Supporting Information

Synthesis of 2α-Heteroarylalkyl Active Vitamin D_3 with Therapeutic Effect on Enhancing Bone Mineral Density *in vivo*

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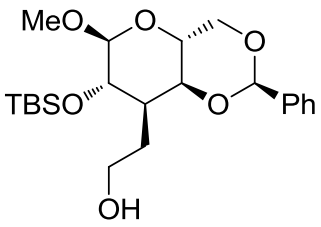
General: ^{1}H and ^{13}C NMR spectra were recorded on JEOL AL-400 NMR (400 MHz) spectrometer. ^{1}H NMR spectra were referenced with $(CH_3)_4Si$ (δ 0.00 ppm) as an internal standard. ^{13}C NMR spectra were referenced with deuterated solvent (δ 77.0 ppm for $CDCl_3$). IR spectra were recorded on JASCO FT-IR-8000 or FT-IR-4200 Fourier Transform Infrared Spectrophotometer. High resolution mass spectra were obtained on SHIMADZU LCMS-IT-TOF mass spectrometer in positive electrospray ionization (ESI) method. EI mass spectra were recorded on a JEOL JMX-SX 102A spectrometer. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Column chromatography was performed on silica gel 60N (Kanto Chemical Co., Inc., 40-63 μm or 100-210 μm) or silica gel 60 (Merck, 0.040-0.063 mm). Preparative thin layer chromatography was performed on silica gel 60 F_{254} (Merck, 0.25 mm). High performance liquid chromatography (HPLC) was carried out on a SHIMADZU HPLC system consisting of the following equipments: pump, LC-6AD; detector, SPD-10A; column, YMC-Pack ODS-A. All experiments were performed under anhydrous conditions in an atmosphere of argon, unless otherwise mentioned.

Methyl 4,6-*O*-Benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-*C*-(2-hydroxyethyl)-α-D-altropyranoside (4).



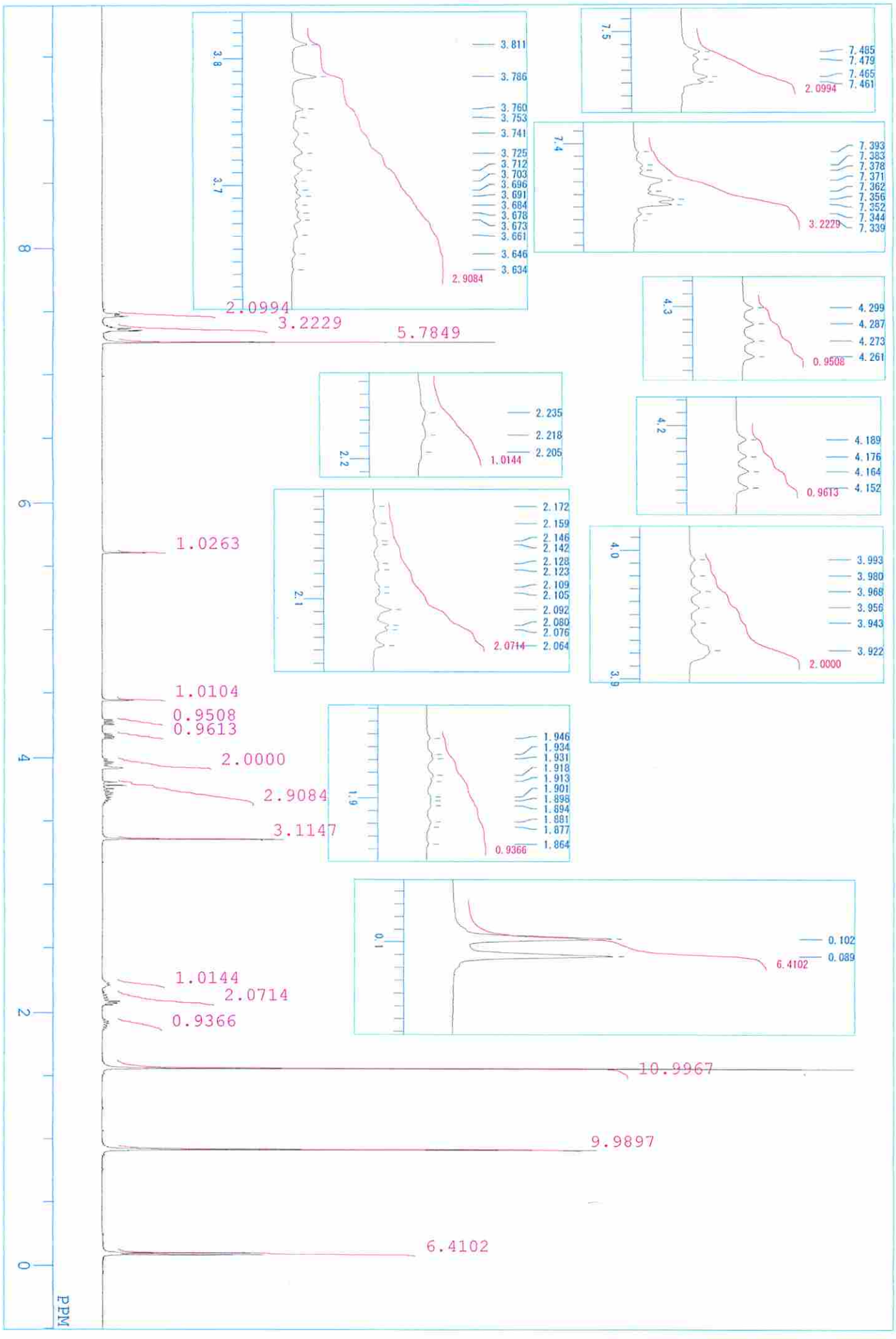
To a solution of methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-ethenyl-α-D-altropyranoside[1] (**3**, 122 mg, 0.417 mmol) in CH_2Cl_2 (5 mL) were added 2,6-lutidine (0.10 mL, 0.860 mmol) and TBSOTf (0.15 mL, 0.653 mmol) at 0°C, and the mixture was stirred at rt for 2 h. To the reaction mixture were further added 2,6-lutidine (0.10 mL, 0.860 mmol) and TBSOTf (0.15 mL, 0.653 mmol) at 0°C, and the mixture was stirred at rt for 1 h. To the mixture was added sat. NH_4Cl aq. at 0°C and the organic layer was separated. The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 100/1-50/1) to yield methyl 4,6-*O*-benzylidene-3-deoxy-2-*O*-(*tert*-butyldimethylsilyl)-3-*C*-ethenyl-α-D-altropyranoside (144.3 mg, 0.355 mmol, 85%) as a colorless oil.

