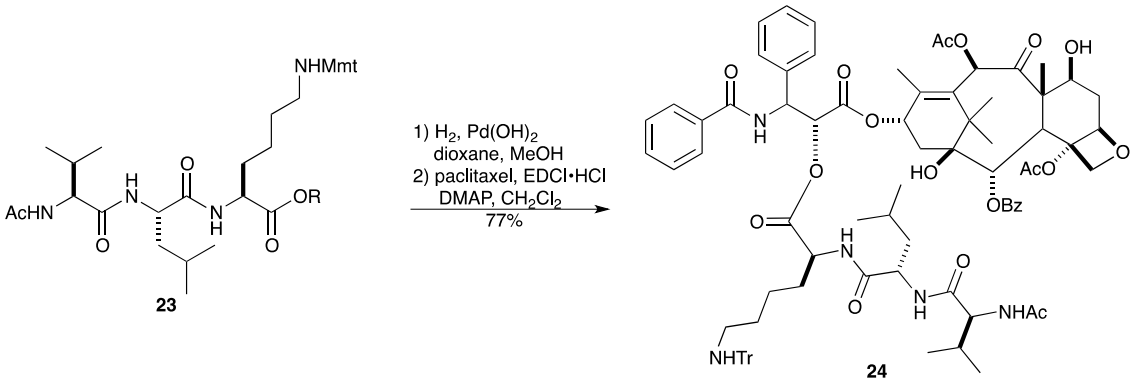
To a stirred solution of Ac-Val-Leu-Lys(Mmt)-aminobenzyl-paclitaxel **21** (50.4 mg, 0.0304 mmol) in 1% TFA containing CH_2Cl_2 (2.3 mL) was added MeOH (20 μL) at r.t. After stirring the mixture at r.t. for 10 min, the reaction mixture was directly purified by gel filtration chromatography (LH-20, $CHCl_3$/MeOH 1/1) to afford Ac-Val-Leu-Lys-aminobenzyl-paclitaxel •TFA **3** (40.5 mg, 89%) as colorless solids.

^{1}H-NMR (400 MHz, CD_3OD) δ 8.10 (d, *J* = 7.6 Hz, 2H), 7.77 (d, *J* = 7.2 Hz, 2H), 7.20-7.70 (m, 15H), 6.44 (s, 1H), 6.06 (app. t, *J* = 8.8 Hz, 1H), 5.83 (d, *J* = 6.4 Hz, 1H), 5.63 (d, *J* = 7.2 Hz, 1H), 5.49 (d, *J* = 6.8 Hz, 1H), 5.19 (d, *J* = 12.0 Hz, 1H), 5.13 (d, *J* = 12.0 Hz, 1H), 4.99 (d, *J* = 9.6 Hz, 1H), 4.46 (dd, *J* = 5.2, 9.2 Hz, 1H), 4.41 (dd, *J* = 5.2, 9.6 Hz, 1H), 4.34 (dd, *J* = 6.8, 10.8 Hz, 1H), 4.18 (s, 2H), 4.10 (d, *J* = 7.2 Hz, 1H), 3.80 (d, *J* = 7.6 Hz, 1H), 2.92 (t, *J* = 7.6 Hz, 1H), 2.35-2.55 (m, 1H), 2.37 (s, 3H), 2.01 (s, 3H), 1.88 (s, 3H), 1.65 (s, 3H), 1.13 (s, 3H), 1.12 (s, 3H), 1.05-2.55 (m, 14H), 0.85-1.05 (m, 12H); ^{13}C-NMR (100 MHz, CD_3OD) δ 204.7, 174.4, 173.9, 173.5, 171.9, 171.3, 171.0, 170.2, 169.9, 167.3, 155.4, 141.9, 139.7, 137.8, 135.2, 134.7, 134.4, 132.7, 132.0, 131.1, 131.0, 130.1, 129.9, 129.5, 129.3, 128.4, 121.0, 119.5, 85.8, 82.1, 79.3, 78.9, 78.5, 77.4, 76.7, 76.2, 73.1, 72.3, 71.1, 61.1, 59.2, 55.3, 55.1, 53.4, 47.9, 44.6, 41.3, 40.6, 37.5, 36.5, 32.5, 31.5, 30.8, 28.2, 27.0, 25.9, 23.9, 23.5, 23.3, 22.6, 22.5, 22.4, 21.9, 21.0, 19.8, 19.0, 15.1, 10.6; HRMS (ESI-TOFMS) calcd for $[C_{74}H_{93}N_6O_{20}+H]^+$ 1385.6445, found 1385.6443, $[\alpha]^{20}_D$ –59.7 (*c* 1.77, MeOH).



To a stirred solution of Fmoc-Val-Leu-Lys(Mmt)-OBn **8** (300 mg, 0.318 mmol) in DMF (1 mL) was added piperidine (0.11 □L, 1.40 mmol) at r.t. After stirring the mixture at r.t. for 10 min, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/AcOEt 9/1 to $CHCl_3$/MeOH 9/1, Et_3N 2%) to afford crude H-Val-Leu-Lys(Mmt)-OBn as a DMF solution. To a stirred solution of the crude amine in pyridine (1 mL) was added acetic anhydride (0.3 mL, 0.636 mmol). After stirring the mixture at r.t. for 40 min, the mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH 95/5, Et_3N 2%) to afford Ac-Val-Leu-Lys(Mmt)-OBn **23** (164 mg, 67%, 2 steps) as colorless amorphous.

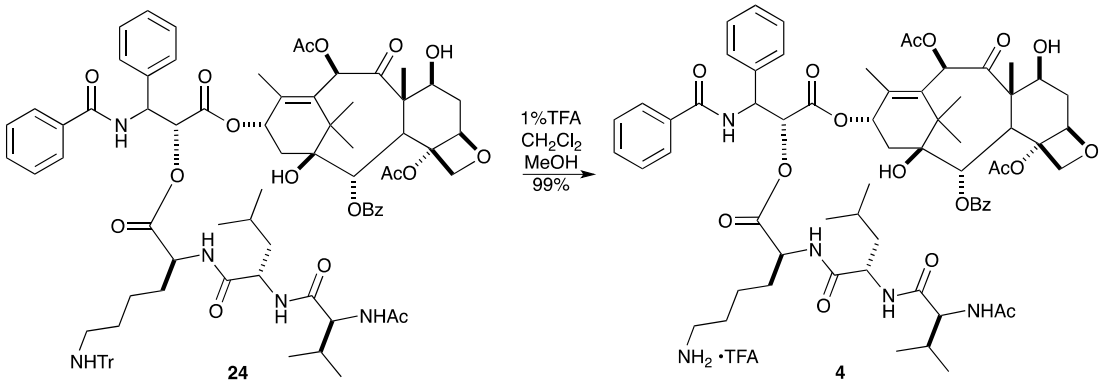
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.65 (brt, 2H), 7.41 (d, J = 7.6 Hz, 4H), 7.05-7.35 (m, 13H), 6.76 (d, J = 9.2 Hz, 4H), 5.15 (d, J = 12.4 Hz, 1H), 5.07 (d, J = 12.4 Hz, 1H), 4.63 (q, J = 6.8 Hz, 1H), 4.54 (q, J = 6.0 Hz, 1H), 4.47 (t, J = 6.8 Hz, 1H), 3.72 (s, 3H), 2.01 (brt, 2H), 1.95 (s, 3H), 1.15-2.00 (m, 10H), 0.75-0.89 (m, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.7, 171.2, 171.1, 169.8, 157.5, 146.2, 138.2, 135.1, 129.5, 128.9, 128.4, 128.3, 128.1, 127.6, 126.0, 112.9, 70.3, 67.1, 58.3, 55.2, 52.2, 51.7, 43.4, 41.0, 32.4, 31.5, 30.7, 24.7, 23.2, 22.8, 22.3, 19.2, 18.5; HRMS (ESI-TOFMS) calcd for $[C_{46}H_{59}N_4O_6+H]^+$ 763.4435, found 736.4448; $[\alpha]^{20}_D$ –26.8 (*c* 0.75, $CHCl_3$).



A suspension of Ac-Val-Leu-Lys(Mmt)-OBn **23** (150 mg, 0.197 mmol) and Pd-ethylenediamine complex (4.6%, 30.0 mg) in dioxane (7 mL) and MeOH (3 mL) was stirred under H_2

atmosphere for 12 h. The reaction mixture was filtered and concentrated *in vacuo*. The residue was purified with by silica gel column chromatography ($CHCl_3$/AcOEt 1/1 to $CHCl_3$/MeOH 4/1, Et_3N 2%) to afford crude Ac-Val-Leu-Lys(Mmt)-OH **24**. To a stirred solution of Ac-Val-Leu-Lys(Mmt)-OH and paclitaxel **11** (32.1 mg, 0.0376 mmol) in CH_2Cl_2 (1 mL) was added EDCI•HCl (14.4 mg, 0.0752 mmol) and DMAP (9.2 mg, 0.0752 mmol) at 0 °C. After stirring the mixture at r.t. for 10 h, the reaction mixture was directly purified by gel filtration chromatography (LH-20, $CHCl_3$/MeOH 1/1) and silica gel column chromatography ($CHCl_3$/MeOH 98/2, 2% Et_3N) to afford Ac-Val-Leu-Lys(Mmt)-paclitaxel **4** (43.7 mg, 77% based on paclitaxel) as a colorless amorphous.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.6 Hz, 2H), 7.77 (d, *J* = 7.2 Hz, 2H), 7.75-7.85 (m, 1H), 7.10-7.65 (m, 23H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.29 (s, 1H), 6.23 (app. t, *J* = 9.6 Hz, 2H), 6.15 (brd, 1H), 6.04 (brd, 1H), 5.77 (brd, 1H), 5.69 (d, *J* = 7.2 Hz, 1H), 5.47 (d, *J* = 2.4 Hz, 1H), 4.97 (d, *J* = 9.2 Hz, 1H), 4.52 (app.q, *J* = 5.6 Hz, 1H), 4.40-4.50 (m, 1H), 4.31 (d, *J* = 8.8 Hz, 1H), 4.21 (d, *J* = 8.8 Hz, 1H), 4.05-4.15 (m, 1H), 3.76 (s, 3H), 3.70-3.85 (m, 2H), 2.47 (s, 3H), 2.22 (s, 3H), 1.93 (s, 3H), 1.91 (s, 3H), 1.21 (s, 3H), 1.14 (s, 3H), 1.05-2.65 (m, 16H), 0.75-0.95 (m, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.5, 171.3, 170.9, 169.6, 167.7, 167.3, 166.7, 157.5, 146.2, 142.6, 138.2, 136.5, 134.1, 133.4, 132.5, 131.5, 130.1, 129.6, 129.0, 128.7, 128.6, 128.3, 128.2, 127.6, 126.6, 126.0, 112.9, 84.4, 81.0, 78.9, 76.4, 75.6, 74.7, 72.1, 71.8, 70.3, 59.7, 58.5, 58.4, 55.2, 52.7, 52.2, 45.6, 43.4, 43.2, 39.9, 35.7, 30.6, 30.0, 29.8, 26.8, 24.8, 23.3, 23.2, 23.1, 22.8, 22.3, 21.5, 20.9, 19.4, 18.5, 18.4, 14.9, 9.7; HRMS (ESI-TOFMS) calcd for $[C_{86}H_{102}N_5O_{19}+H]^+$ 1508.7169, found 1508.7167; $[\alpha]^{20}_D$ –44.6 (*c* 1.25, $CHCl_3$).



Ac-Val-Leu-Lys(Mmt)-paclitaxel (20.5 mg, 0.0118 mmol) was dissolved in 1% TFA containing CH_2Cl_2 (1 mL), and MeOH (8 μL) was added. After stirring the mixture at r.t. for 10 min, The

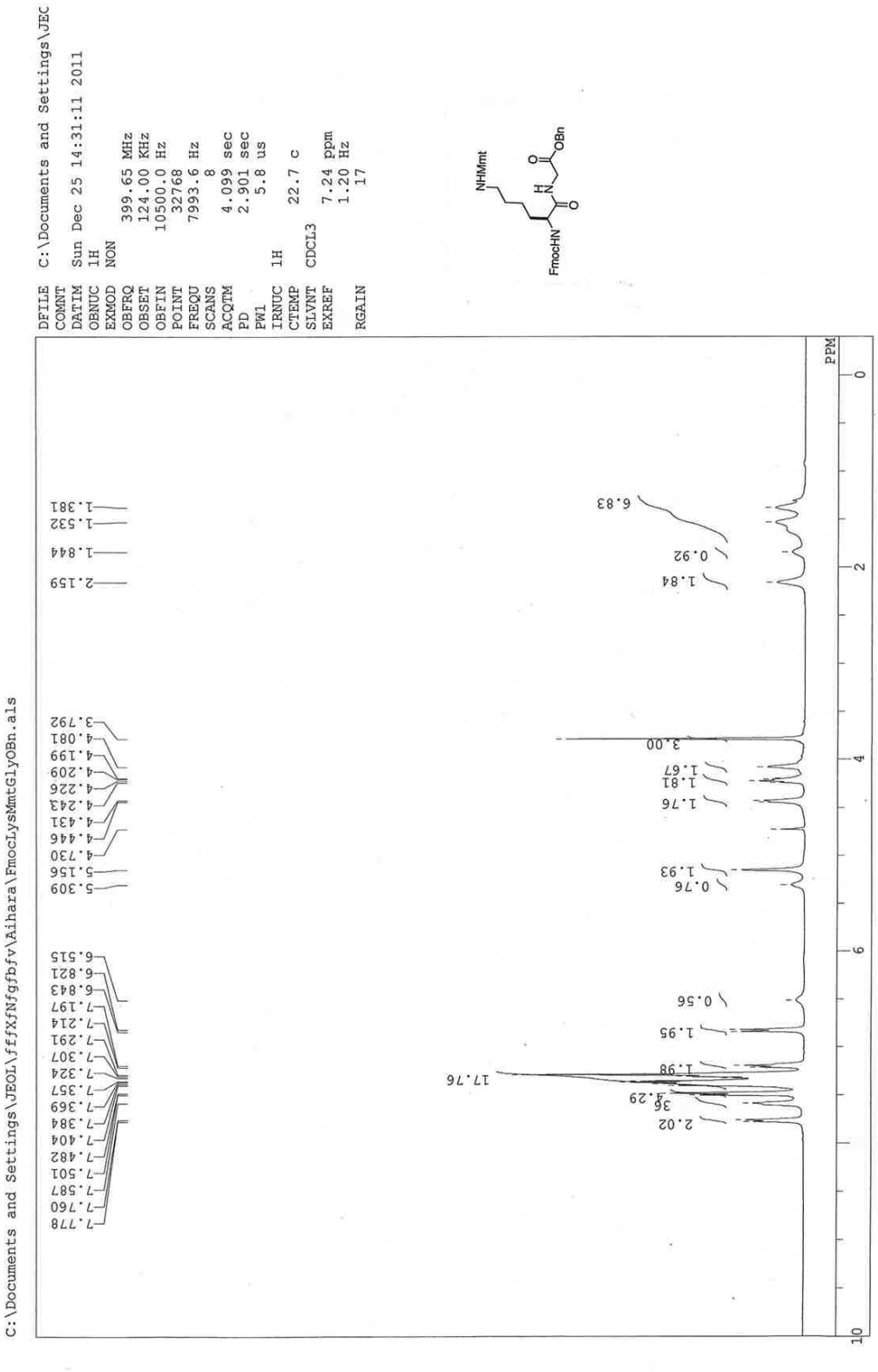
reaction mixture was directly purified by gel filtration chromatography (LH-20, $CHCl_3$/MeOH 1/1) to afford Ac-Val-Leu-Lys-paclitaxel•TFA (18.4 mg, 99%) as colorless amorphous. ^{1}H-NMR (400 MHz, CD_3OD) δ 8.11 (d, *J* = 7.2 Hz, 2H), 7.83 (d, *J* = 6.8 Hz, 2H), 7.35-7.70 (m, 10H), 7.28 (t, *J* = 7.2 Hz, 1H), 6.44 (s, 1H), 6.07 (app. t, *J* = 5.2 Hz, 1H), 5.55 (d, *J* = 6.4 Hz, 1H), 5.63 (d, *J* = 7.2 Hz, 1H), 5.55 (d, *J* = 6.0 Hz, 1H), 4.99 (d, *J* = 9.6 Hz, 1H), 4.54 (dd, *J* = 5.2, 9.2 Hz, 1H), 4.32 (dd, *J* = 6.4, 10.8 Hz, 1H), 4.27 (dd, *J* = 6.5, 9.6 Hz, 1H), 4.25 (s, 2H), 3.98 (d, *J* = 7.2 Hz, 1H), 3.80 (d, *J* = 7.2 Hz, 1H), 2.81 (t, *J* = 7.6 Hz, 2H), 2.40 (s, 3H), 2.16 (s, 3H), 1.97 (s, 3H), 1.91 (s, 3H), 1.65 (s, 3H), 1.14 (s, 3H), 1.12 (s, 3H), 1.10-2.50 (m, 14H), 0.80-1.00 (m, 12H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 204.7, 174.5, 173.7, 173.7, 172.3, 171.3, 170.9, 170.2, 169.6, 167.3, 141.9, 137.9, 135.3, 134.8, 134.4, 132.8, 131.2, 131.0, 131.0, 129.9, 129.5, 129.5, 129.5, 129.4, 129.4, 128.6, 128.5, 128.4, 85.7, 82.2, 78.9, 77.4, 76.7, 76.1, 72.9, 72.3, 71.5, 61.3, 59.2, 55.1, 53.1, 47.9, 44.6, 41.0, 40.5, 37.5, 36.4, 31.8, 31.3, 30.8, 28.1, 27.0, 25.8, 23.6, 23.5, 23.4, 23.3, 22.6, 22.5, 22.5, 22.1, 21.9, 20.9, 20.8, 19.7, 18.9, 15,0, 10.5; HRMS (ESI-TOFMS) calcd for $[C_{66}H_{86}N_5O_{18}+H]^+$ 1236.5968, found 1236.5955; $[\alpha]^{20}_D$ –50.1 (*c* 0.84, MeOH).

Plasmine cleavage evaluation

Hundred μM of each prodrug was treated with 94nM plasmin at 37˚C in TBS (oH7.5) for 0, 1, 3 hours and the reaction was stopped by adding 25μl of 5x0.2% SDS in phosphate buffer and then each sample was filtered through Ultrafree-MC HV (MILLIPORE, USA). Reversed-phase HPLC was performed at 35 ˚C on a CAPCELL PAK C18 AQ column 4.6mm I.D. x 100mm (SHISEIDO, Japan). Fifty μl of a sample was injected into an Nexera HPLC system (Shimadzu Corporation, Kyoto, Japan). The mobile phase was 0.2% SDS solution mixed with 50% of phosphate buffer and 50% of acetonitrile. The flow rate was 1ml/min and the detector was set at 227 nm.