$[\alpha]_D^{23}$ +29.6 (c 1.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.094 (s, 3H), 0.11 (s, 3H), 0.92 (s, 9H), 2.83-2.86 (m, 1H), 3.38 (s, 3H), 3.79 (dd, *J* = 10.0, 10.3 Hz, 1H), 3.83-3.82 (m, 1H), 4.03 (ddd, *J* = 4.9, 9.8, 10.0 Hz, 1H), 4.10 (dd, *J* = 5.1, 9.8 Hz, 1H), 4.27 (dd, *J* = 4.9, 10.3 Hz, 1H), 4.48 (brs, 1H), 5.17 (ddd, *J* = 0.98, 1.7, 10.3 Hz, 1H), 5.21 (ddd, *J* = 1.7, 2.0, 17.1 Hz, 1H), 5.59 (s, 1H) , 6.24 (ddd, *J* = 9.8, 10.3, 17.1 Hz, 1H), 7.32-7.37 (m, 3H), 7.45-7.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.02, -4.90, 18.1, 25.8 (3C), 48.8, 55.0, 59.8, 69.5, 73.7, 75.5, 101.9, 102.2, 118.0, 126.2 (2C), 128.1 (2C), 128.8, 134.0 137.6; IR (neat) 1468, 1379, 1258 cm^{-1}. ESI-HRMS calcd for $C_{22}H_{34}O_5Si$ ($[M+H]^+$) 407.2248, found 407.2249.

To a solution of the above *O*-silylated product (265 mg, 0.652 mmol) in THF (1.3 mL) was added 9-BBN (2.6 mL, 1.304 mmol) at 0°C, and the mixture was stirred at rt for 1.5 h. To the reaction mixture were added 3 M NaOH (2 mL) and 30% H_2O_2 (2 mL),

and the mixture was stirred at rt for 16 h. To the mixture were added sat. $NaHCO_3$ aq. and $Na_2S_2O_3$ aq. at 0°C, and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 20/1) to afford **4** (254 mg, 0.598 mmol, 92%) as a colorless oil.

$[\alpha]_D^{23}$ +47.1 (c 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.089 (s, 3H), 0.10 (s, 3H), 0.92 (s, 9H), 1.91 (dddd, *J* = 6.3, 6.8, 7.1, 14.4 Hz, 1H), 2.08 (dd, *J* = 4.9, 6.3 Hz, 1H), 2.12 (dddd, *J* = 7.1, 7.3, 7.8, 14.4 Hz, 1H), 2.21-2.24 (m, 1H), 3.36 (s, 3H), 3.63-3.75 (m, 2H), 3.79 (dd, *J* = 10.0, 10.3 Hz, 1H), 3.92-3.93 (br, 1H), 3.96 (ddd, *J* = 4.9, 9.8, 10.0 Hz, 1H), 4.17 (dd, *J* = 5.1, 9.8 Hz, 1H), 4.28 (dd, *J* = 4.9, 10.3 Hz, 1H), 4.45 (brs, 1H), 5.61 (s, 1H), 7.34-7.39 (m, 3H), 7.46-7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.99, -4.87, 18.1, 25.8 (3C), 29.0, 41.6, 55.0, 59.4, 62.4, 69.5, 72.1 76.2, 102.1, 102.3, 126.1 (2C), 128.1 (2C), 129.0, 137.3; IR (neat) 3451, 1468, 1383 cm^{-1}. ESI-HRMS calcd for $C_{22}H_{36}O_6Si$ ($[M+Na]^+$) 447.2173, found 447.2162.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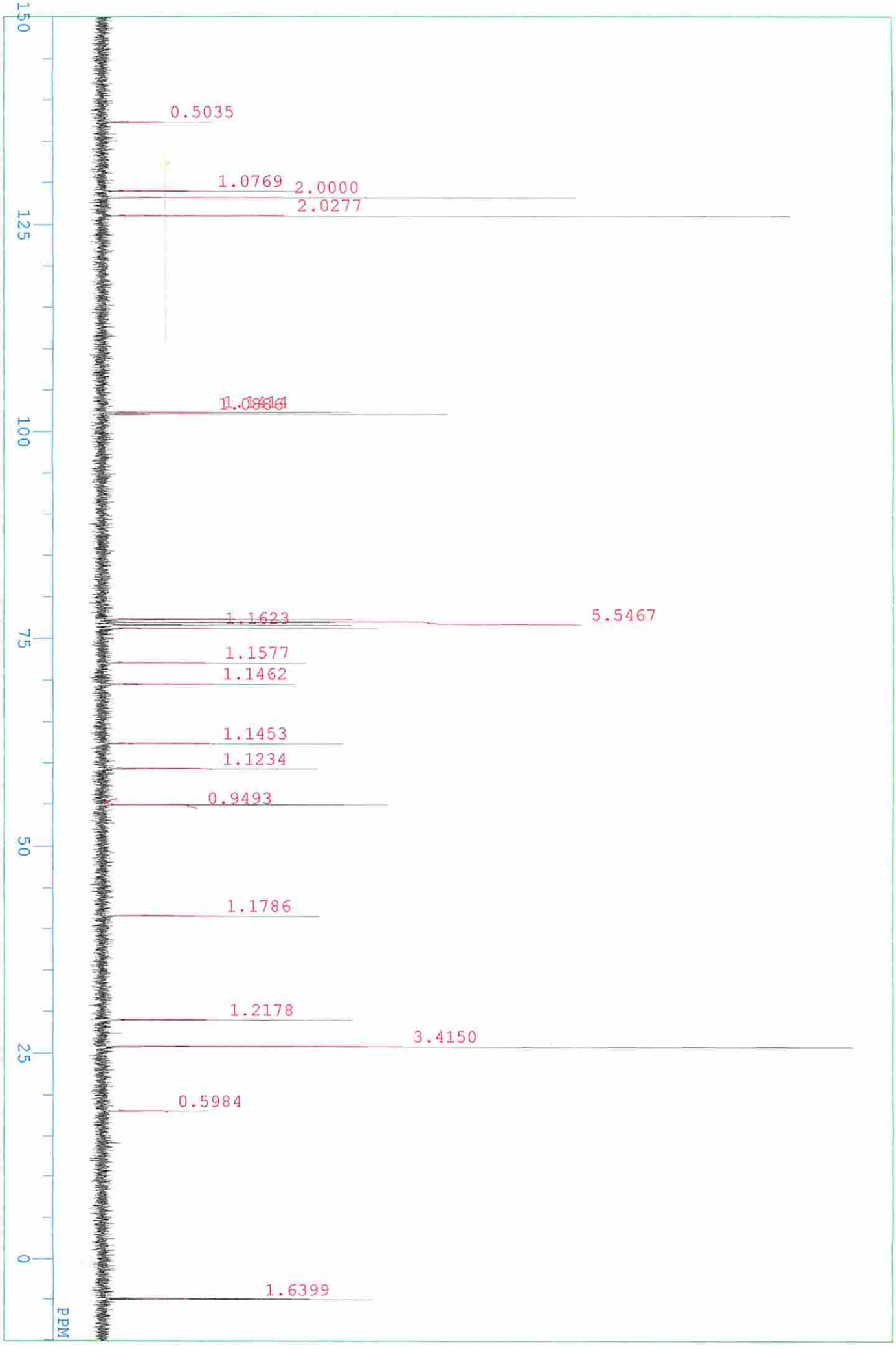
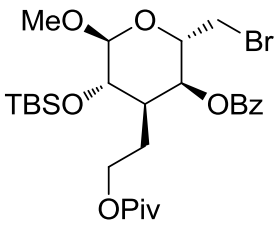


Methyl

4-*O*-Benzoyl-6-bromo-2-*O*-(*tert*-butyldimethylsilyl)-3,6-dideoxy-3-*C*-(2-pivaloyloxyethyl)-α-D-altropyranoside (5).