Table 1. Releasing rate of paclitaxel from compounds **1**-**4**.

time (h)	**1** Av	**1** SD	**2** Av	**2** SD	**3** Av	**3** SD	**4** Av	**4** SD
0	0.62	0.55	0.00	0.01	2.54	1.11	0.00	0.00
1	13.95	2.24	4.91	1.99	18.63	4.35	3.23	0.71
3	29.38	3.87	14.87	2.02	29.03	7.30	8.87	3.38
24	65.10	8.71	50.09	8.55	56.75	15.52	59.32	6.77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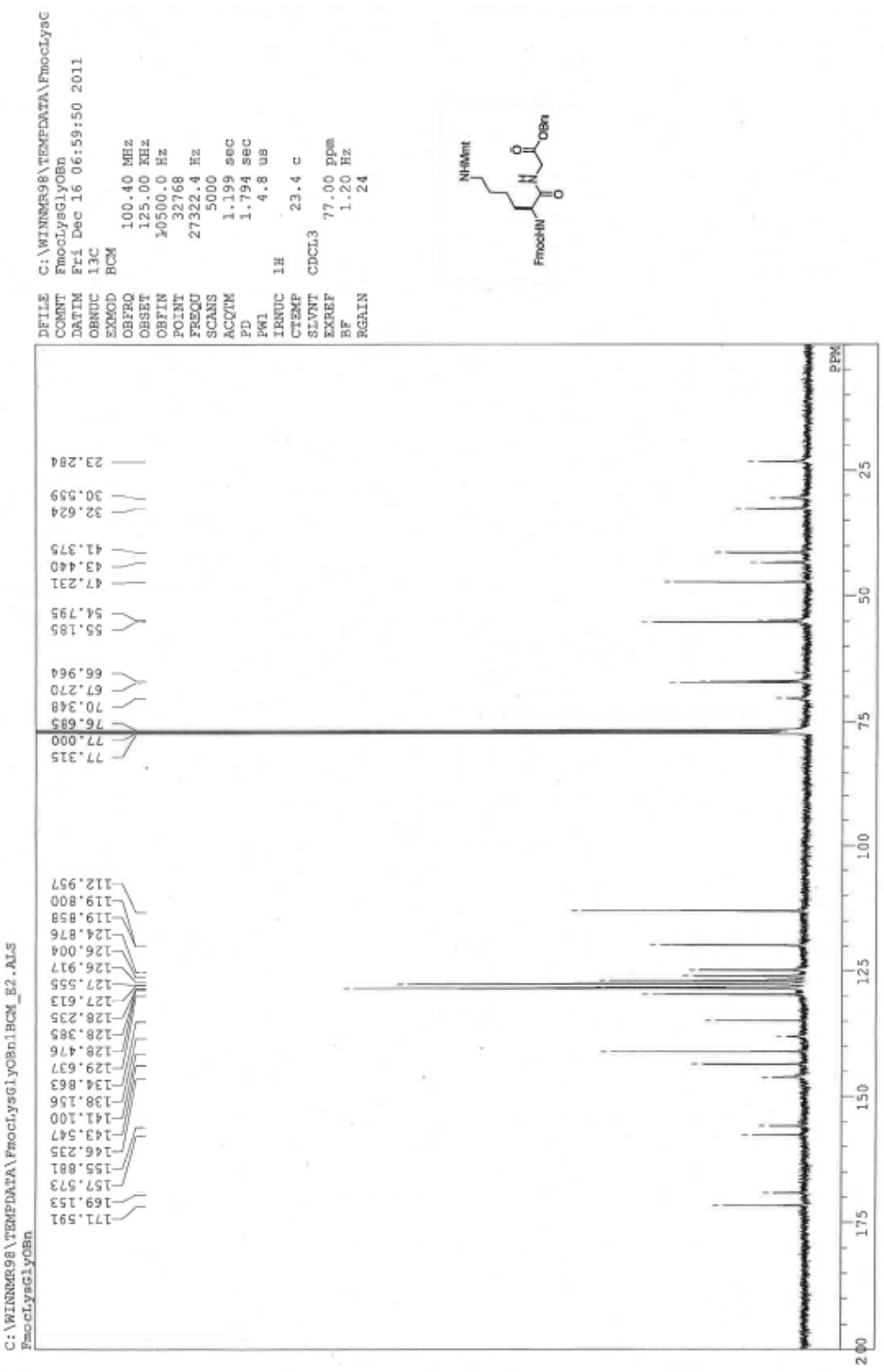