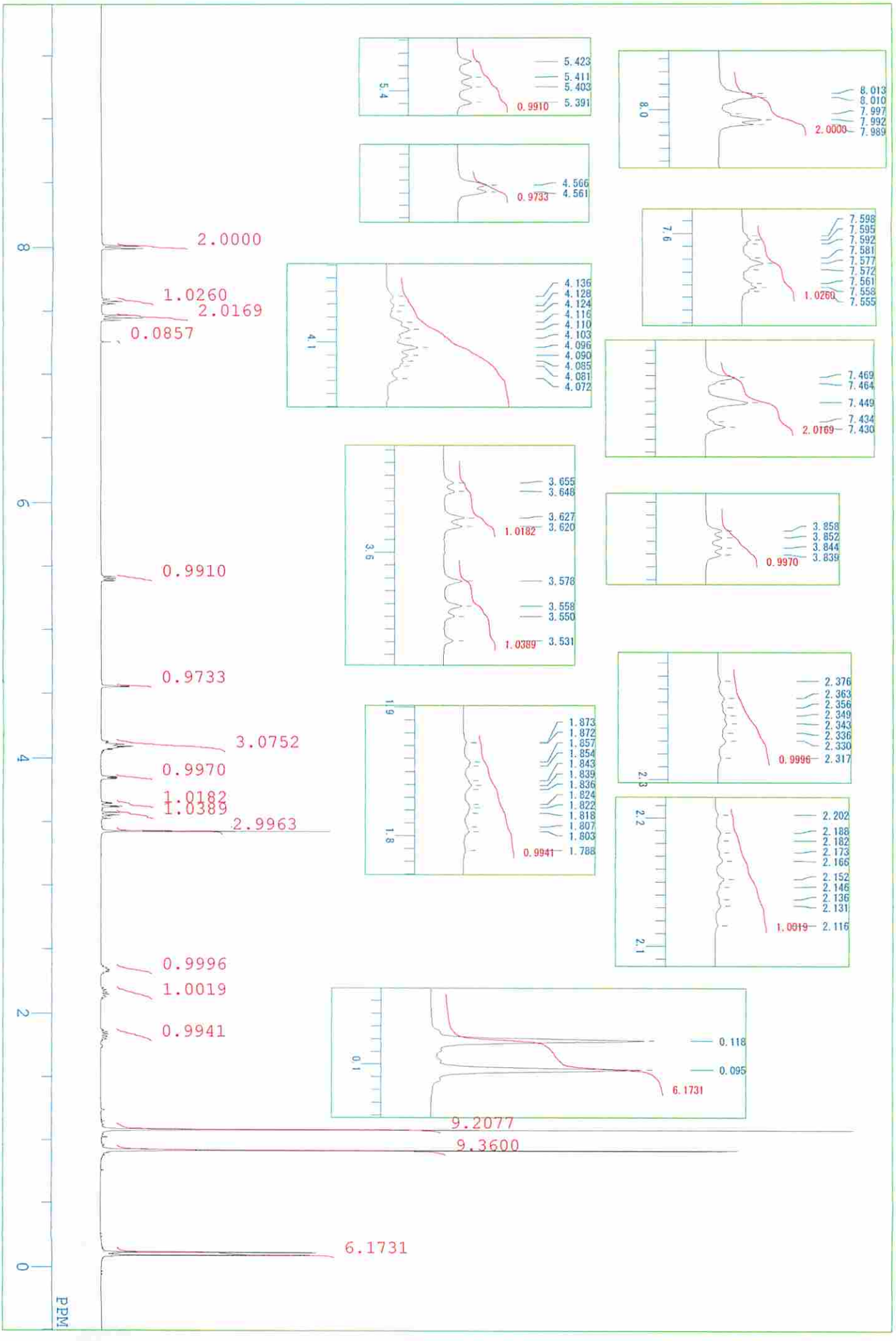
To a solution of alcohol **4** (352.6 mg, 0.830 mmol) in CH_2Cl_2 (8 mL) were added pyridine (0.17 mL, 1.83 mmol) and PivCl (0.22 mL, 1.83 mmol) at 0°C, and the mixture was stirred at rt for 1 h. To the mixture was added sat. NH_4Cl aq. at 0°C, and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 40/1-10/1) to give methyl 4,6-*O*-benzylidene-2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-*C*-(2-pivaloyloxyethyl)-α-D-altropyranoside (401.5 mg, 0.789 mmol, 95%) as a colorless oil.