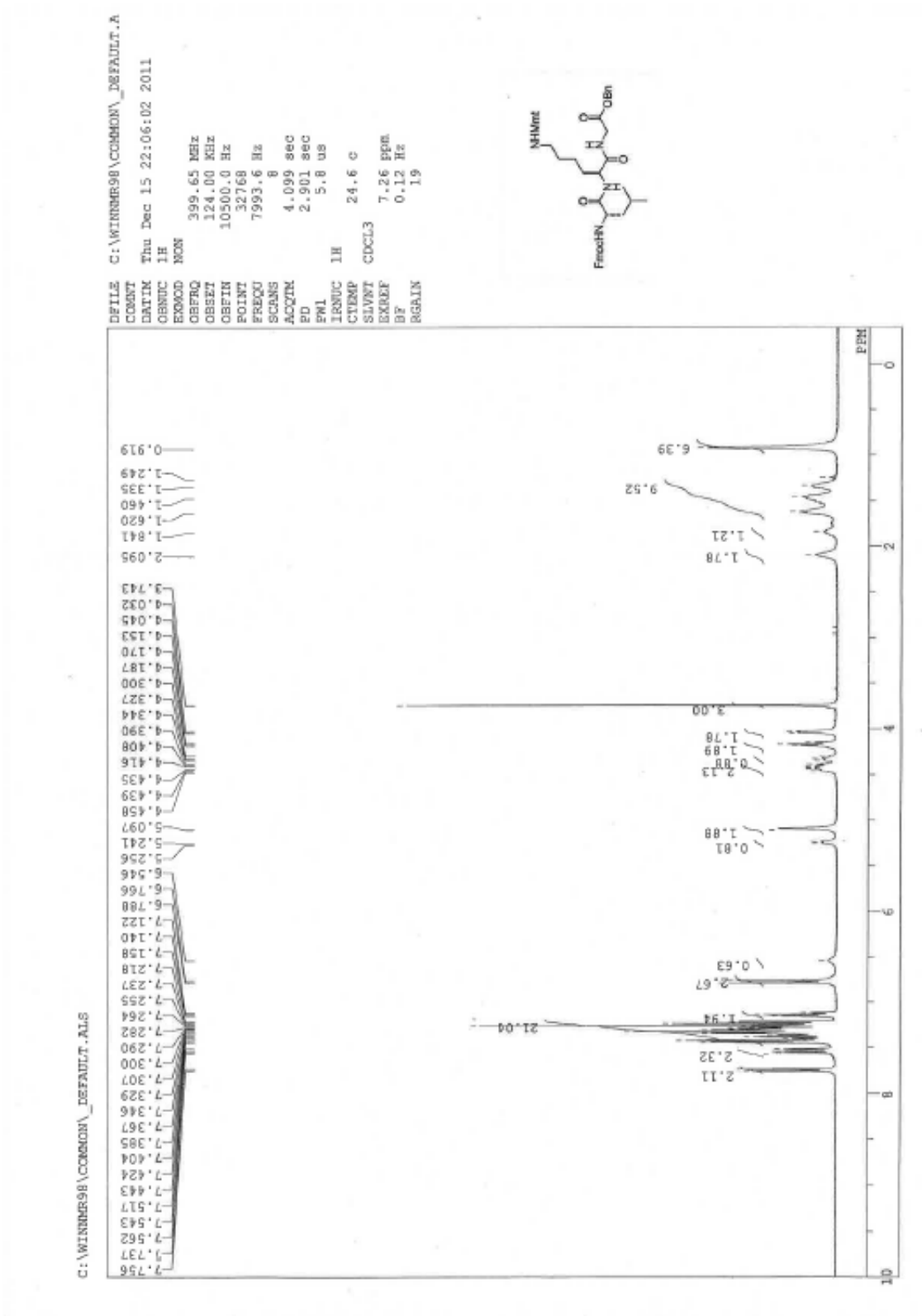
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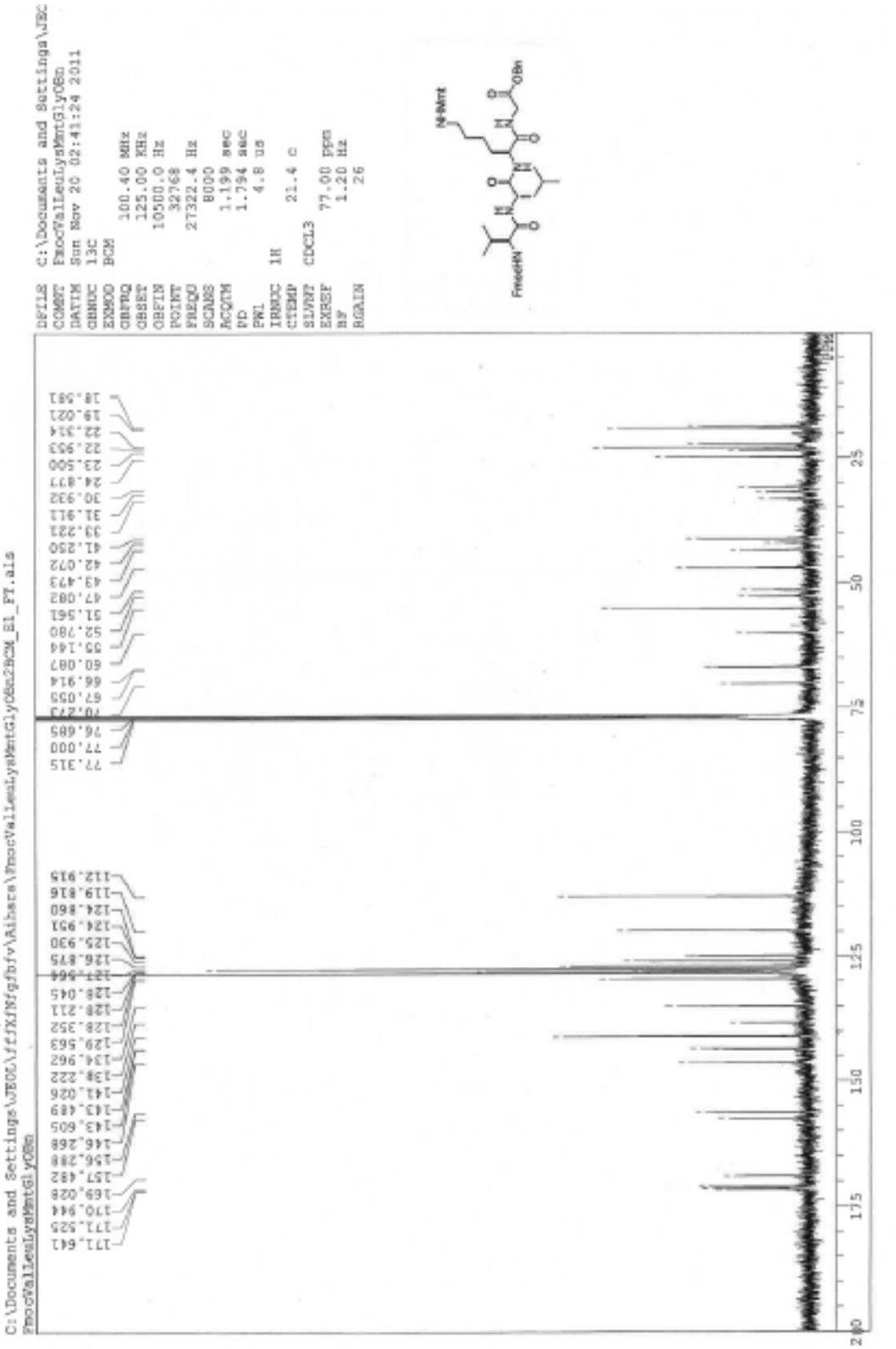
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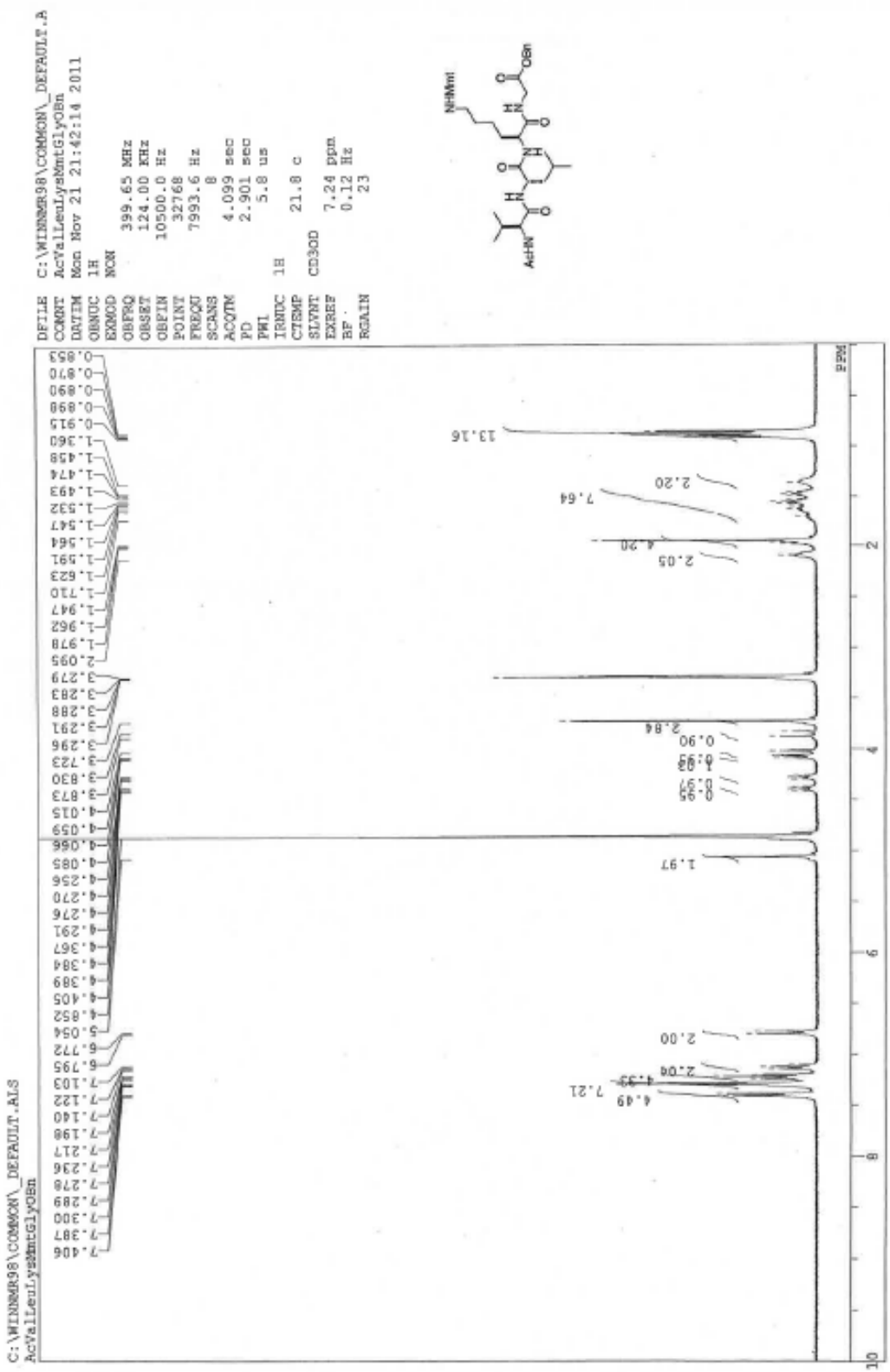
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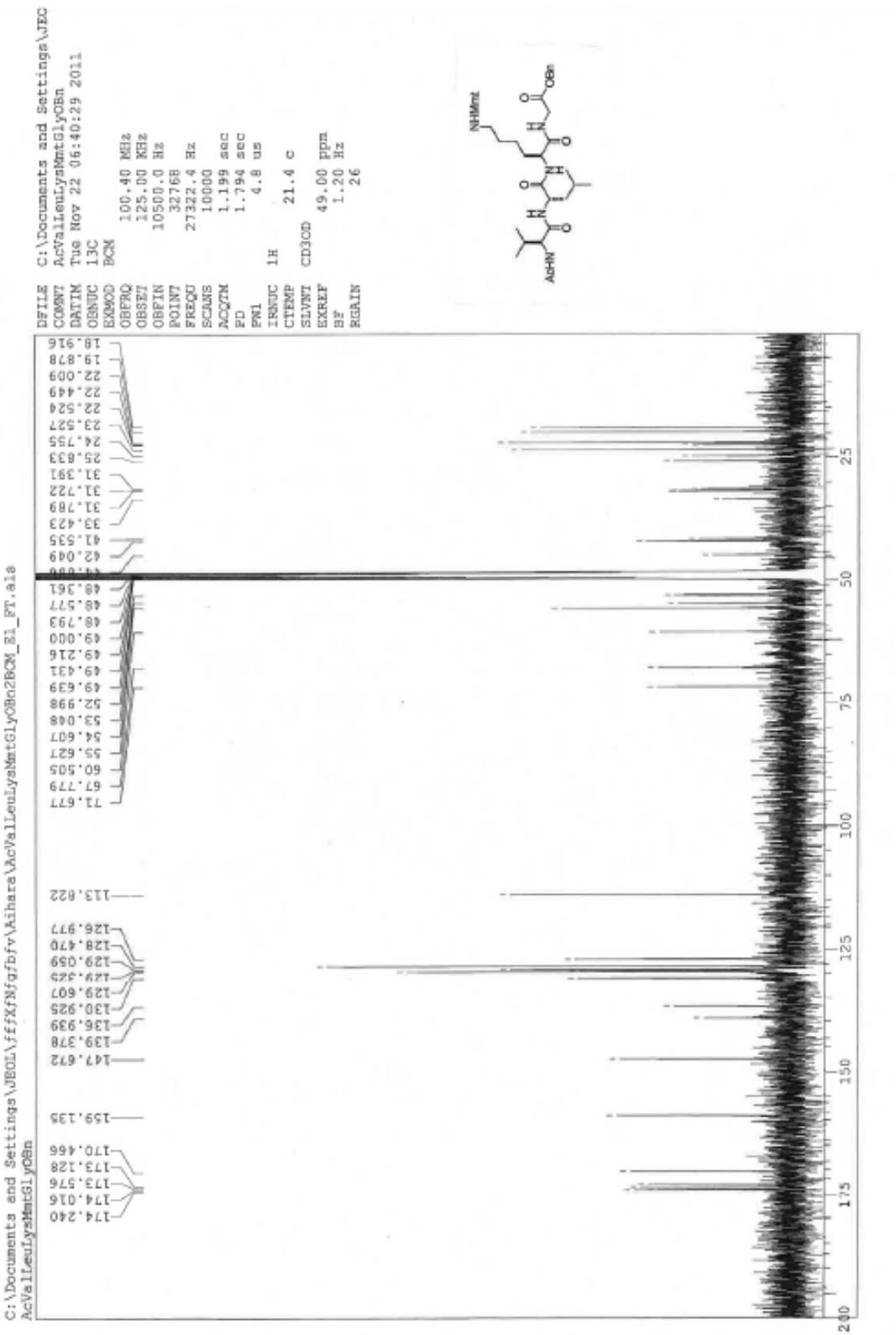
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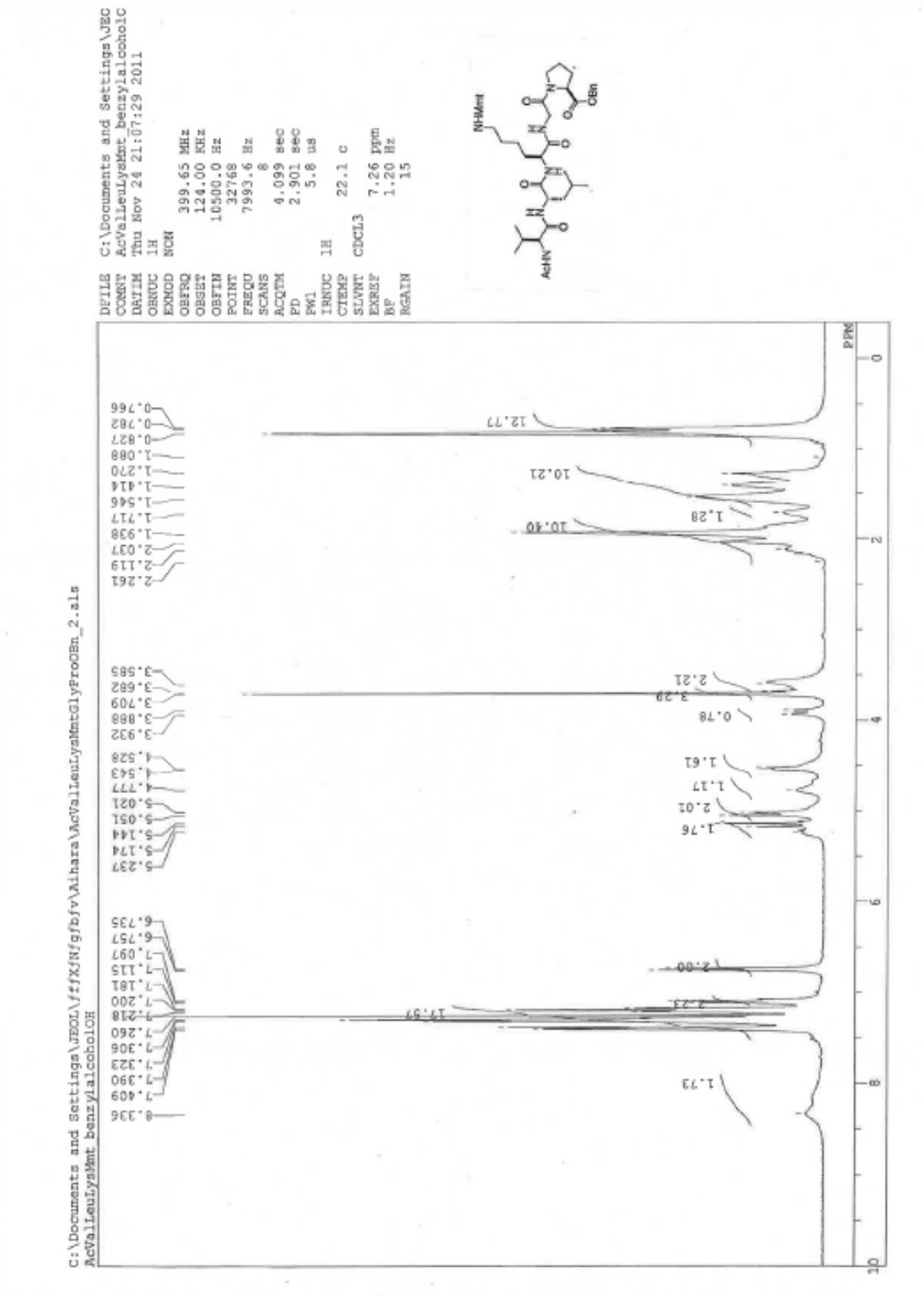
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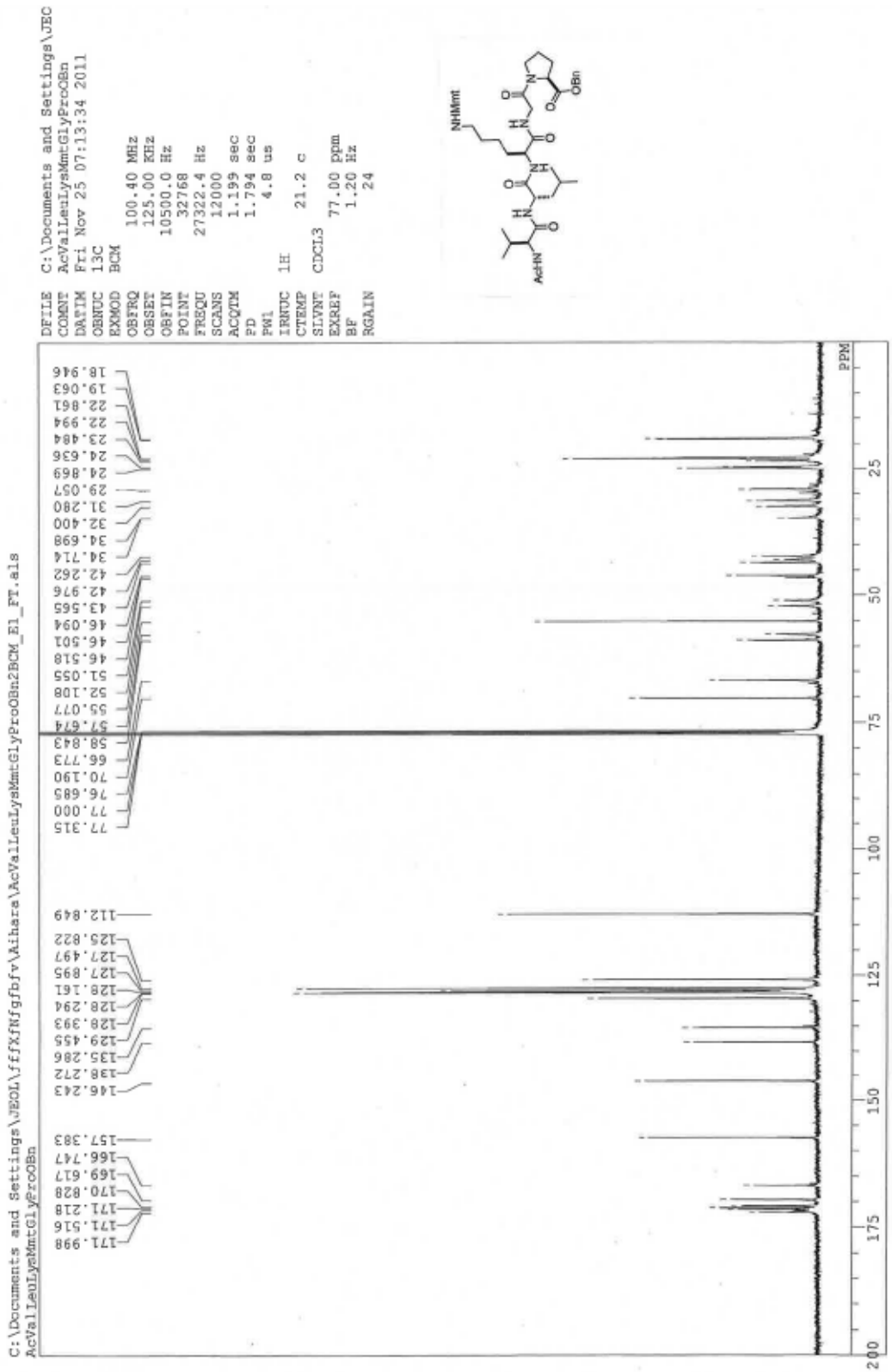
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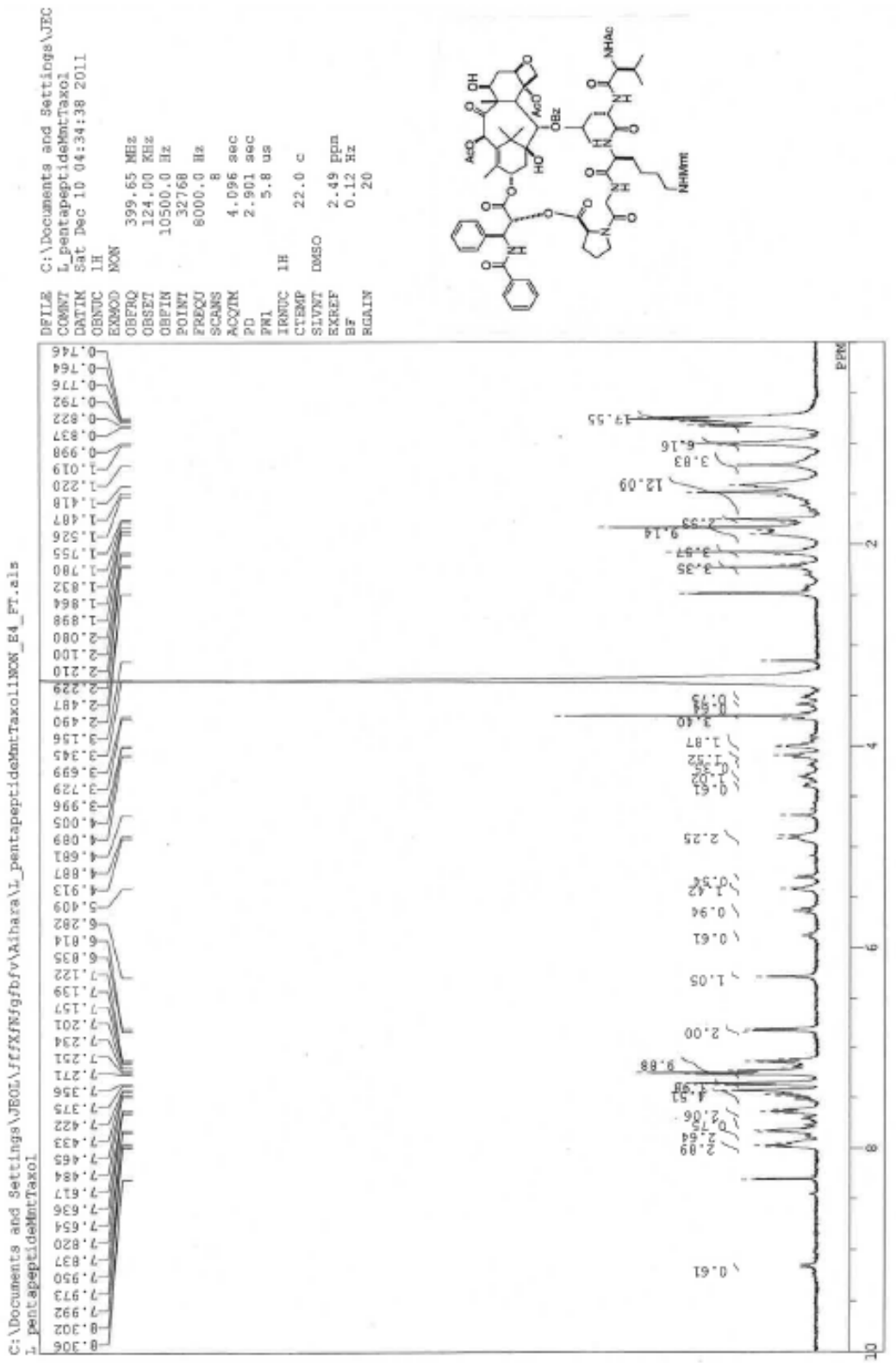
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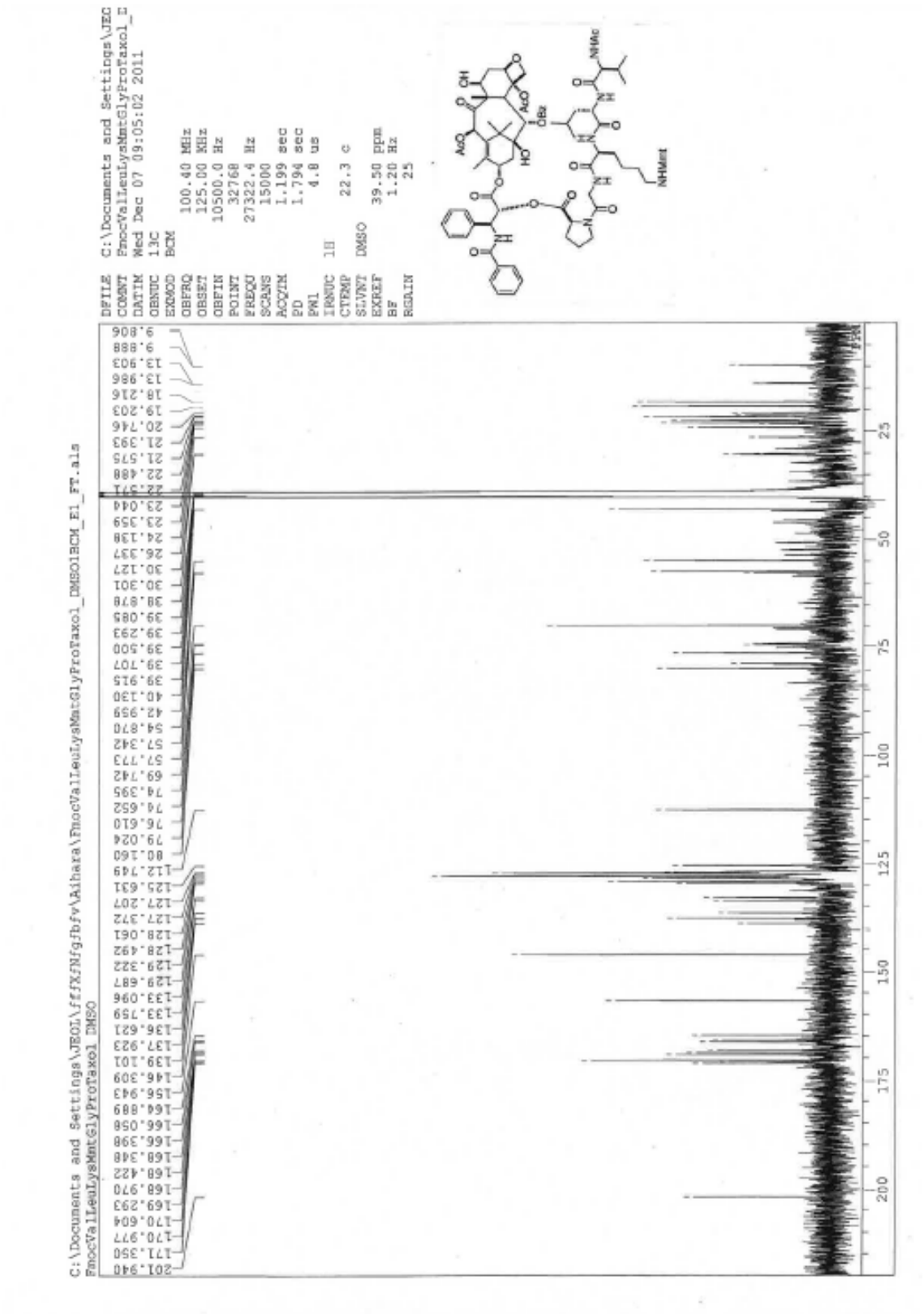
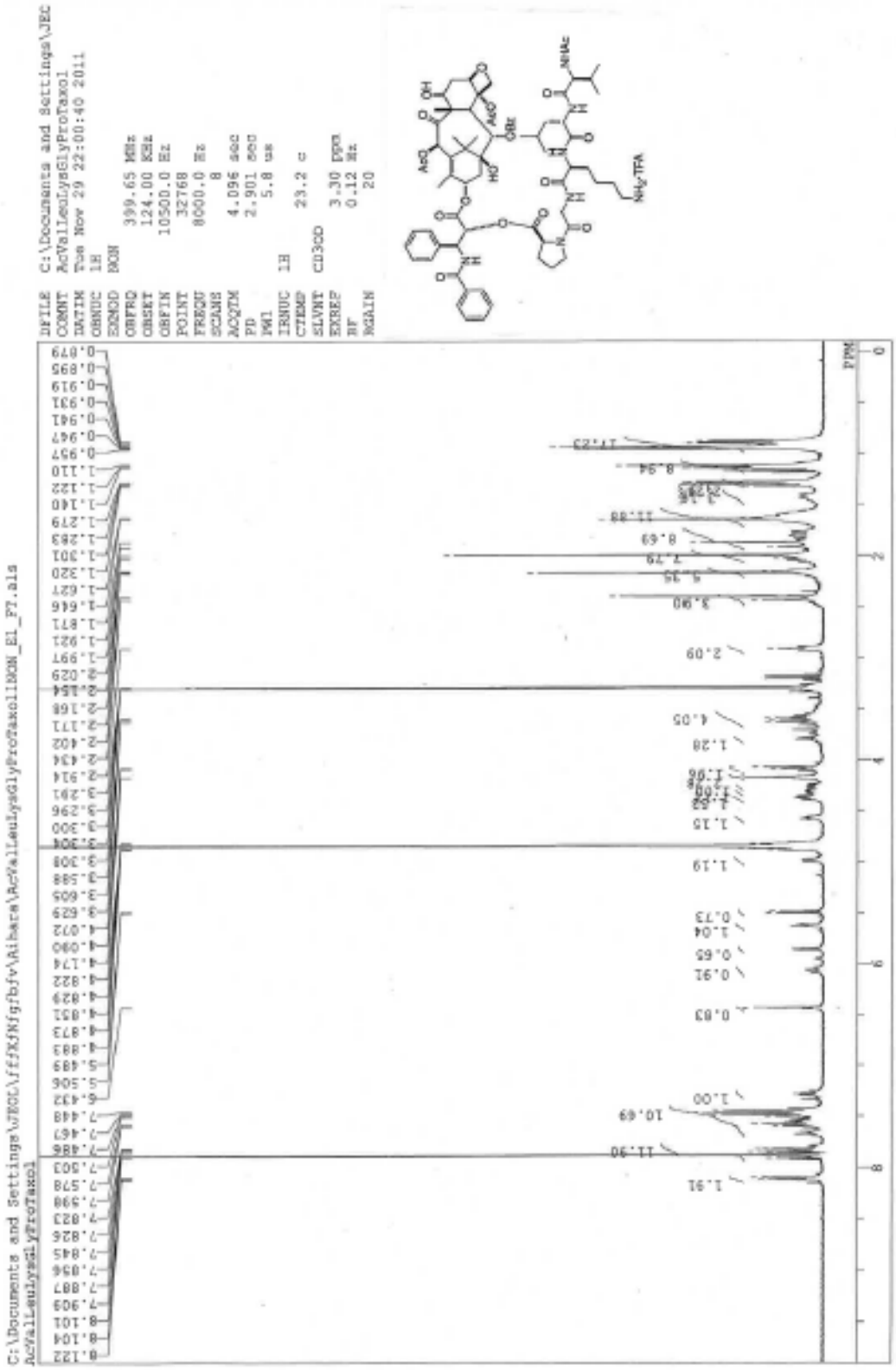
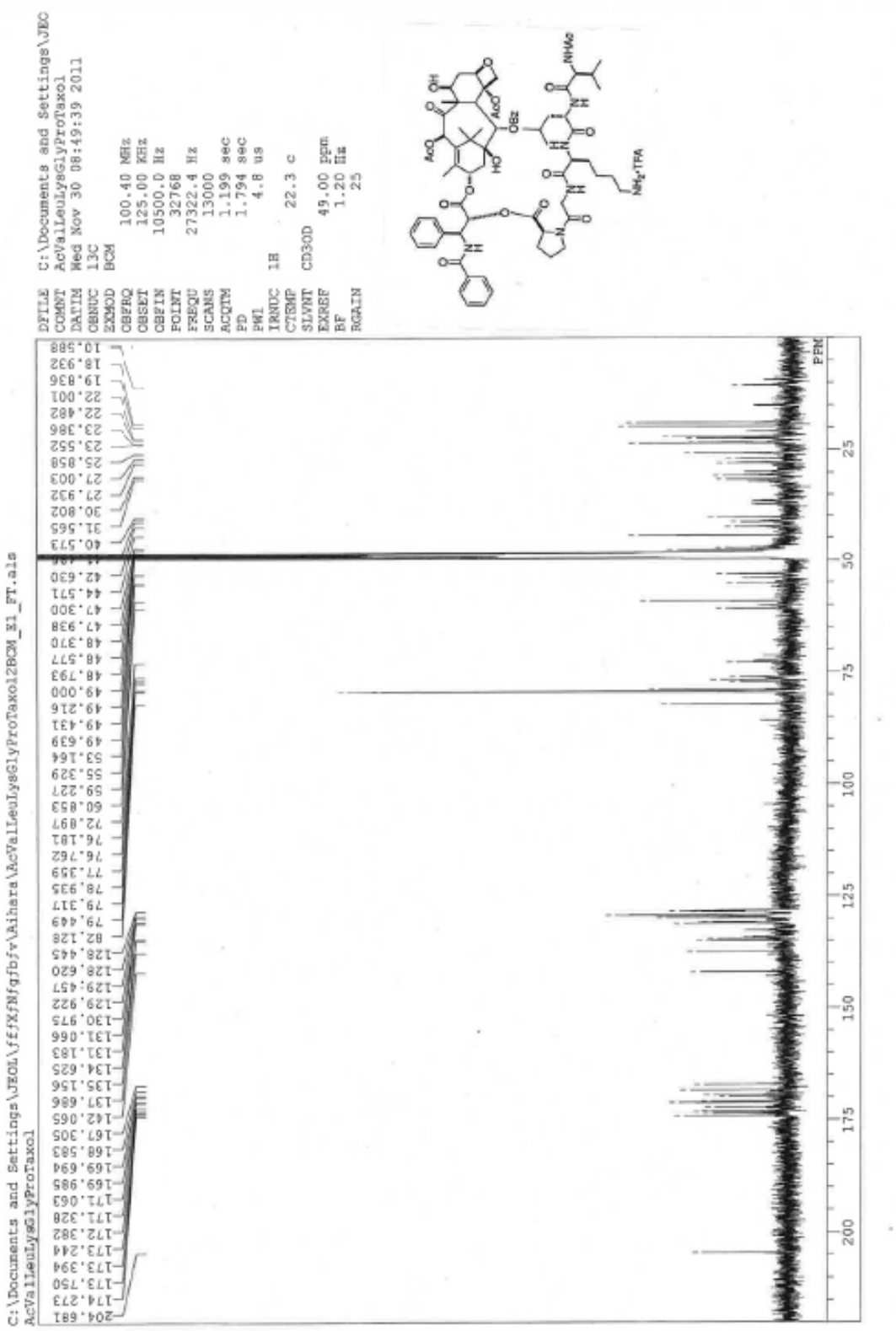
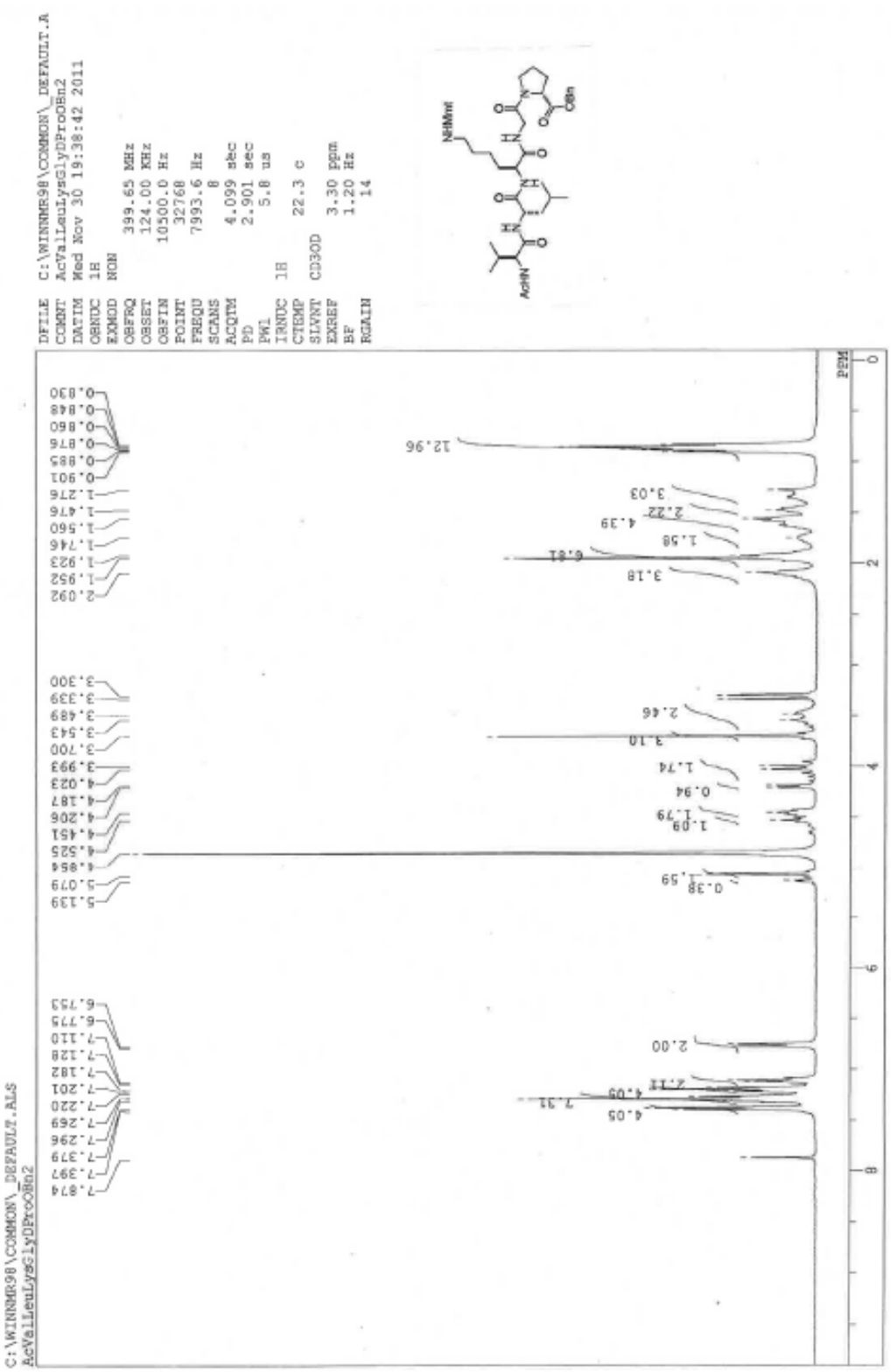
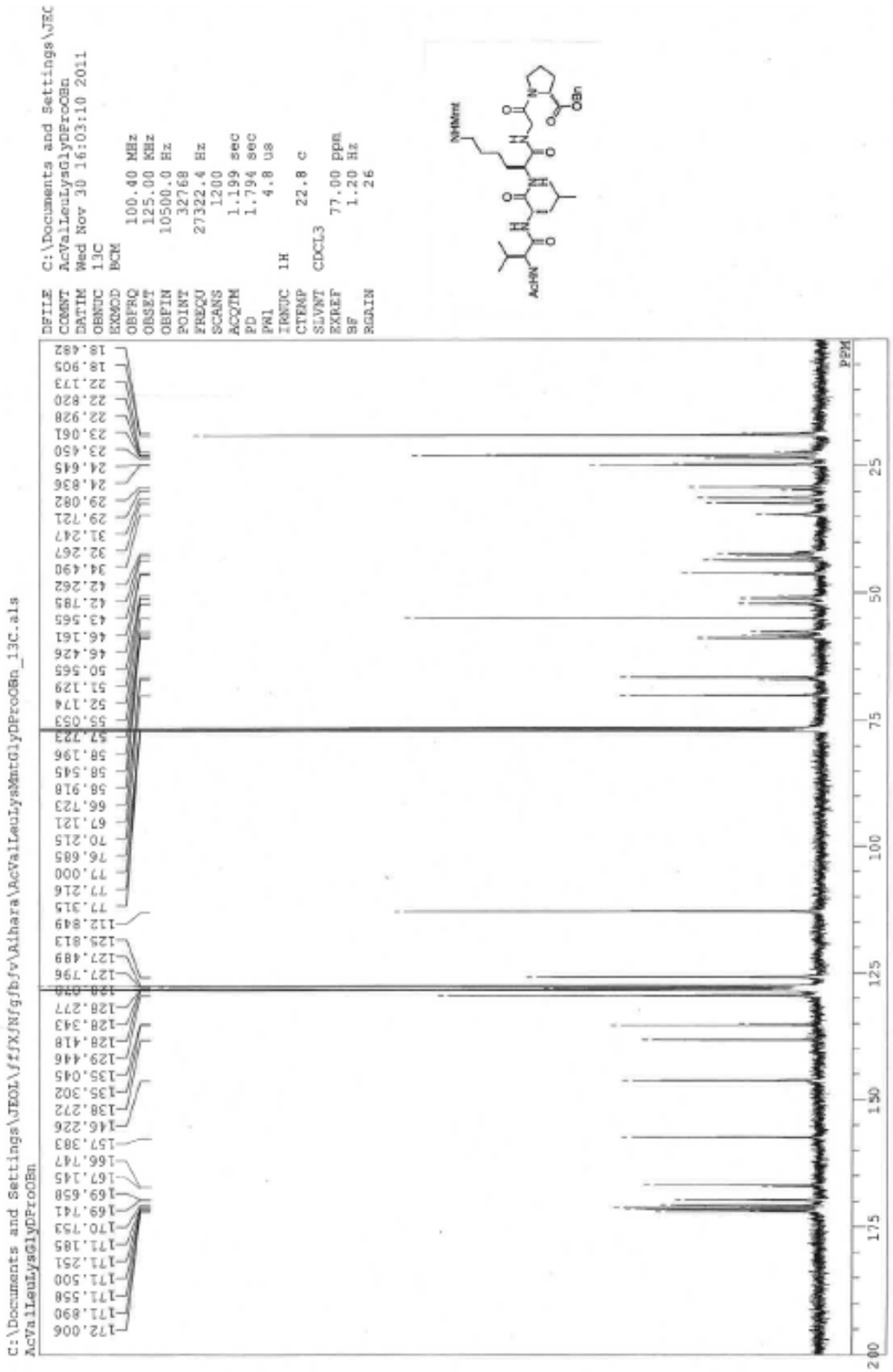
NHAc
NHMmt
PPM

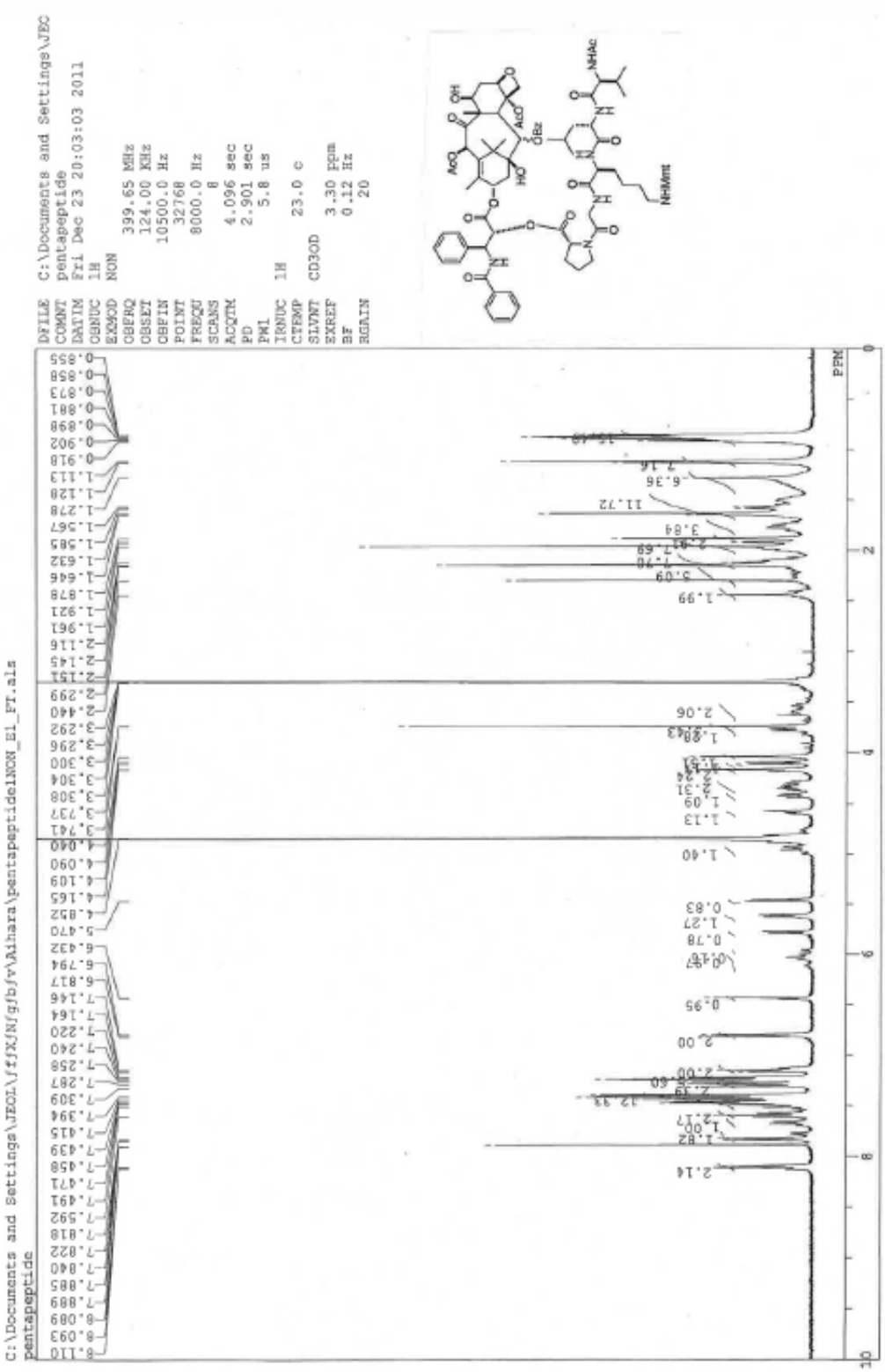

C:\Documents and Settings\JEO\ffffXfNfgfbfv\Aihara\FmocValLeuLysMmtGlyProTaxol_DMSO13CM_E1_FT.als
FmocValLeuLysMmtGlyProTaxol DMSO
C:\Documents and Settings\JEO
FmocValLeuLysMmtGlyProTaxol_E
Wed Dec 07 09:05:02 2011
13C
100.40 MHz
125.00 KHz
10500.0 Hz
32768
27322.4 Hz
15000
1.199 sec
1.794 sec
4.8 us
1H
22.3 c
DMSO
39.50 ppm
1.20 Hz
25
AcO
OH
HO
OBz
NHMmt
NHMtc
25
50
75
100
125
150
175
200

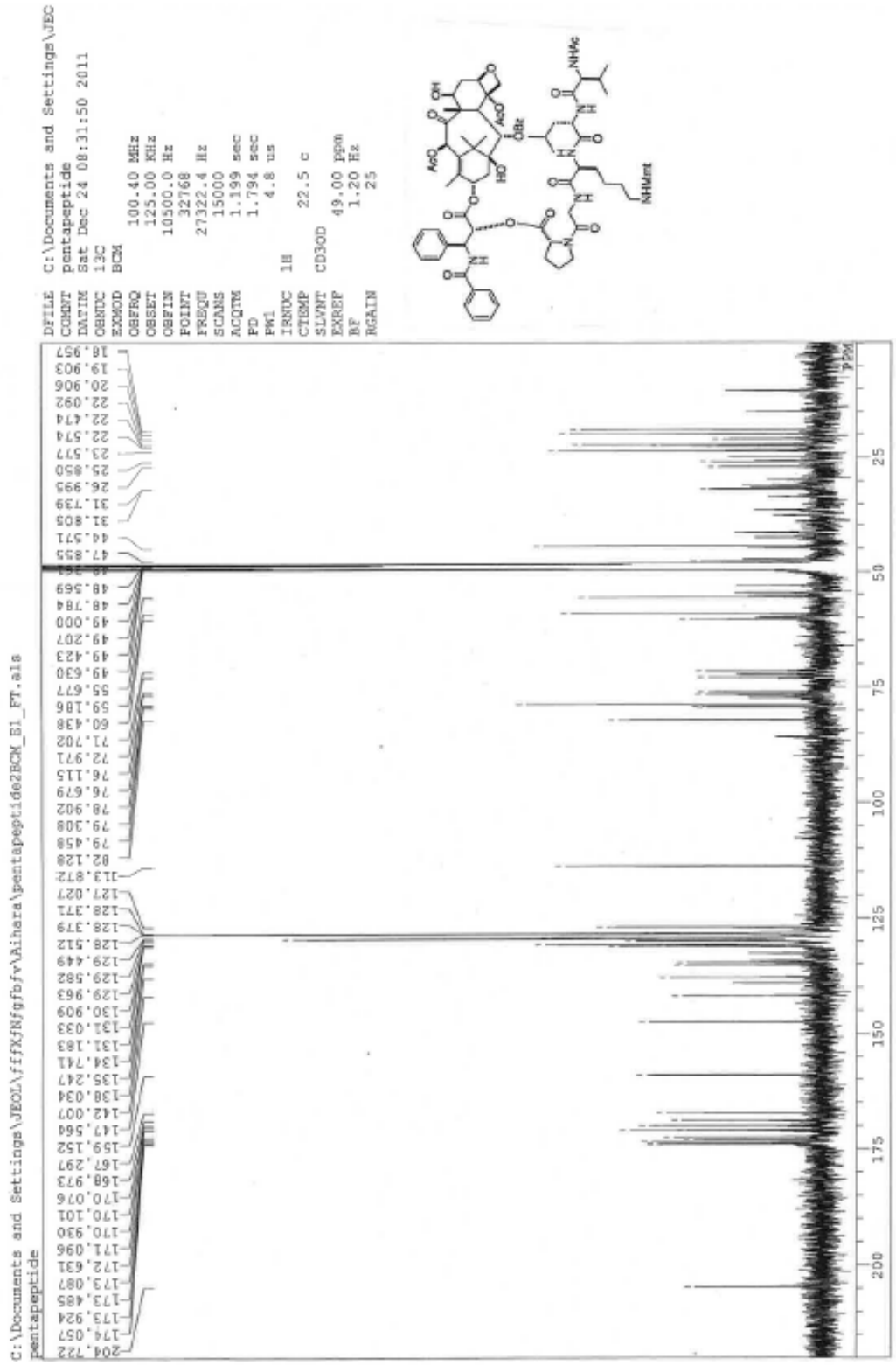

C:\Documents and Settings\JEC
AcValLeuLysGlyProTaxol
Tue Nov 29 22:00:40 2011
1H
PROTON
399.65 MHz
124.00 KHz
10500.0 Hz
32768
8000.0 Hz
8
4.096 sec
2.901 sec
5.8 us
1H
23.2 c
CD3OD
3.30 ppm
0.12 Hz
20
NH2/TFA
C:\Documents and Settings\JEC\ffXfNfgfbfv\Aibara\AcValLeuLysGlyProTaxol1HON_E1_P7.als
AcValLeuLysGlyProTaxol

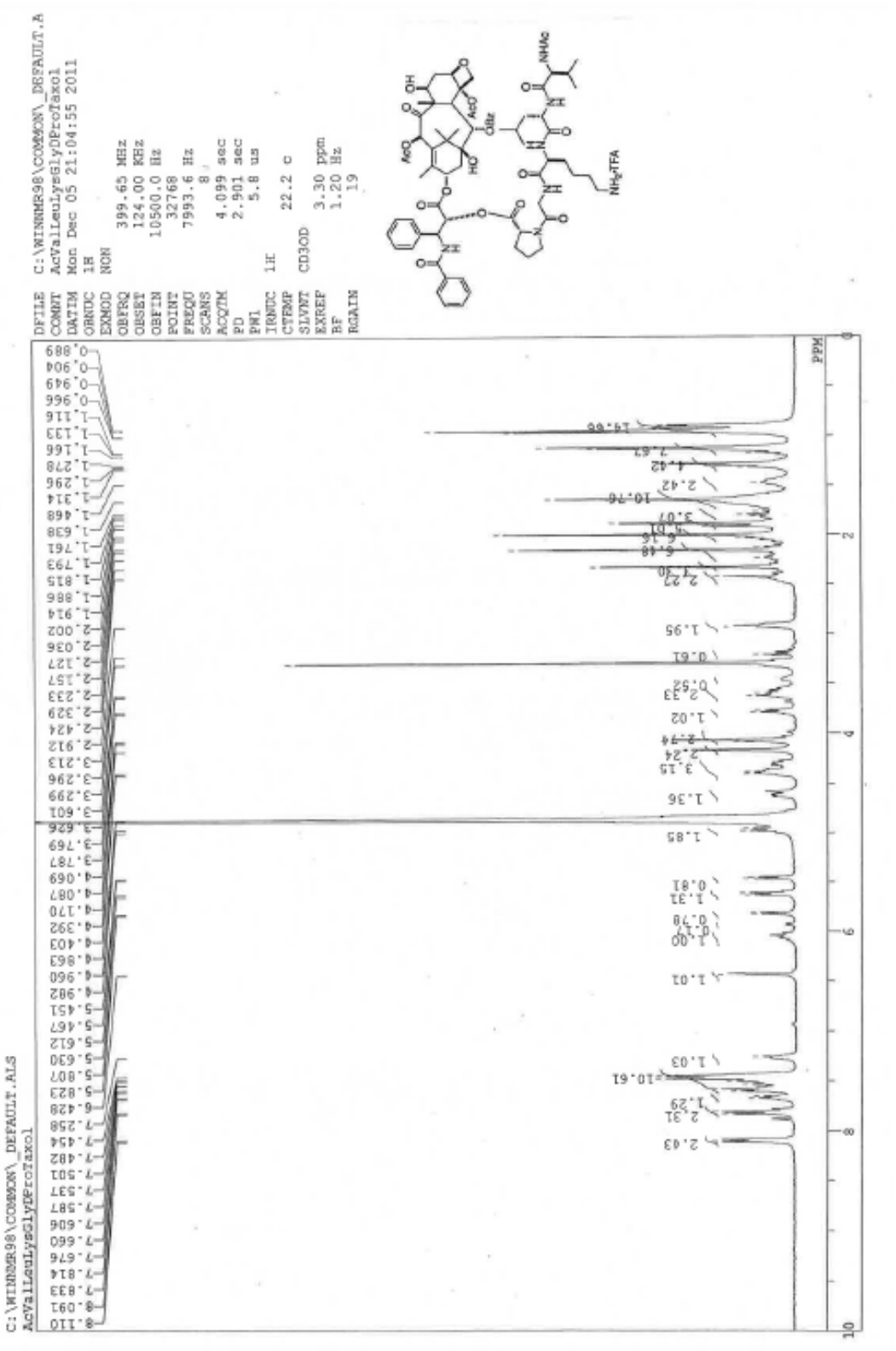

C:\Documents and Settings\JEOL\ffXfNfgfbfv\Aihara\AcValLeuLysGlyProTaxol2BCM_E1_FT.als
AcValLeuLysGlyProTaxol
C:\Documents and Settings\JEO
AcValLeuLysGlyProTaxol
Wed Nov 30 08:49:39 2011
13C
BCM
100.40 MHz
125.00 KHz
10500.0 Hz
32768
27322.4 Hz
13000
1.199 sec
1.794 sec
4.8 us
1H
22.3 c
CD3OD
49.00 ppm
1.20 Hz
25
DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRQ
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN
AcO
OH
HO
OBz
NHAc
NH2•TFA
PPM

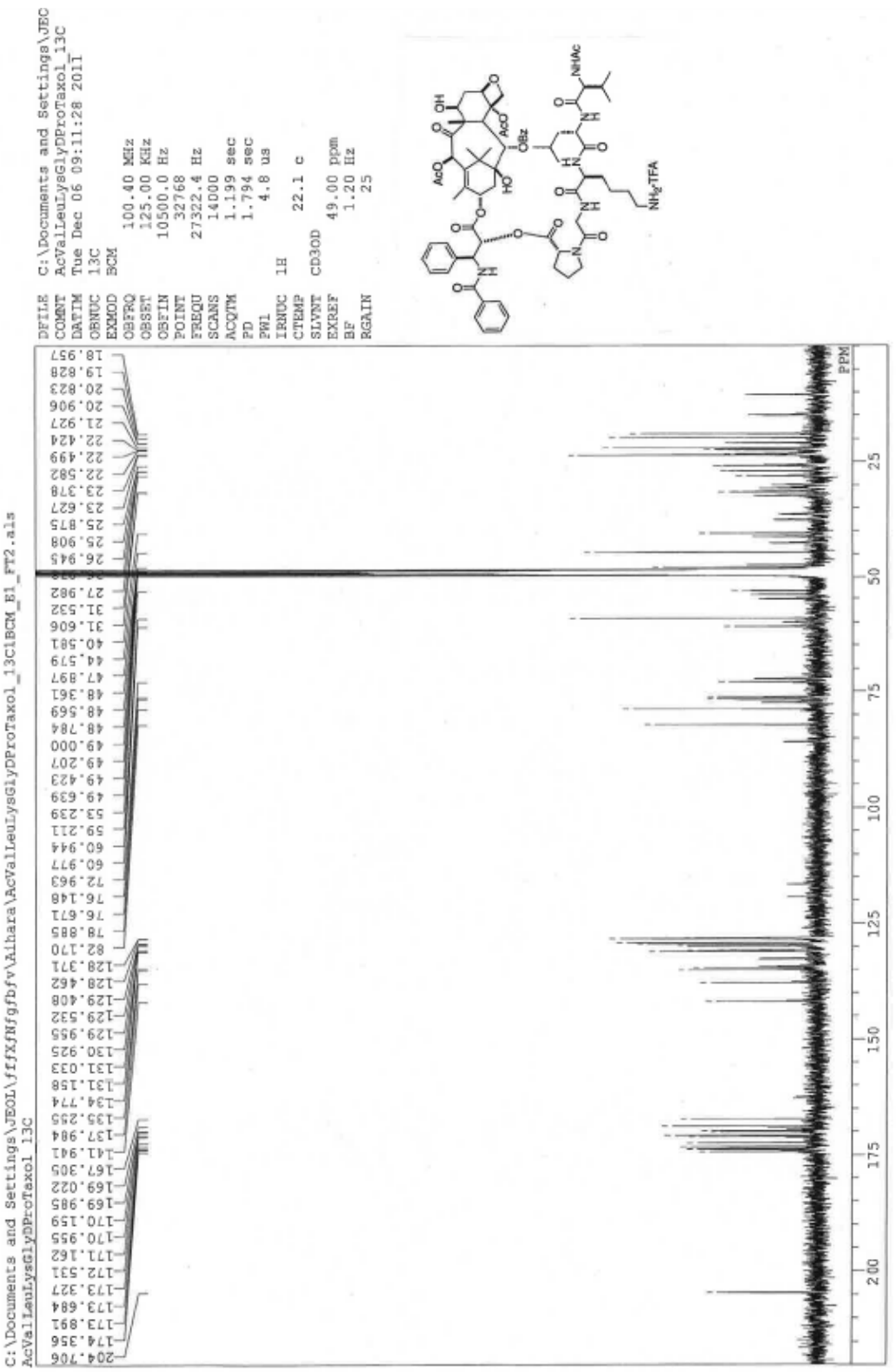

DFILE C:\WINNMR98\COMMON_DEFAULT.A
COMNT AcValLeuLysGlyDProOBn2
DATIM Wed Nov 30 19:38:42 2011
OBNDC 1H
EXMOD NON
OBFRQ 399.65 MHz
OBSET 124.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 7993.6 Hz
SCANS 8
ACQTM 4.099 sec
PD 2.901 sec
PW1 5.8 us
IRNUC 1H
CTEMP 22.3 c
SLVNT CD3OD
EXREF 3.30 ppm
BF 1.20 Hz
RGAIN 14
C:\WINNMR98\COMMON_DEFAULT.ALS
AcValLeuLysGlyDProOBn2
PPM