$[\alpha]_D^{26}$ +30.7 (c 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.085 (s, 3H), 0.094 (s, 3H), 0.92 (s, 9H), 1.19 (s, 9H), 2.03 (dddd, *J* = 6.1, 6.3, 8.5, 14.4 Hz, 1H), 2.14 (dddd, *J* = 6.3, 7.1, 7.8, 14.4 Hz, 1H), 2.19-2.23 (m, 1H), 3.35 (s, 3H), 3.78 (dd, *J* = 10.0, 10.3 Hz, 1H), 3.89-3.91 (brs, 1H), 3.92 (ddd, *J* = 4.9, 10.0, 10.0 Hz, 1H), 4.17 (dd, *J* = 5.1, 10.0 Hz, 1H), 4.12-4.23 (m, 2H), 4.27 (dd, *J* = 4.9, 10.3 Hz, 1H), 4.45 (brs, 1H), 5.59 (s, 1H), 7.33-7.39 (m, 3H), 7.46-7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.93, -4.84, 18.0, 24.5, 25.8 (3C), 27.2 (3C), 38.6, 40.3, 55.0, 59.3, 63.6, 69.5, 71.1, 76.1, 101.7, 102.3, 126.0 (2C), 128.1 (2C), 128.8, 137.7 178.2; IR (neat) 1730, 1464, 1383 cm^{-1}. ESI-HRMS calcd for $C_{27}H_{44}O_7Si$ ($[M+Na]^+$) 531.2749, found 531.2750.

To a solution of the above *O*-protected product (403.1 mg, 0.792 mmol) in CCl_4 (16 mL) were added $BaCO_3$ (0.174 g, 0.882 mmol) and NBS (0.156 g, 0.876 mmol) at 0°C, and the mixture was refluxed for 2 h. To the mixture were added sat. $NaHCO_3$ aq. and sat. $Na_2S_2O_3$ aq. at 0°C, and the mixture was filtered through Celite pad. The filtrate was extracted with EtOAc, the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography

on silica gel (hexane/EtOAc = 40/1) to give **5** (404.3 mg, 0.688 mmol, 87%) as a colorless oil.