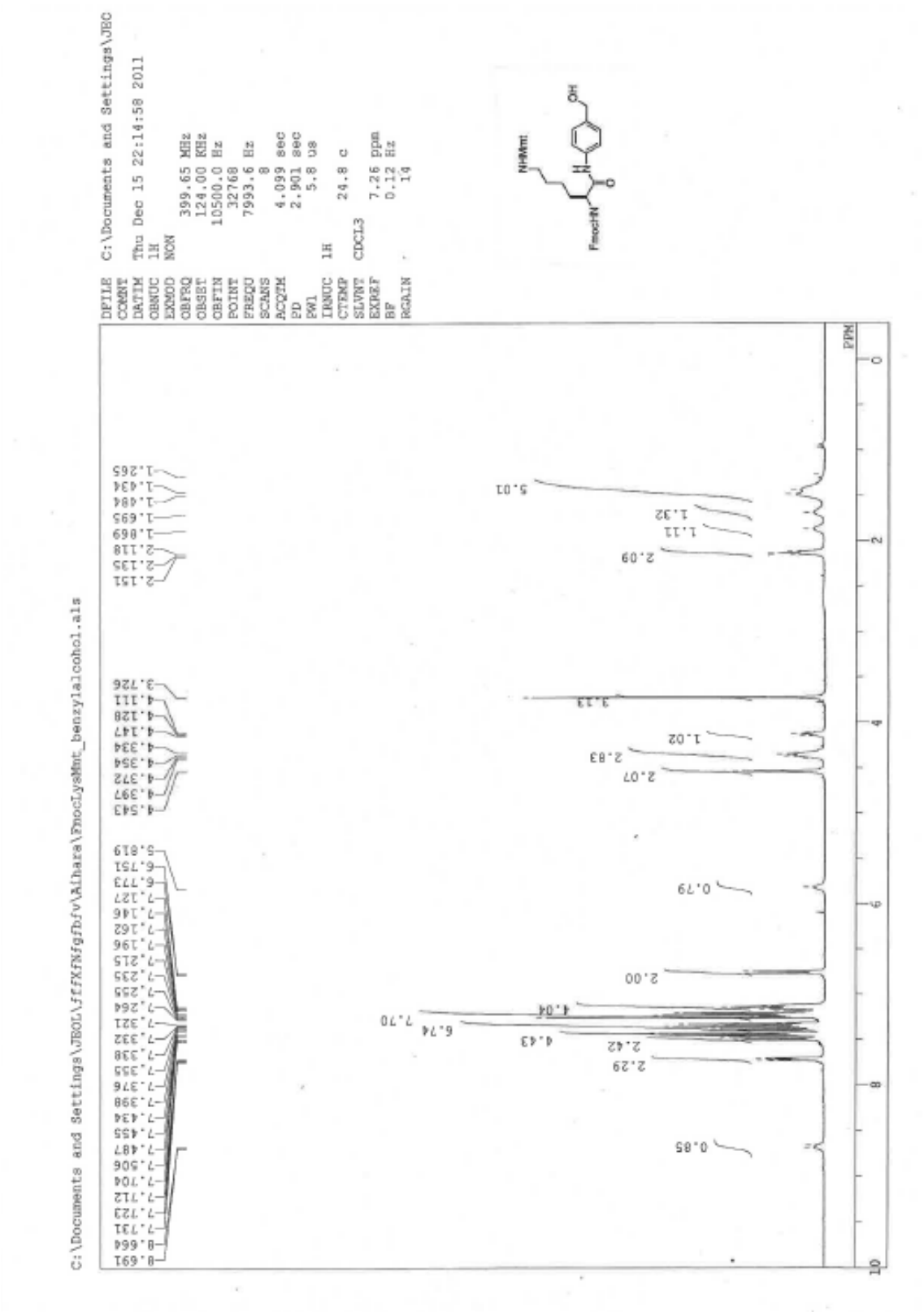

C:\Documents and Settings\JEOL\ff7XJNfg7bfv\Aihara\AcValLeuLysMmtGlyDProOBn_13C.als
AcValLeuLysGlyDProOBn
DFILE C:\Documents and Settings\JEC
COMNT AcValLeuLysGlyDProOBn
DATIM Wed Nov 30 16:03:10 2011
OBNUC 13C
EXMOD BCM
OBFRQ 100.40 MHz
OBSET 125.00 MHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 27322.4 Hz
SCANS 1200
ACQTM 1.199 sec
PD 1.794 sec
PW1 4.8 us
IRNUC 1H
CTEMP 22.8 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 1.20 Hz
RGAIN 26
AcHN
NHMmt
OBn
PPM
200
175
150
125
100
75
50
25

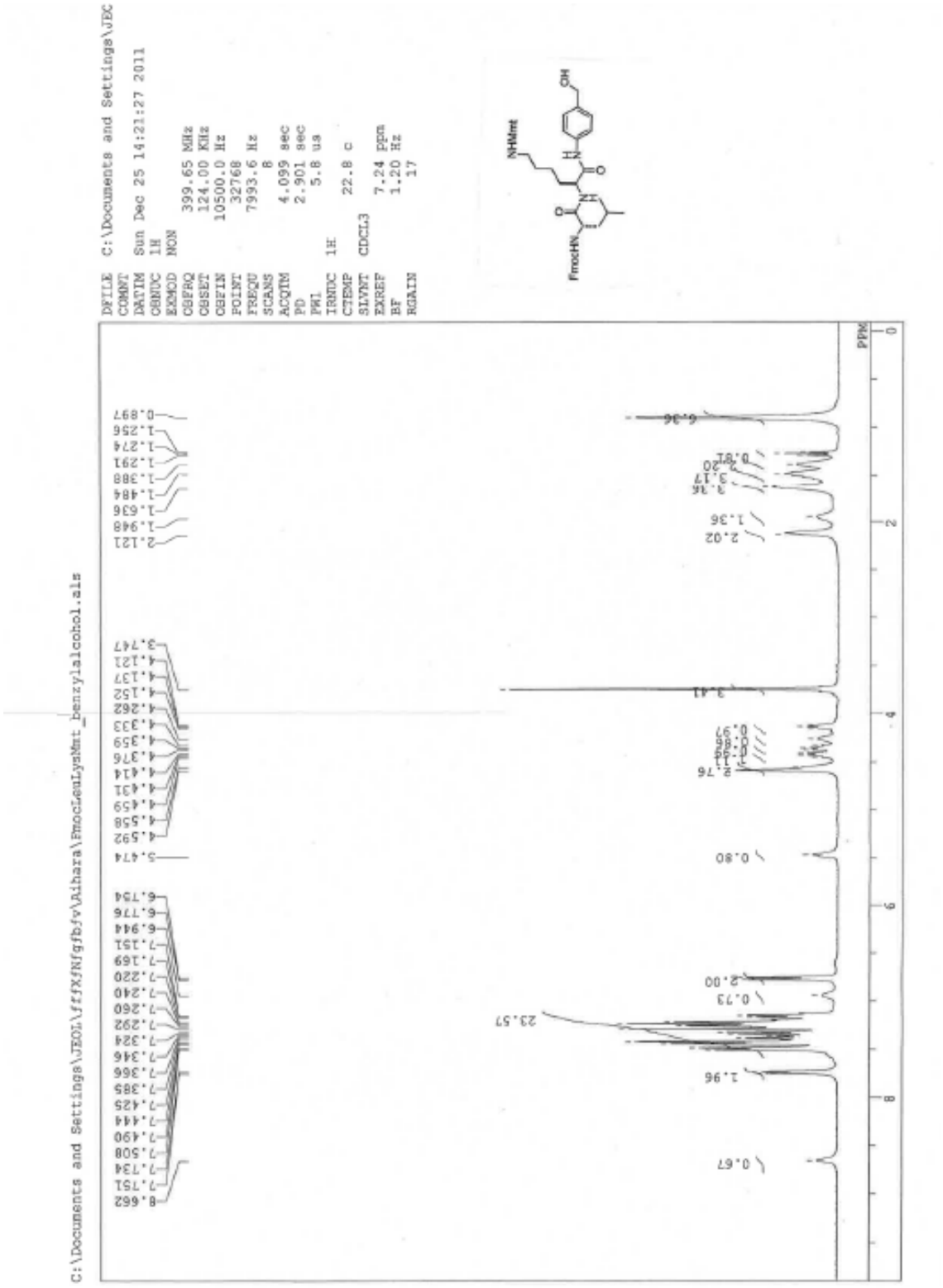

C:\Documents and Settings\JEO
pentapeptide
Fri Dec 23 20:03:03 2011
1H
NON
399.65 MHz
124.00 KHz
10500.0 Hz
32768
8000.0 Hz
8
4.096 sec
2.901 sec
5.8 us
1H
23.0 c
CD3OD
3.30 ppm
0.12 Hz
20
DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRQ
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
SF
WDW
SSB
LB
GB
PC
1.00
1.82
2.14
2.00
0.95
1.40
1.13
1.09
1.99
2.06
1.83
5.09
1.78
1.68
3.84
11.72
6.36
7.16
7.18
PPM
C:\Documents and Settings\JEOL\ffJX/NJg/bfv\Aihara\pentapeptideNON_E1_FT.als
pentapeptide

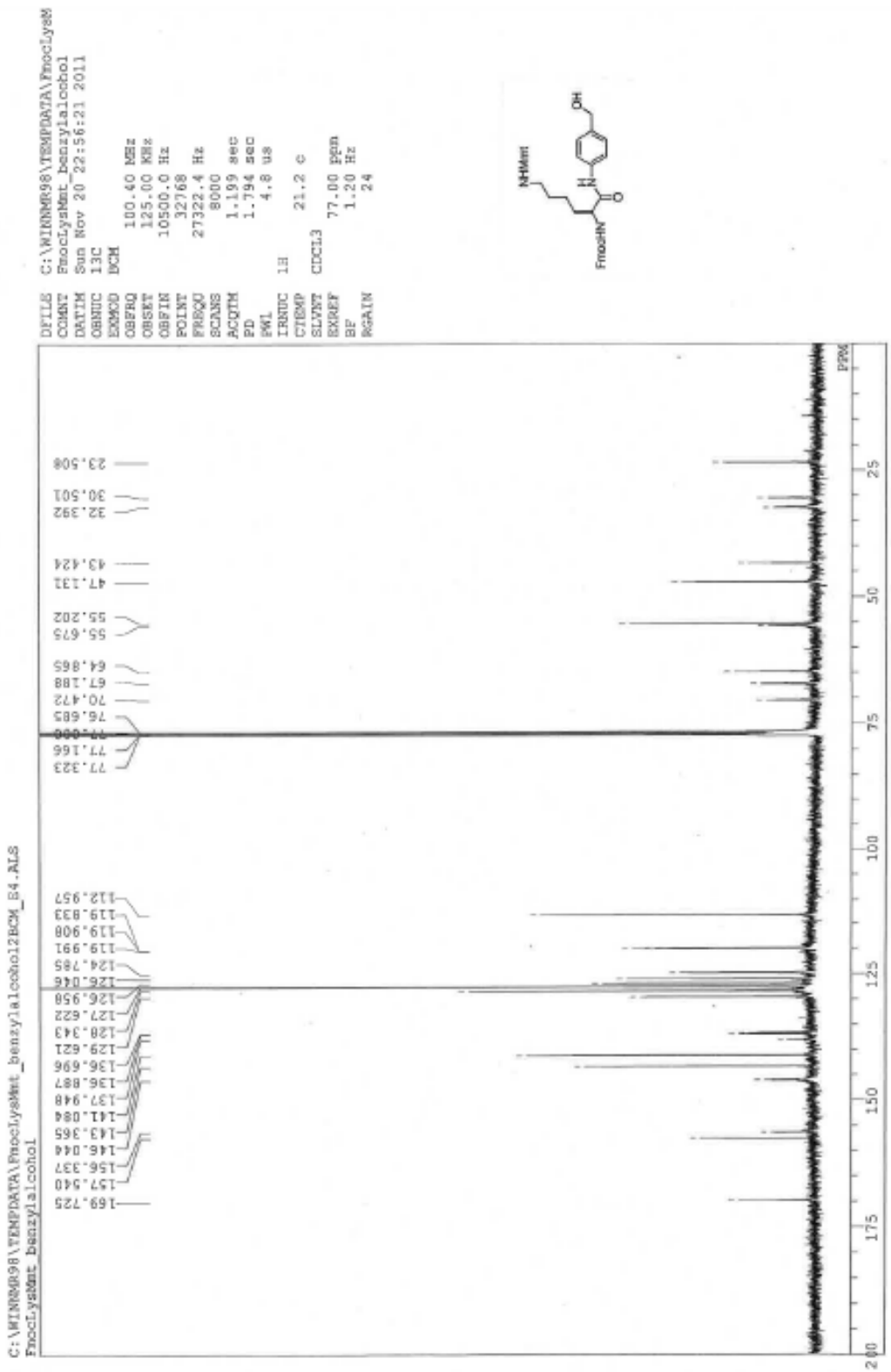

C:\Documents and Settings\JEOL\fffXfNfgfbfv\Aihara\pentapeptide2BCM_E1_FT.als
pentapeptide
C:\Documents and Settings\JEO
pentapeptide
Sat Dec 24 08:31:50 2011
13C
BCM
100.40 MHz
125.00 KHz
10500.0 Hz
32768
27322.4 Hz
15000
1.199 sec
1.794 sec
4.8 us
1H
22.5 c
CD3OD
49.00 ppm
1.20 Hz
25
AcO
OBz
HO
NHAc
NHAmt
PPM

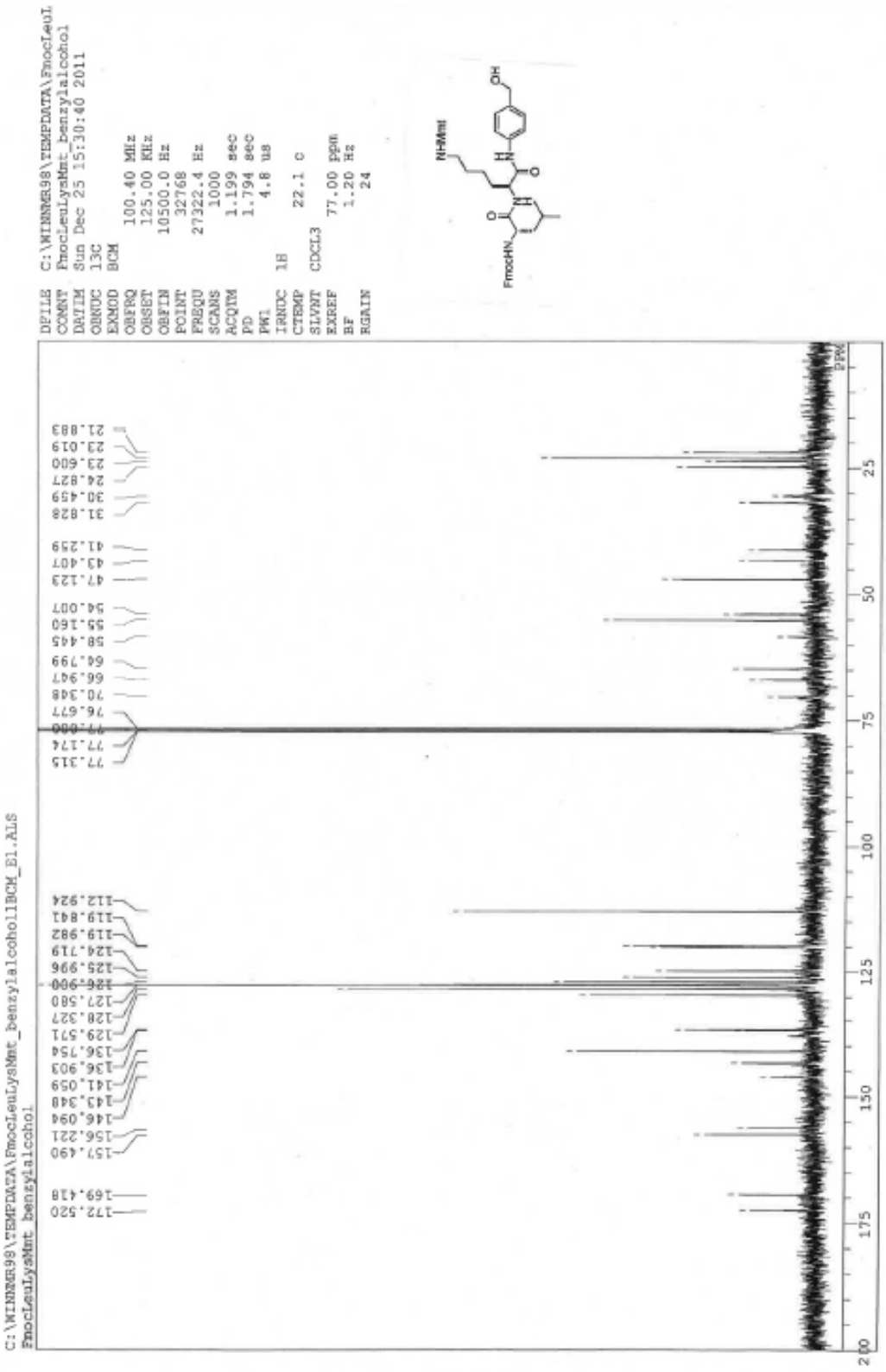

C:\WINNMR98\COMMON_DEFAULT.A
AcValLeuLysGlyDProTaxol
Mon Dec 05 21:04:55 2011
1H
399.65 MHz
124.00 KHz
10500.0 Hz
32768
7993.6 Hz
8
4.099 sec
2.901 sec
5.8 us
22.2 c
CD3OD
3.30 ppm
1.20 Hz
19
NH2-TFA
PPM
C:\WINNMR98\COMMON_DEFAULT.ALS
AcValLeuLysGlyDProTaxol