$[\alpha]_D^{24}$ +24.4 (c 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.095 (s, 3H), 0.12 (s, 3H), 0.92 (s, 9H), 1.09 (s, 9H), 1.83 (dddd, *J* = 7.3, 7.8, 8.5, 14.4 Hz, 1H), 2.16 (dddd, *J* = 6.3, 8.1, 8.3, 14.4 Hz, 1H), 2.35 (dddd, *J* = 4.9, 5.4, 7.8, 8.3 Hz, 1H), 3.43 (s, 3H), 3.55 (dd, *J* = 7.8, 11.0 Hz, 1H), 3.64 (dd, *J* = 2.7, 11.0 Hz, 1H), 3.85 (dd, *J* = 2.2, 5.4 Hz, 1H), 4.07-4.14 (m, 3H), 4.56 (d, *J* = 2.2 Hz, 1H), 5.41 (dd, *J* = 4.9, 8.1 Hz, 1H), 7.43-7.47 (m, 2H), 7.56-7.60 (m, 1H), 7.99-8.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.93, -4.68, 18.0, 24.2, 25.8 (3C), 27.1 (3C), 33.2, 38.6, 39.2, 55.4, 62.4, 68.5, 70.8 (2C), 103.3, 128.4 (2C), 129.4, 129.5 (2C), 133.3, 165.1, 178.1; IR (neat) 1468, 1379, 1258 cm^{-1}. ESI-HRMS calcd for $C_{27}H_{43}O_7SiBr$ ($[M+Na]^+$) 609.1854, found 609.1857.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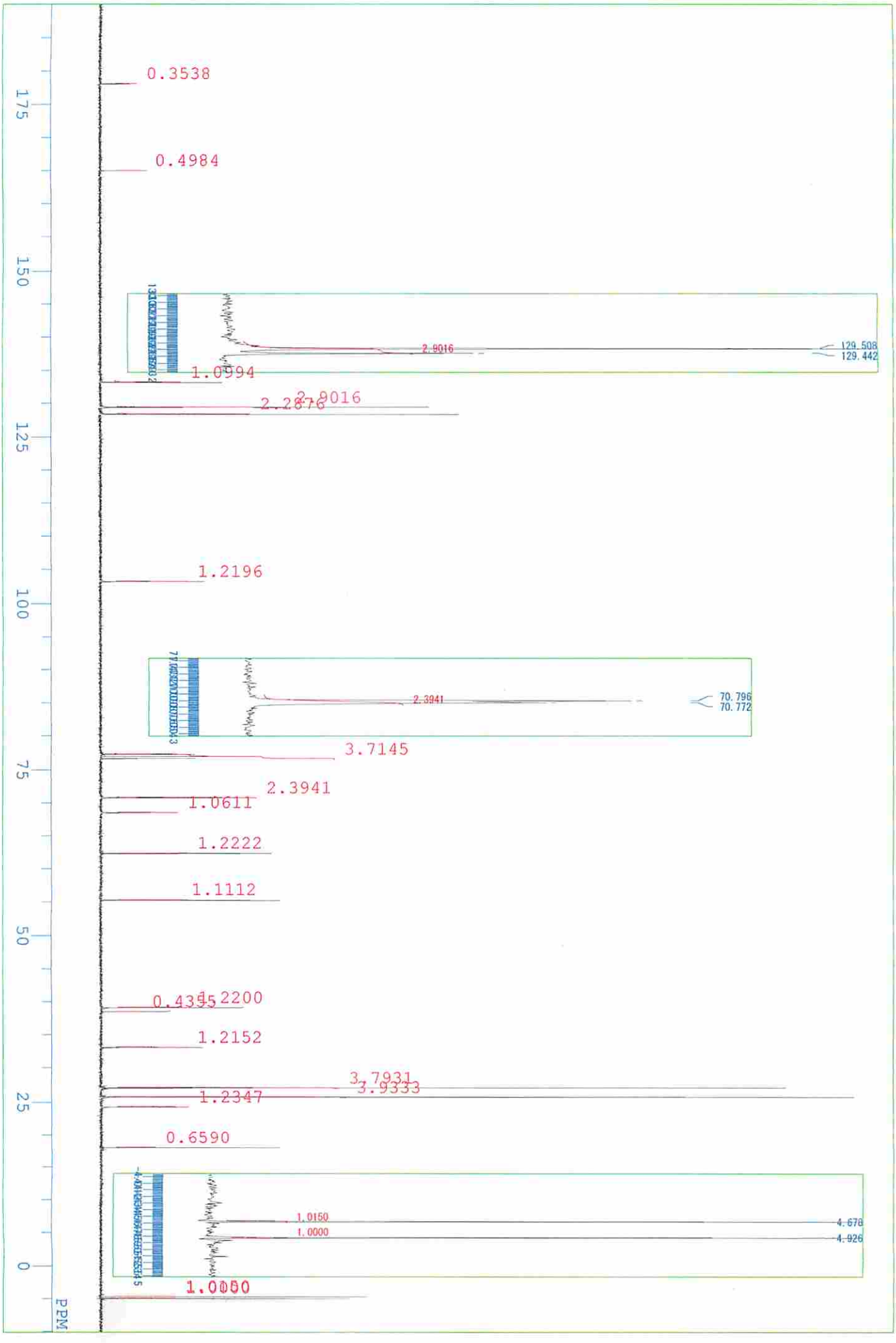