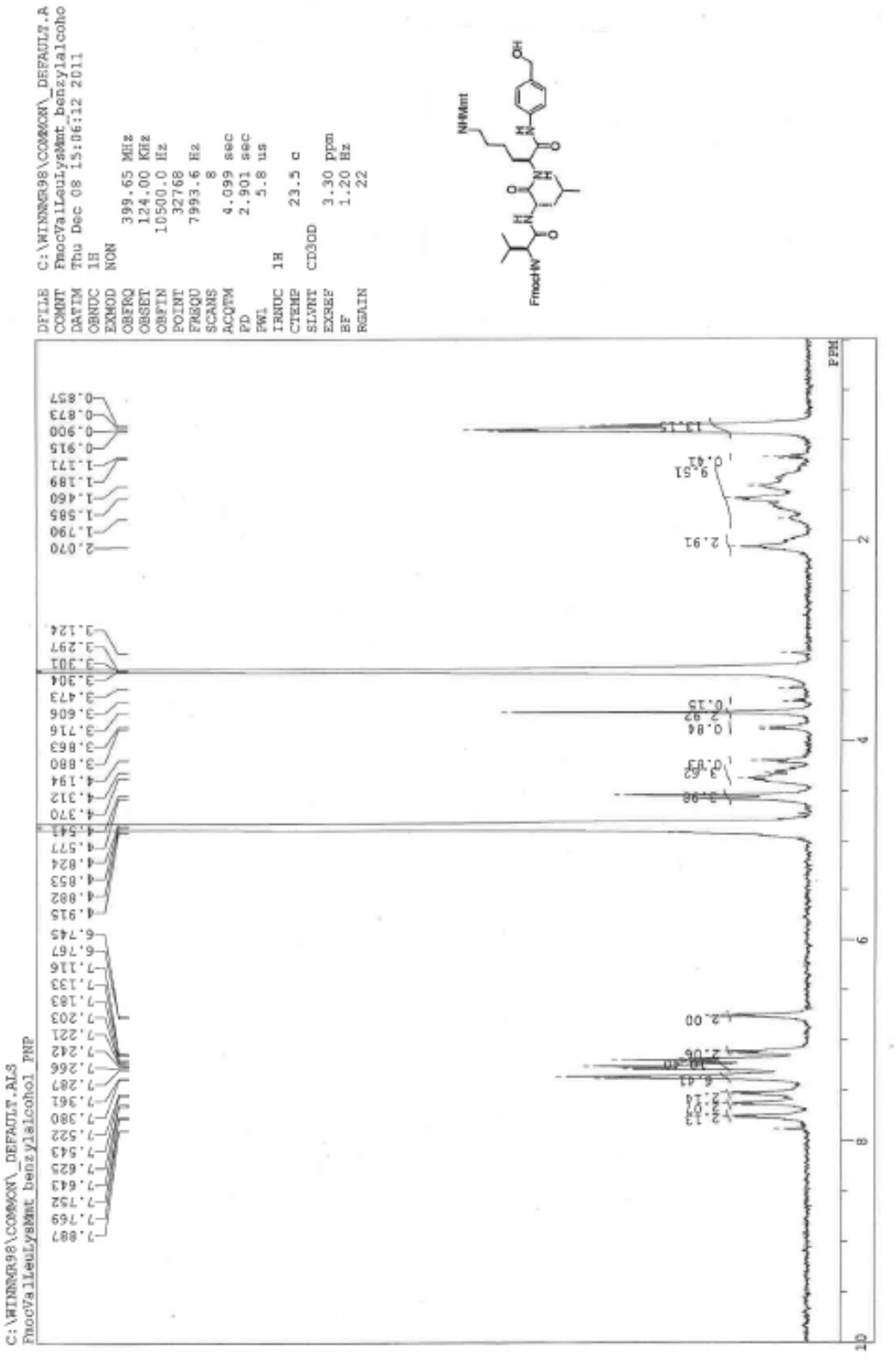

C:\Documents and Settings\JEOL\fffXfNfgfbfv\Aihara\AcValLeuLysGlyDProTaxol_13C1BCM_E1_FT2.als
AcValLeuLysGlyDProTaxol 13C
DFILE C:\Documents and Settings\JEC
COMNT AcValLeuLysGlyDProTaxol 13C
DATIM Tue Dec 06 09:11:28 2011
OBNUC 13C
EXMOD BCM
OBFRQ 100.40 MHz
OBSPT 125.00 KHz
OBSIN 10500.0 Hz
POINT 32768
FREQU 27322.4 Hz
SCANS 14000
ACQTM 1.199 sec
PD 1.794 sec
PW1 4.8 us
IRNUC 1H
CTEMP 22.1 c
SLVNT CD3OD
EXREF 49.00 ppm
BF 1.20 Hz
RGAIN 25
AcO
OH
HO
OBz
NHAc
NH2.TFA
PPM

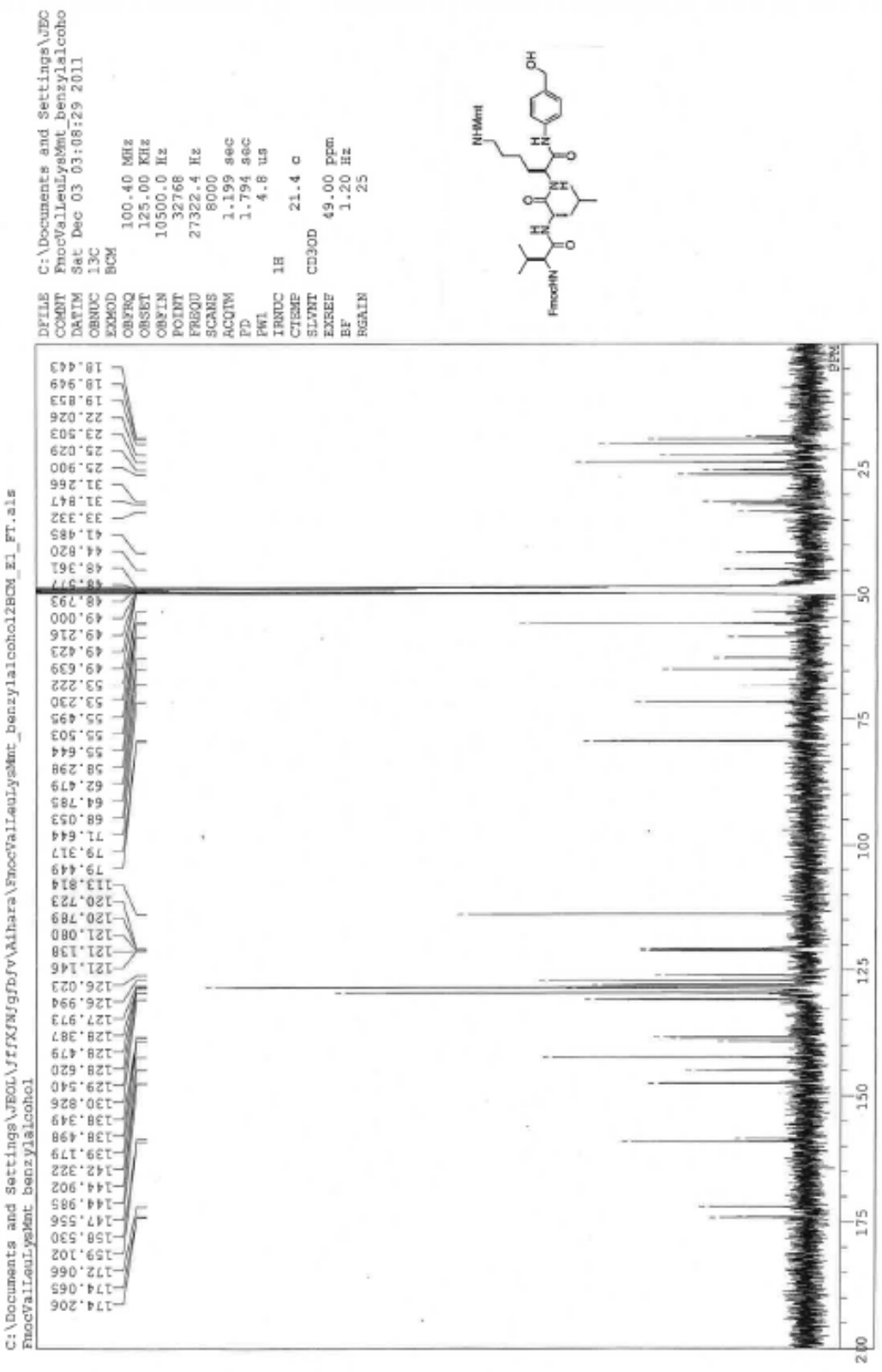

C:\Documents and Settings\JBEC\fffXfNfgfbfv\Alhara\BocLysMmt_benzylalcohol.als
DPFILE C:\Documents and Settings\JBEC
COMMNT
DATIM Thu Dec 15 22:14:58 2011
OBNUC 1H
EXMOD NOE
OBFRQ 399.65 MHz
OBSET 124.00 MHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 7993.6 Hz
SCANS 8
ACQTM 4.099 sec
PD 2.901 sec
PW1 5.8 us
IN1NUC 1H
CTEMP 24.8 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.12 Hz
RGAIN 14
NHMmt
FmocHN
OH
PPM
5.01
1.32
1.11
2.09
3.13
1.02
2.83
2.07
0.79
2.00
4.04
7.70
6.74
4.43
2.42
2.29
0.85

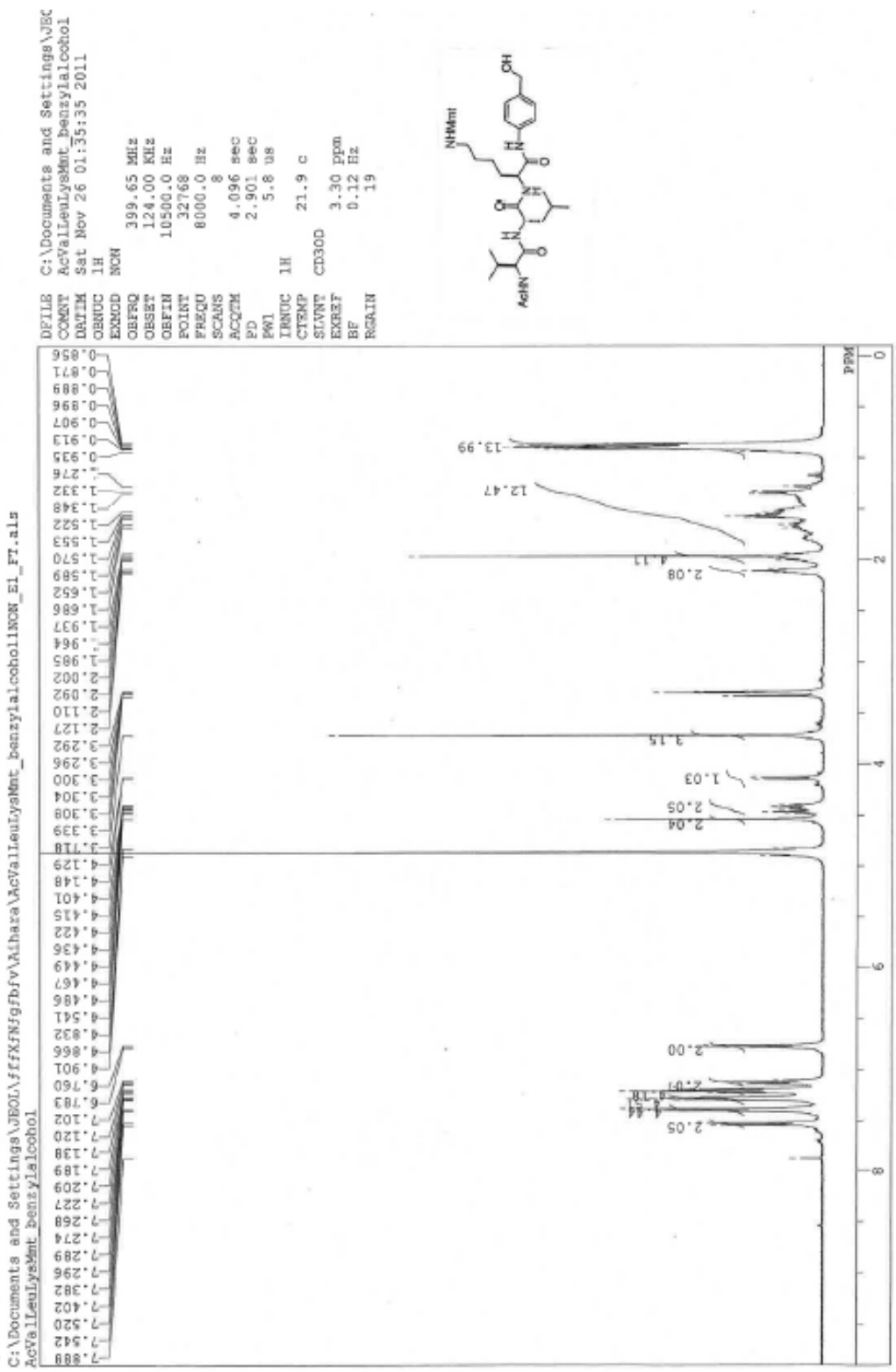

DFILE C:\Documents and Settings\JEC
COMNT
DATIM Sun Dec 25 14:21:27 2011
OBNUC 1H
EXMOD NON
OBFRQ 399.65 MHz
OBSET 124.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 7993.6 Hz
SCANS 8
ACQTM 4.099 sec
PD 2.901 sec
PW1 5.8 us
IRNUC 1H
CTEMP 22.8 c
SLVNT CDCL3
EXREF 7.24 ppm
BF 1.20 Hz
RGAIN 17
NHMmt
OH
FmocHN
C:\Documents and Settings\JEOL\ffIXfNfgfbjv\Aihara\FmocLeuLysMmt_benzylalcohol.als
PPM

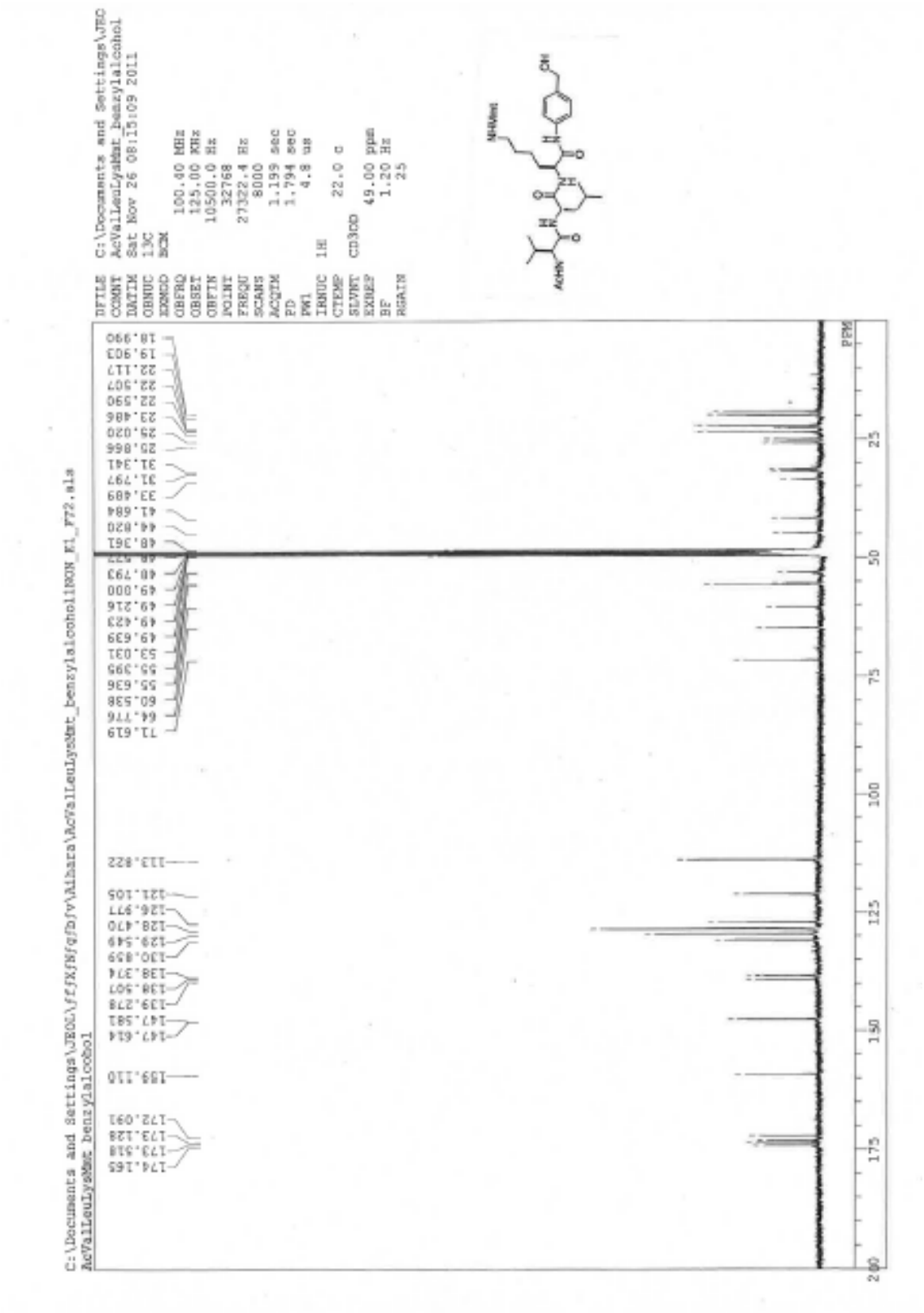

C:\WINNMR98\TEMPDATA\FmocLysMmt_benzylalcohol2BCM_E4.ALS
FmocLysMmt benzylalcohol
DFILE C:\WINNMR98\TEMPDATA\FmocLysM
COMNT FmocLysMmt benzylalcohol
DATIM Sun Nov 20 22:56:21 2011
OBNUC 13C
EXMOD BCM
OBFRQ 100.40 MHz
OBSET 125.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FRQQQ 27322.4 Hz
SCANS 8000
ACQTM 1.199 sec
PD 1.794 sec
PW1 4.8 us
IRNUC 1H
CTEMP 21.2 c
SLVNT CDCl3
EXREF 77.00 ppm
BF 1.20 Hz
RGAIN 24
NHMmt
FmocHN
OH
23.508
30.501
32.392
43.424
47.131
55.202
55.675
64.865
67.188
70.472
76.685
77.000
77.166
77.323
112.957
119.833
119.908
119.991
124.785
126.046
126.958
127.622
128.343
129.621
136.696
136.887
137.948
141.084
143.365
146.044
156.337
157.340
169.725
PPM
200
175
150
125
100
75
50
25

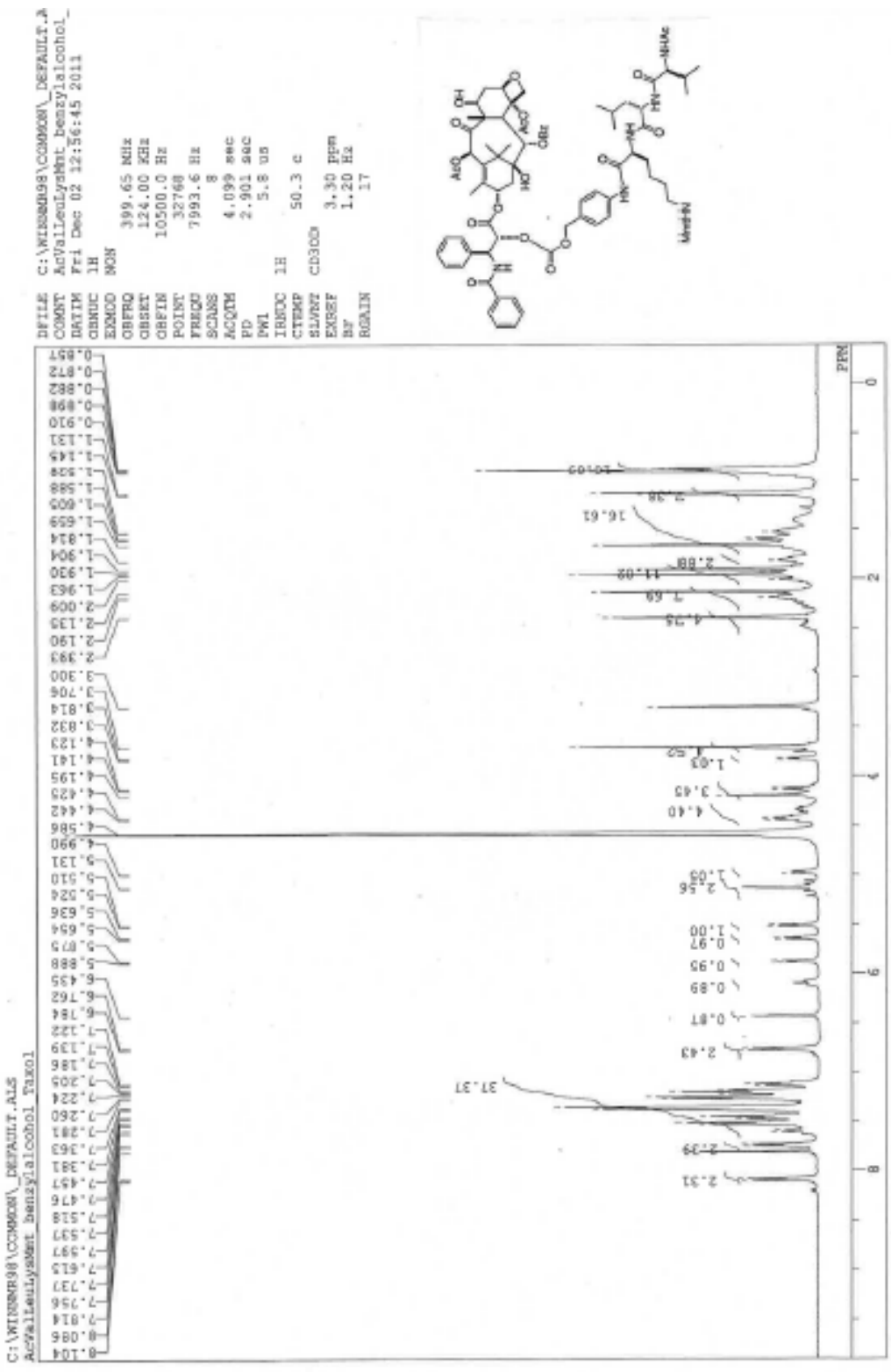

C:\WINNMR98\TEMPDATA\FmocLeuL
FmocLeuLysMmt_benzylalcohol
Sun Dec 25 15:30:40 2011
DFILE
COMNT
DATIM
OBNUC 13C
EXMOD BCM
OBFRQ 100.40 MHz
OBSET 125.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 27322.4 Hz
SCANS 1000
ACQTM 1.199 sec
PD 1.794 sec
PW1 4.8 us
IRNUC 1H
CTEMP 22.1 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 1.20 Hz
RGAIN 24
NHMmt
FmocHN
OH
C:\WINNMR98\TEMPDATA\FmocLeuLysMmt_benzylalcohol1BCM_E1.ALS
FmocLeuLysMmt_benzylalcohol
21.883
23.019
23.600
24.827
30.459
31.828
41.259
43.407
47.123
54.007
55.160
58.445
64.799
66.947
70.348
76.677
77.000
77.174
77.315
112.924
119.841
119.982
124.719
125.996
126.900
127.580
128.327
129.571
136.754
136.903
141.059
143.348
146.094
156.221
157.490
169.418
172.520
PPM
200
175
150
125
100
75
50
25

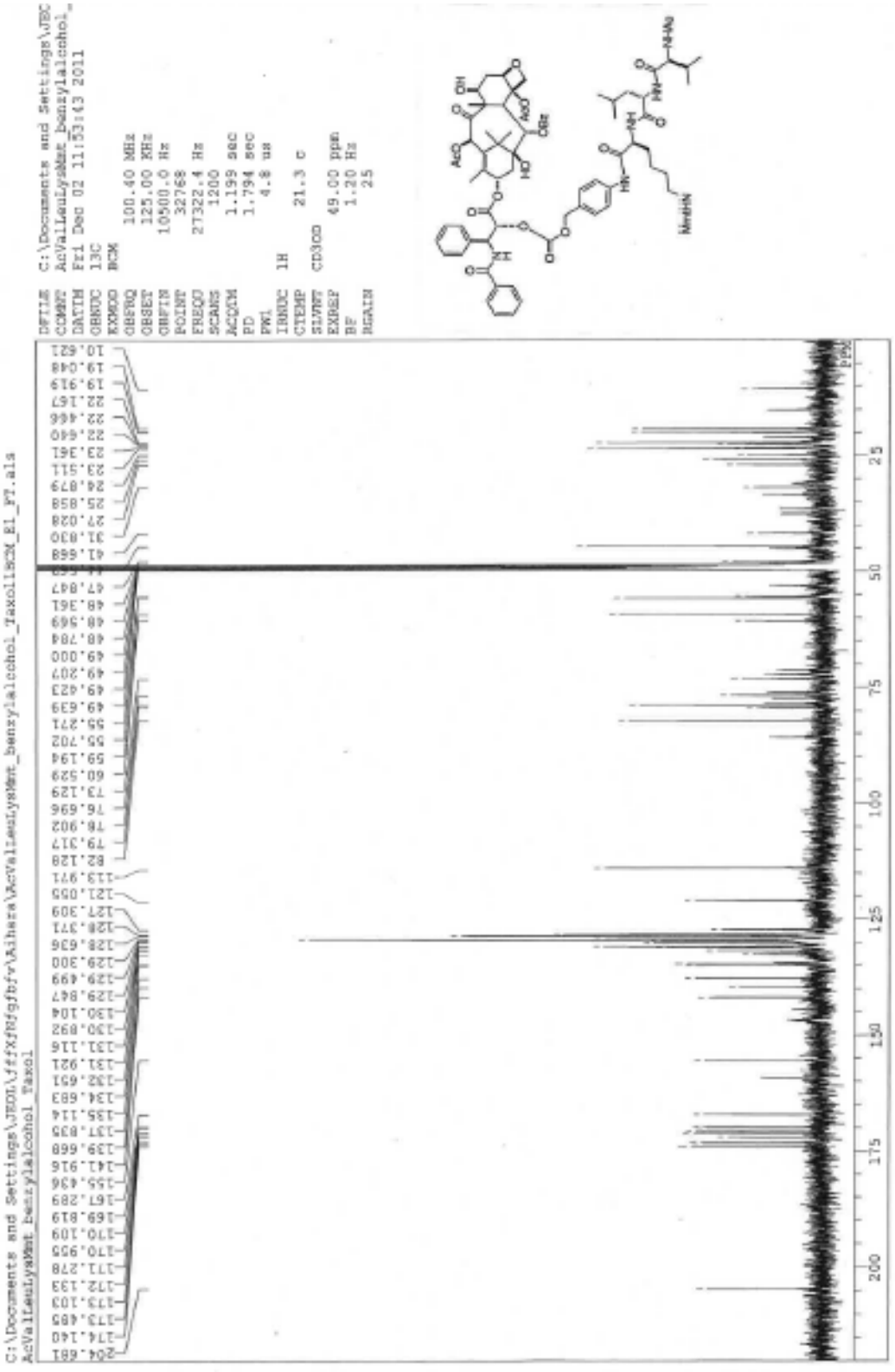


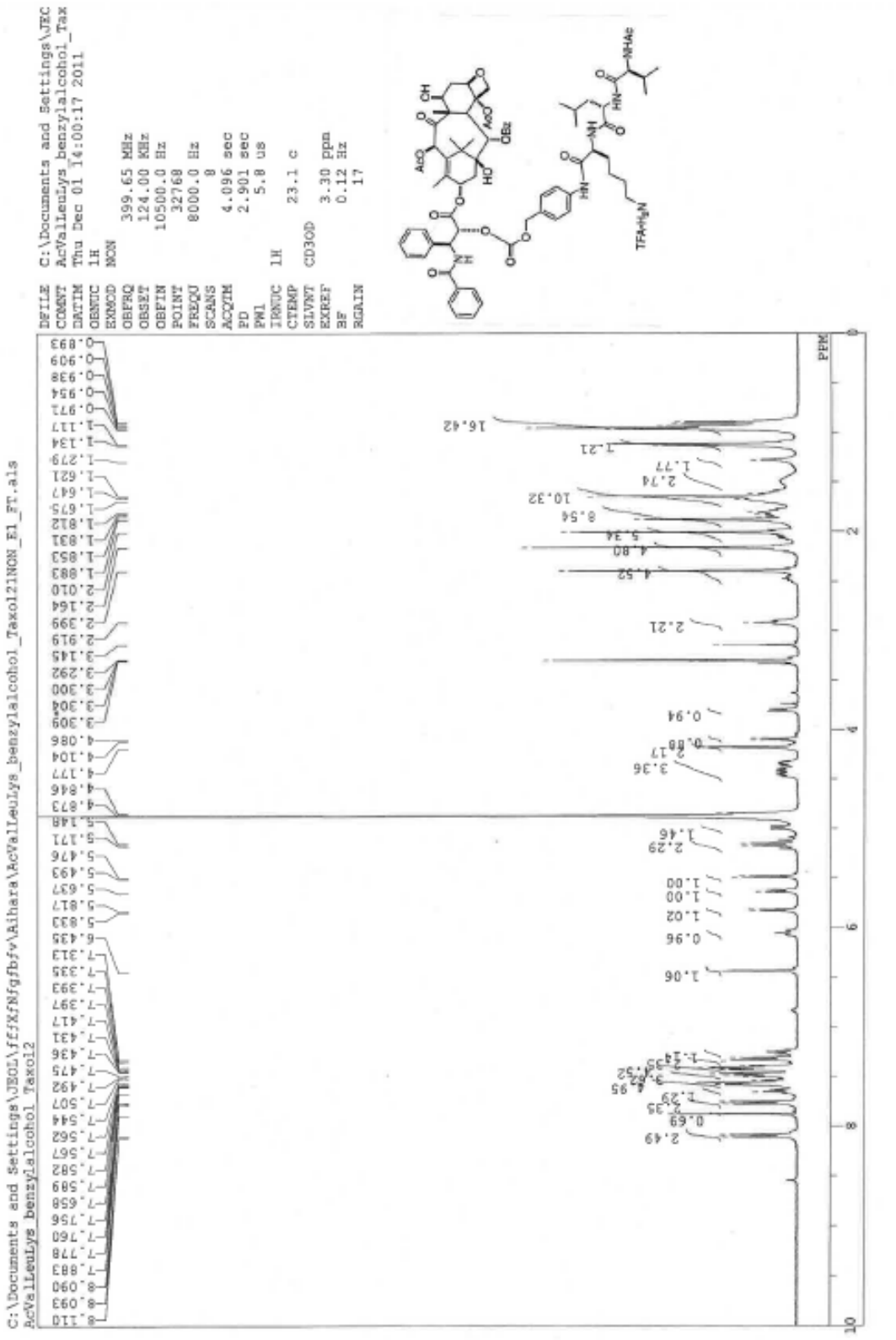

C:\Documents and Settings\JEOL\ffXfWJgfbfv\Aihara\FmocValLeuLys2Mnt_benzylalcohol2BCM_E1_FT.als
FmocValLeuLys2Mnt_benzylalcohol
DFILE C:\Documents and Settings\JEO
COMNT FmocValLeuLys2Mnt_benzylalcoho
DATIM Sat Dec 03 03:08:29 2011
OBNUC 13C
EXMOD BCM
OBFRQ 100.40 MHz
OBSET 125.00 KHz
OBWIN 10500.0 Hz
POINT 32768
FRQUD 27322.4 Hz
SCANS 8000
ACQTM 1.199 sec
PD 1.794 sec
PW1 4.8 us
IRNUC 1H
CTEMP 21.4 c
SLVNT CD3OD
EXREF 49.00 ppm
BF 1.20 Hz
RGAIN 25
NHMmt
OH
FmocHN
ppm

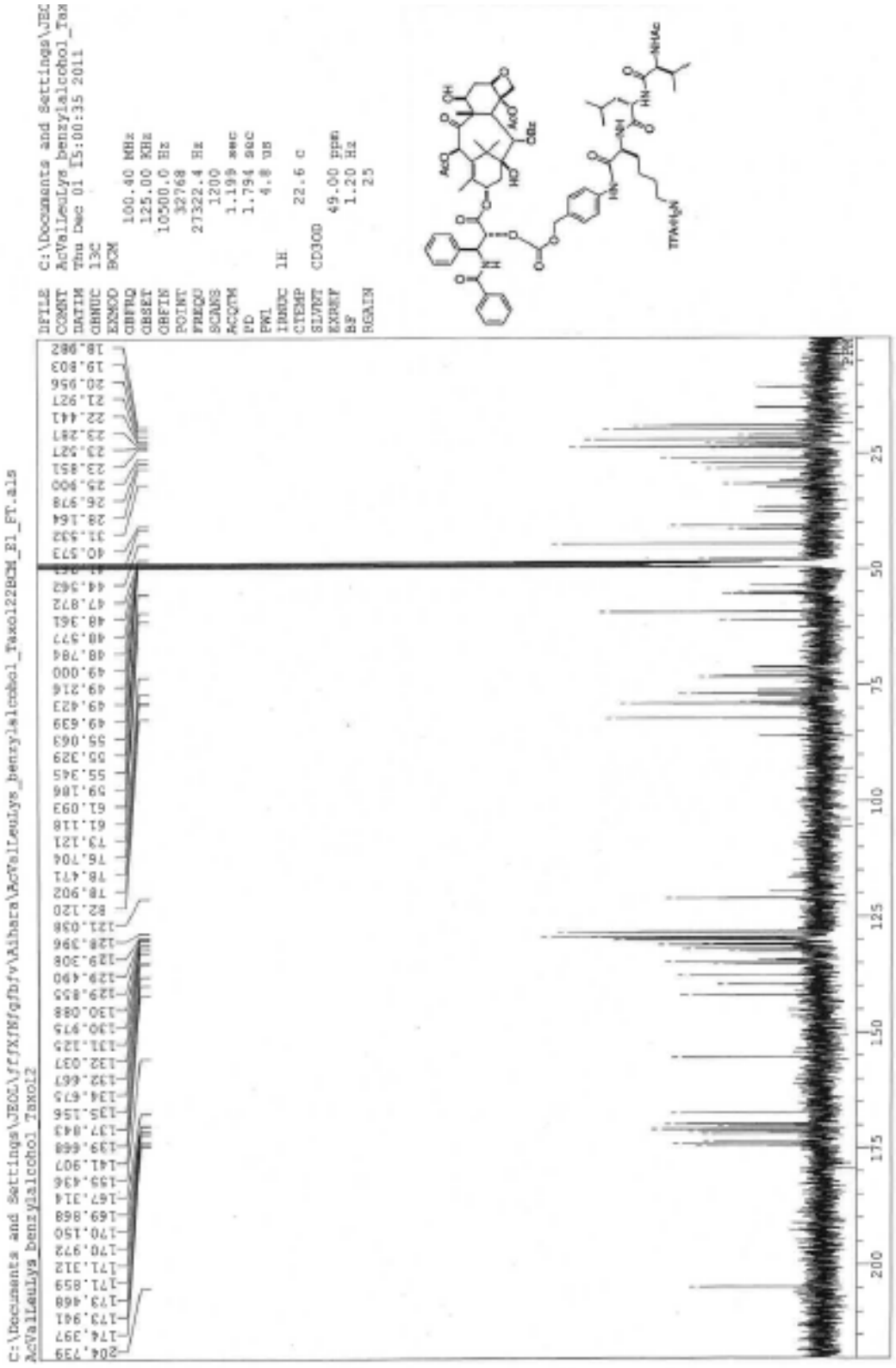

C:\Documents and Settings\JEOL\ffFXfNfgfbfv\Afhara\AcValLeuLysMmt_benzylalcohol1HCN_E1_FT.als
AcValLeuLysMmt benzylalcohol
DFILE C:\Documents and Settings\JEO
COMNT AcValLeuLysMmt_benzylalcohol
DATIM Sat Nov 26 01:35:35 2011
OBNUC 1H
EXMOD HCN
OBFRQ 399.65 MHz
OBSET 124.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 8000.0 Hz
SCANS 8
ACQTM 4.096 sec
PD 2.901 sec
PW1 5.8 us
IRNUC 1H
CTEMP 21.9 c
SLVNT CD3OD
EXREF 3.30 ppm
BF 0.12 Hz
RGAIN 19
NHMmt
OH
AcHN
13.99
12.47
4.11
2.08
3.15
1.03
2.04
2.05
2.00
2.05
PPM

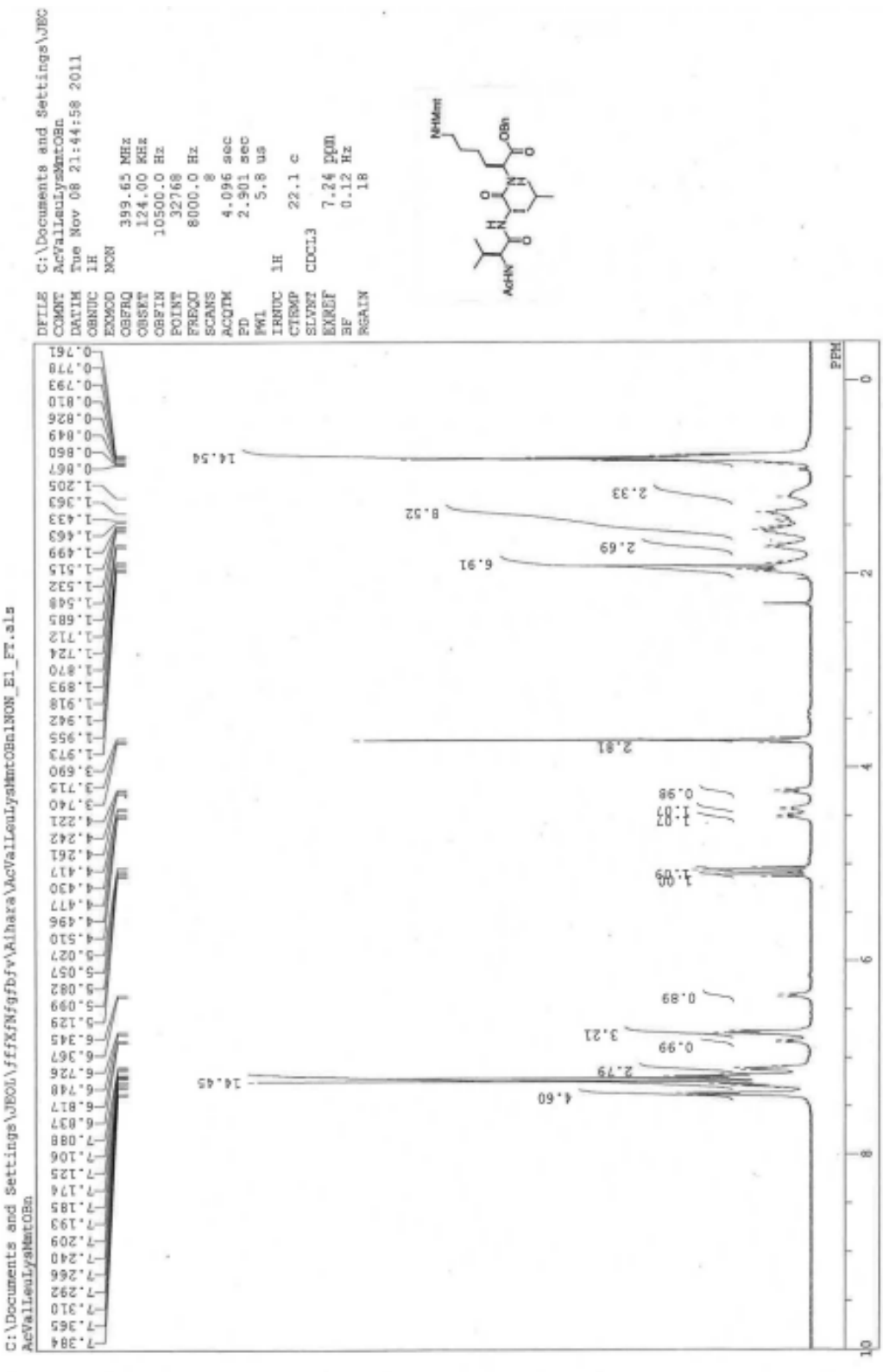

C:\Documents and Settings\JEO
AcValLeuLysMet_benzylalcohol
Sat Nov 26 08:15:09 2011
13C
DMSO
100.40 MHz
125.00 KHz
10500.0 Hz
32768
27322.4 Hz
8000
1.199 sec
1.794 sec
4.8 us
1H
22.0 c
CD3OD
49.00 ppm
1.20 Hz
25
NHAlkyl
OH
AcHN
PPM


C:\WIN98NT98\COMMON_DEFAULT.AS
AcValLeuLysMnt benzylalcohol Taxol
DFILE C:\WIN98NT98\COMMON_DEFAULT.A
COMNT AcValLeuLysMnt benzylalcohol_
DATIM Fri Dec 02 12:56:45 2011
OBNUC 1H
EXMOD NOE
OBFRQ 399.65 MHz
OBSET 124.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 7993.6 Hz
SCANS 8
ACQTM 4.099 sec
PD 2.901 sec
PW1 5.8 us
IRNUC 1H
CTEMP 50.3 c
SLVNT CD3OD
EXREF 3.30 ppm
BF 1.20 Hz
RGAIN 17
PPM


C:\Documents and Settings\JEOL\Desktop\AcValLeuLysMet_benzylalcohol_Taxol.als
AcValLeuLysMet_benzylalcohol_Taxol
C:\Documents and Settings\JEOL\Desktop\AcValLeuLysMet_benzylalcohol_Taxol_E1_F7.als
AcValLeuLysMet_benzylalcohol_Taxol
DATIM Fri Dec 02 11:53:43 2011
OBNUC 13C
EXMOD BCM
OBSFRQ 100.40 MHz
OBSET 125.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 27322.4 Hz
SCANS 1200
ACQTM 1.199 sec
PD 1.794 sec
PW1 4.8 us
IRNUC 1H
CTEMP 21.3 c
SLVNT CD3OD
EXREF 49.00 ppm
BF 1.20 Hz
RGAIN 25
AcO
OH
HO
OBz
HN
NH
NH2
NH2HN
ppm


C:\Documents and Settings\JEC
AcValLeuLys_benzylalcohol_Tax
Thu Dec 01 14:00:17 2011
1H
MCN
399.65 MHz
124.00 KHz
10500.0 Hz
32768
8000.0 Hz
8
4.096 sec
2.901 sec
5.8 us
1H
23.1 c
CD3OD
3.30 ppm
0.12 Hz
17
AcO
OH
HO
OBz
HN
NH
NHAc
TFA•H2N
PPM
16.42
7.21
1.77
2.74
10.32
8.54
5.34
4.80
4.52
2.21
0.94
0.88
2.17
3.36
1.46
2.29
1.00
1.00
1.02
0.96
1.06
2.49
0.69
2.35
2.29
C:\Documents and Settings\JBOl\fEfXfNfgfbfv\Aihara\AcValLeuLys_benzylalcohol_Taxol21NON_E1_FT.als
AcValLeuLys_benzylalcohol_Taxol2