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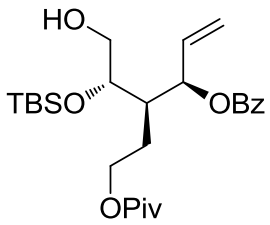
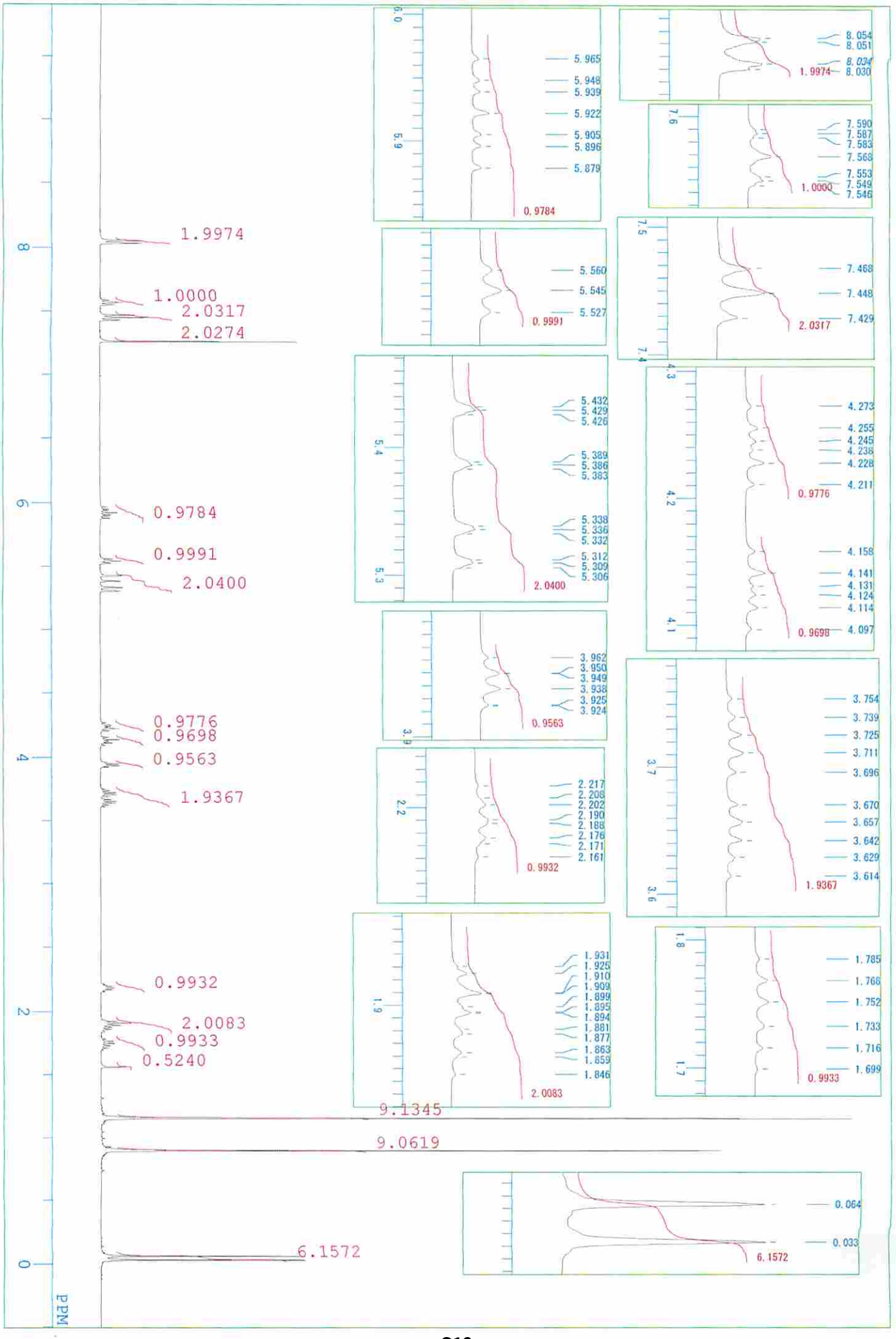
(2*S*,3*R*,4*R*)-4-Benzoyloxy-2-(*tert*-butyldimethylsilyl)oxy-3-(2-pivaloyloxyethyl)hex-5-en-1-ol (6).



To a solution of **5** (401.6 mg, 0.683 mmol) in 1-propanol/H_2O (30 mL, 1-propanol/H_2O = 5/1) were added $NaBH_3CN$ (0.219 g, 3.49 mmol) and Zn dust (0.897 g, 13.7 mmol) at rt, and the mixture was refluxed for 20 min. To the reaction mixture were re-added $NaBH_3CN$ (0.220 g, 3.50 mmol) and Zn dust (0.896 g, 13.7 mmol) at rt, and the mixture was refluxed for 20 min. This process was repeated further three times. The mixture was filtered through Celite pad (EtOAc), and the filtrate was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 10/1) to give **6** (227.5 mg, 0.475 mmol, 70%) as a colorless oil.