C:\Documents and Settings\JE
AcValLeuLys_benzylalcohol_Tax
Thu Dec 01 15:00:35 2011
13C
BCM
100.40 MHz
125.00 KHz
10500.0 Hz
32768
27322.4 Hz
1200
1.199 sec
1.794 sec
4.8 us
1H
22.6 c
CD3OD
49.00 ppm
1.20 Hz
25
C:\Documents and Settings\JE0\ffffXfNfgfbfv\Aihara\AcValLeuLys_benzylalcohol_taxol22BCM_E1_FT.als
AcValLeuLys_benzylalcohol_Taxol2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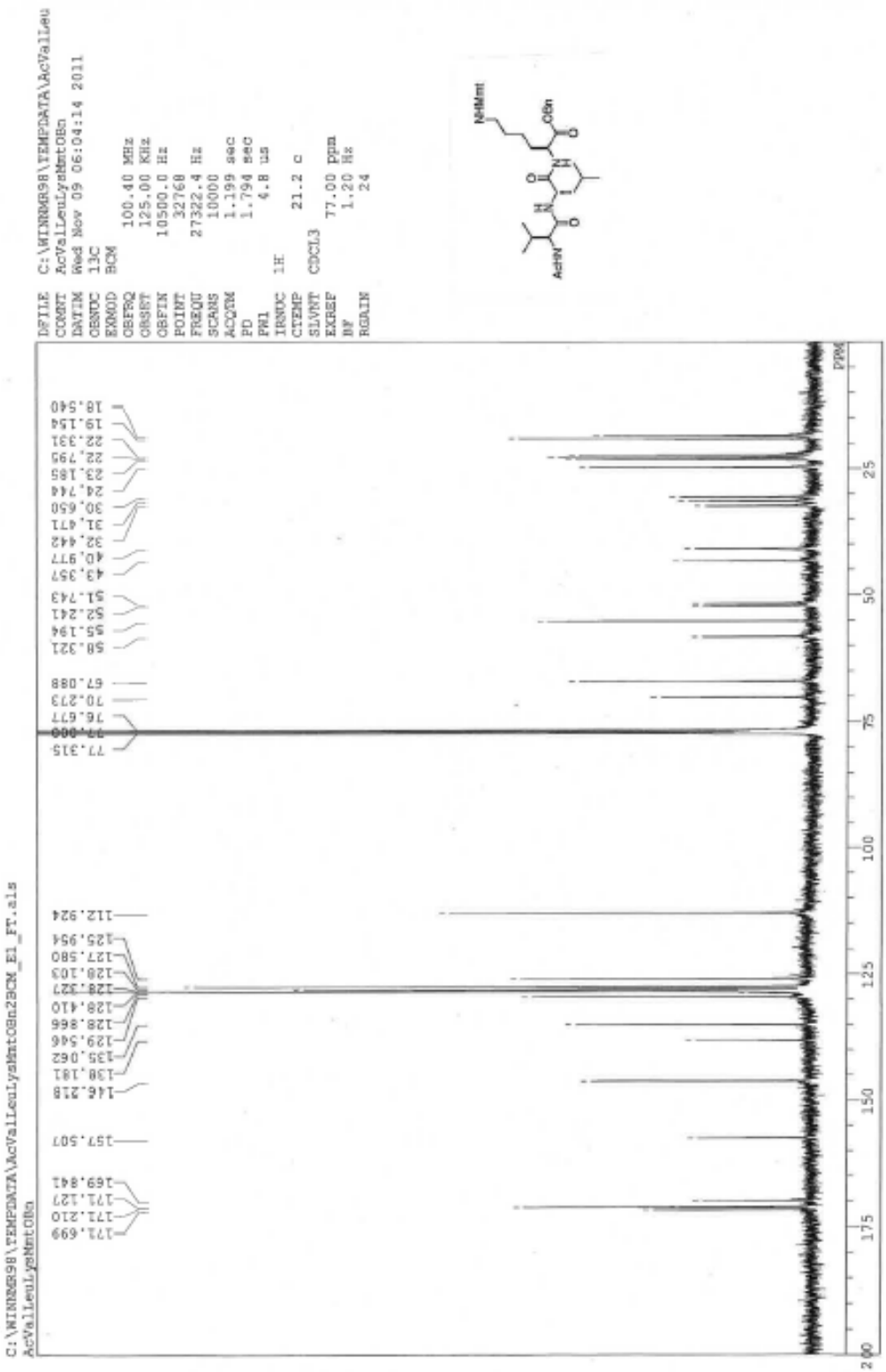
AcValLeuLysMmtOBn
DFILE C:\Documents and Settings\JEO
COMNT AcValLeuLysMmtOBn
DATIM Tue Nov 08 21:44:58 2011
OBNUC 1H
EXMOD NON
OBFRQ 399.65 MHz
OBSET 124.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 8000.0 Hz
SCANS 8
ACQTM 4.096 sec
PD 2.901 sec
PW1 5.8 us
IRNUC 1H
CTEMP 22.1 c
SLVNT CDCl3
EXREF 7.24 ppm
BF 0.12 Hz
RGAIN 18
NHMmt
OBn
AcHN
PPM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DATIM Wed Nov 09 06:04:14 2011
OBSNUC 13C
EXMOD BCM
OBSFRQ 100.40 MHz
ORSET 125.00 KHz
OBFIN 10500.0 Hz
POINT 32768
FREQU 27322.4 Hz
SCANS 10000
ACQTM 1.199 sec
PD 1.794 sec
PW1 4.8 us
IRNUC 1H
CTEMP 21.2 c
SLVNT CDCL3
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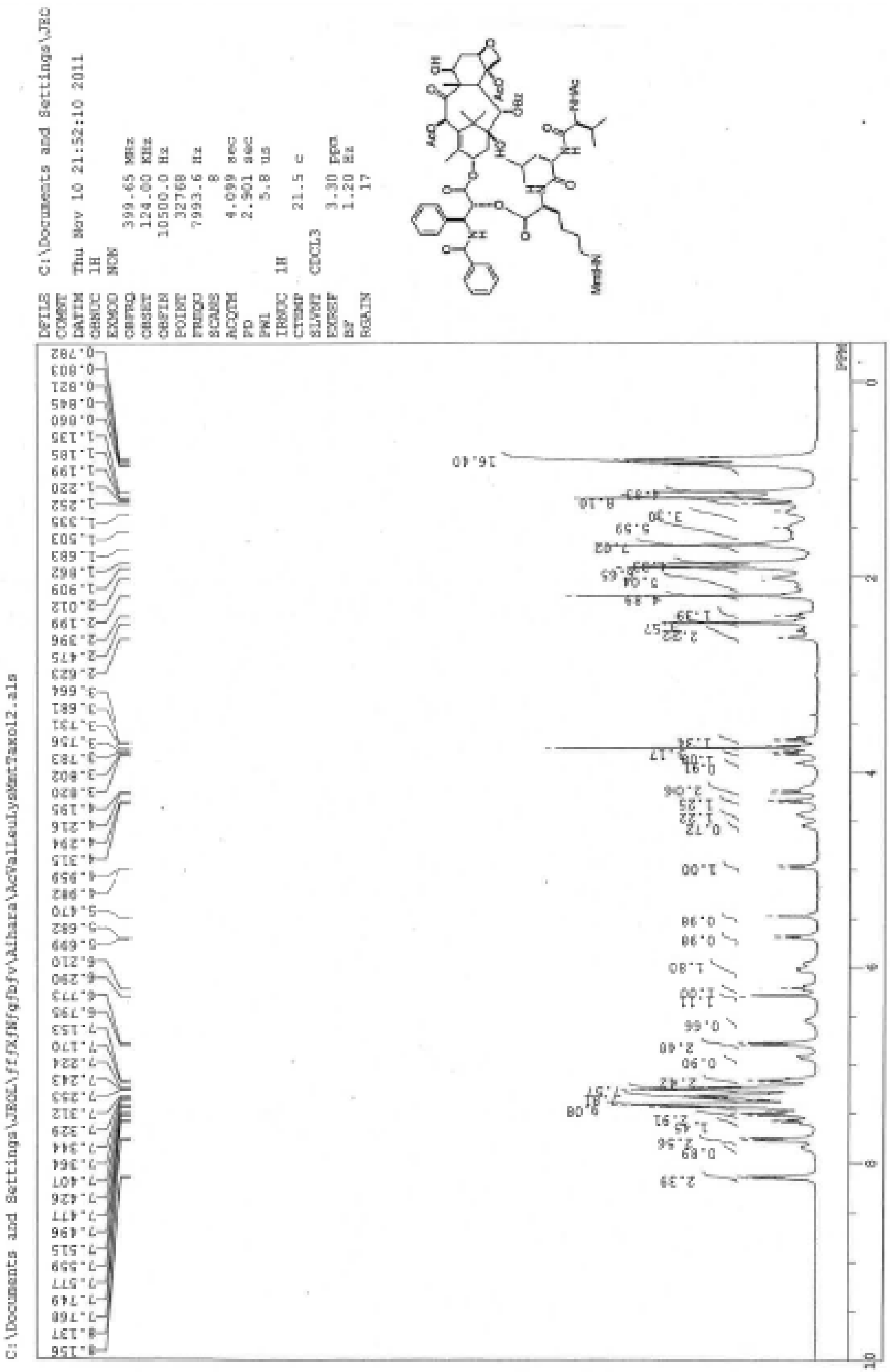
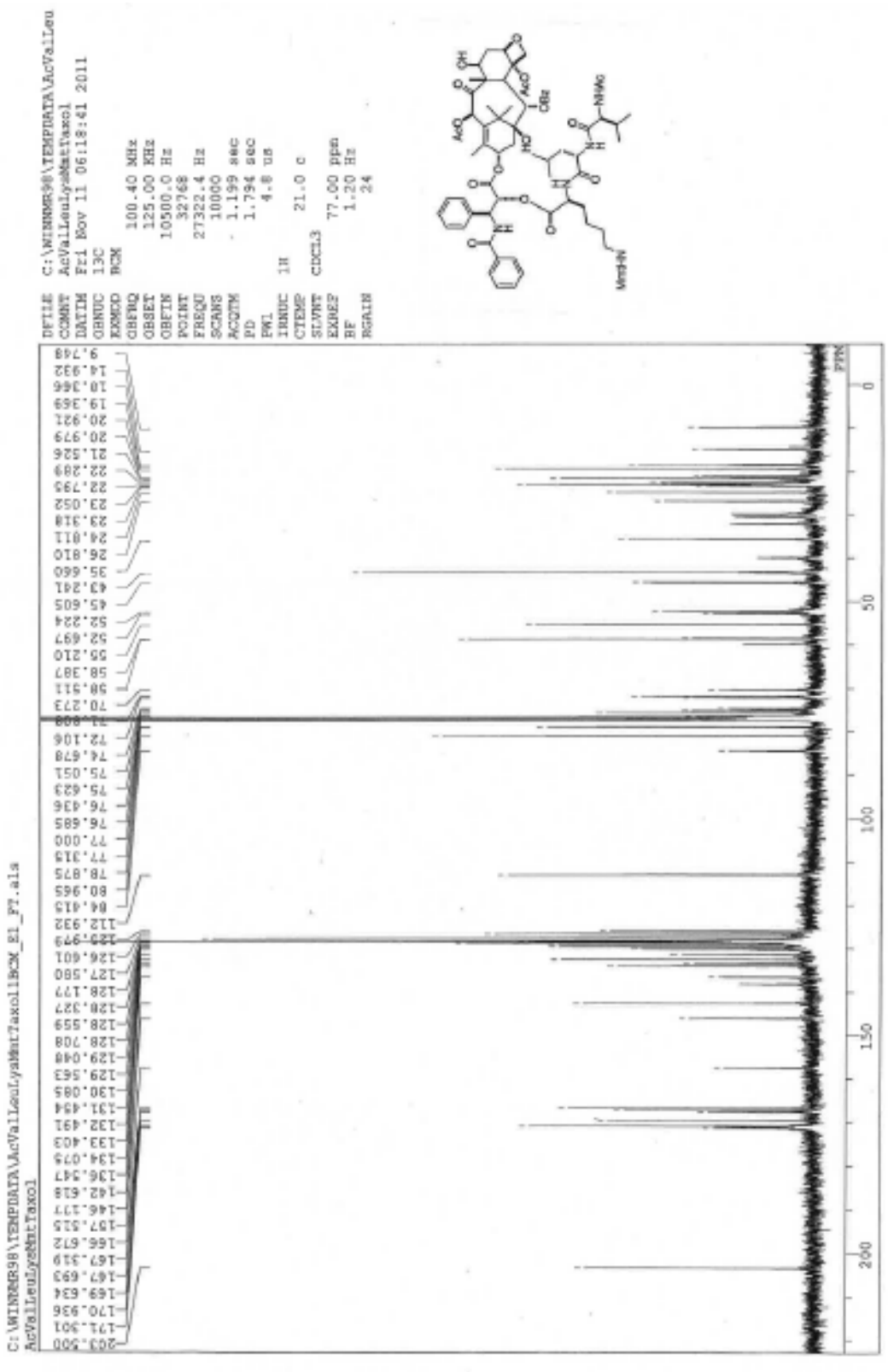
BF 1.20 Hz
RGAIN 24
NHMmt
OBn
AcHN
PPM

Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

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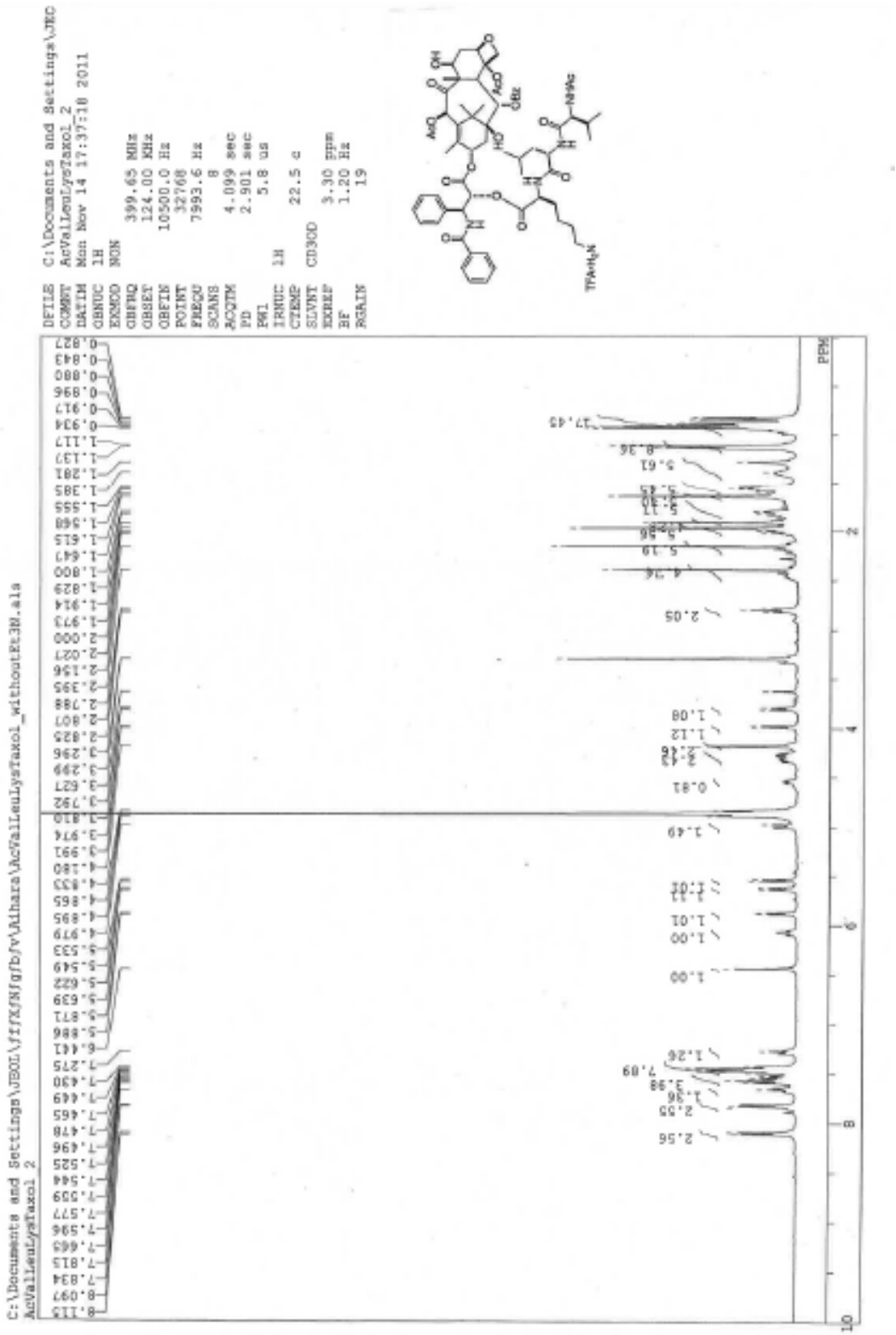
Fri Nov 11 06:18:41 2011
13C
WCM
100.40 MHz
125.00 KHz
10500.0 Hz
32768
27322.4 Hz
10000
1.199 sec
1.794 sec
4.8 us
1H
21.0 c
CDCl3
77.00 ppm
1.20 Hz
24
C:\WINNMR98\TEMPDATA\AcValLeuLysMet7axol13CW_21_F7.als
AcValLeuLysMet7axol
PPM
0
50
100
150
200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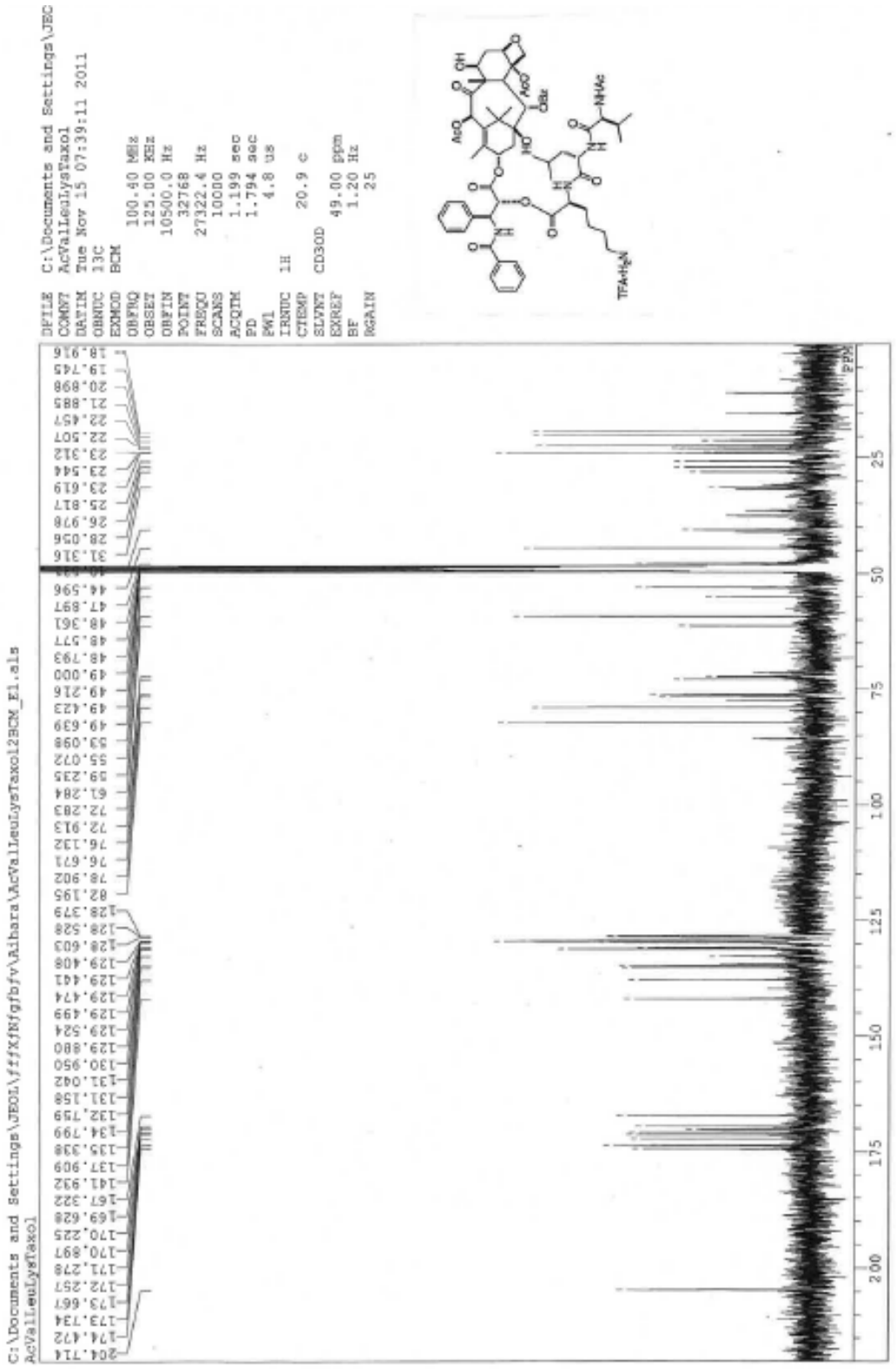
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AcValLeuLysTaxol
C:\Documents and Settings\JEO
AcValLeuLysTaxol
Tue Nov 15 07:39:11 2011
13C
BCM
100.40 MHz
125.00 KHz
10500.0 Hz
32768
27322.4 Hz
10000
1.199 sec
1.794 sec
4.8 us
1H
20.9 c
CD3OD
49.00 ppm
1.20 Hz
25
AcO
OH
OBz
NHAc
TFA•H2N
ppm