$[\alpha]_D^{19}$ +25.2 (c 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.033 (s, 3H), 0.064 (s, 3H), 0.90 (s, 9H), 1.16 (s, 9H), 1.74 (dddd, *J* = 6.6, 6.8, 6.8, 12.7 Hz, 1H), 1.89 (dddd, *J* = 6.1, 6.8, 6.8, 12.7 Hz, 1H), 1.90 (dd, *J* = 5.4, 6.1 Hz, 1H), 2.19 (dddd, *J* = 5.9, 6.1, 6.3, 6.6 Hz, 1H), 3.64 (ddd, *J* = 5.4, 5.9, 11.2 Hz, 1H), 3.73 (ddd, *J* = 5.9, 5.9, 11.2 Hz, 1H), 3.94 (ddd, *J* = 5.4, 5.9, 5.9 Hz, 1H), 4.13 (ddd, *J* = 6.8, 6.8, 11.0 Hz, 1H), 4.24 (ddd, *J* = 6.8, 6.8, 11.0 Hz, 1H), 5.32 (ddd, *J* = 0.98, 1.5, 10.5 Hz, 1H), 5.41 (ddd, *J* = 0.98, 1.5, 17.1 Hz, 1H), 5.55 (dddd, *J* = 0.98, 0.98, 6.3, 6.8 Hz, 1H), 5.92 (ddd, *J* = 6.8, 10.5, 17.1 Hz, 1H), 7.43-7.47 (m, 2H), 7.55-7.59 (m, 1H), 8.03-8.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.88, -4.20, 18.0, 25.2, 25.8 (3C), 27.1 (3C), 38.6, 41.5, 63.4, 64.8, 72.5, 75.7, 118.7, 128.2 (2C), 129.4 (2C), 130.1, 132.8 134.1, 165.2, 178.4; IR (neat) 1468, 1379, 1258 cm^{-1}. ESI-HRMS calcd for $C_{26}H_{42}O_6Si$ ($[M+Na]^+$) 501.2643, found 501.2617.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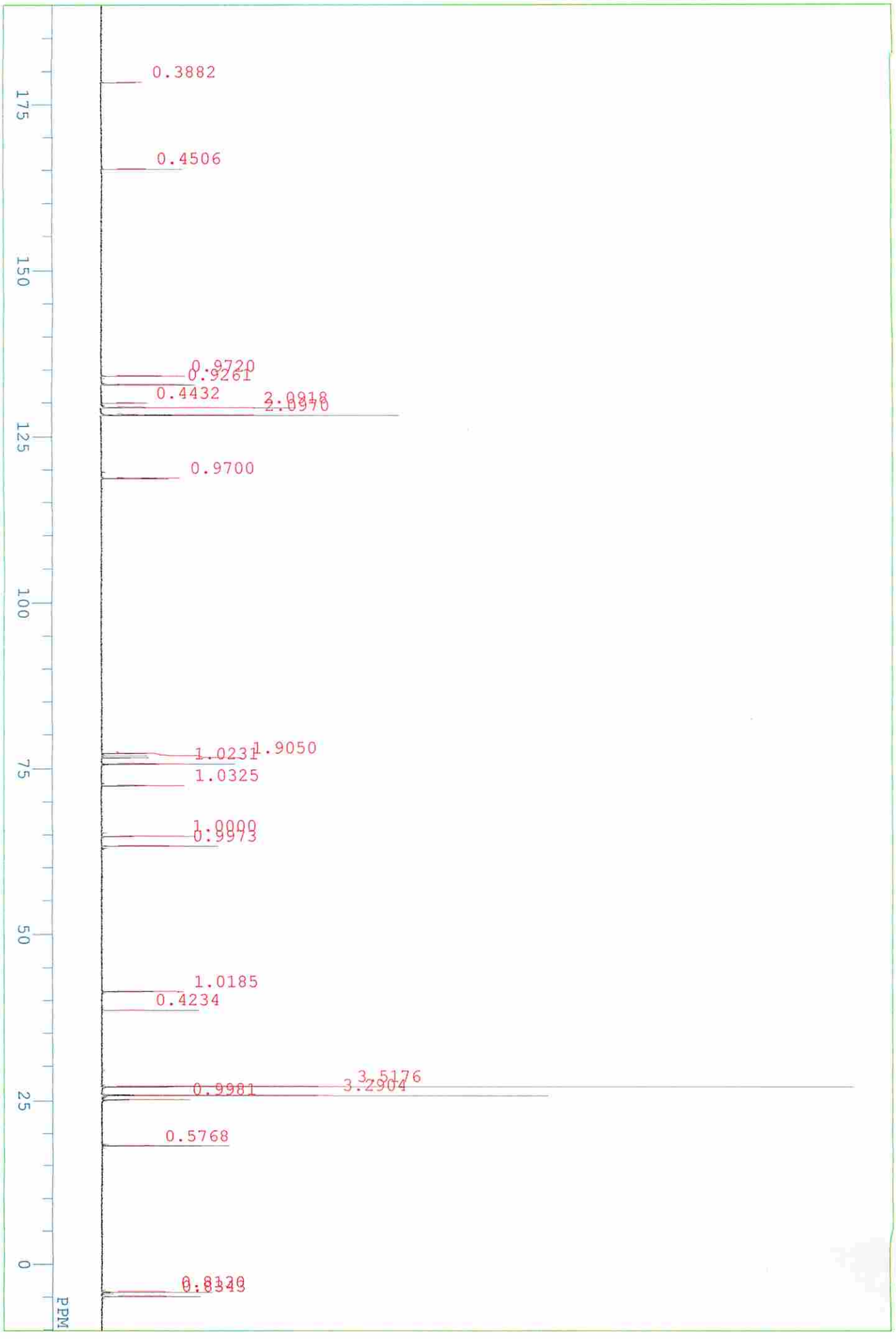

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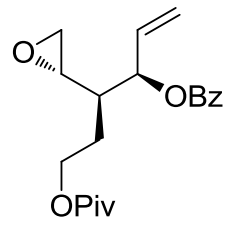
6

(3*R*,4*R*,5*S*)-3-Benzoyloxy-5,6-epoxy-4-[(2-pivaloyloxy)ethyl]hex-1-ene (7).



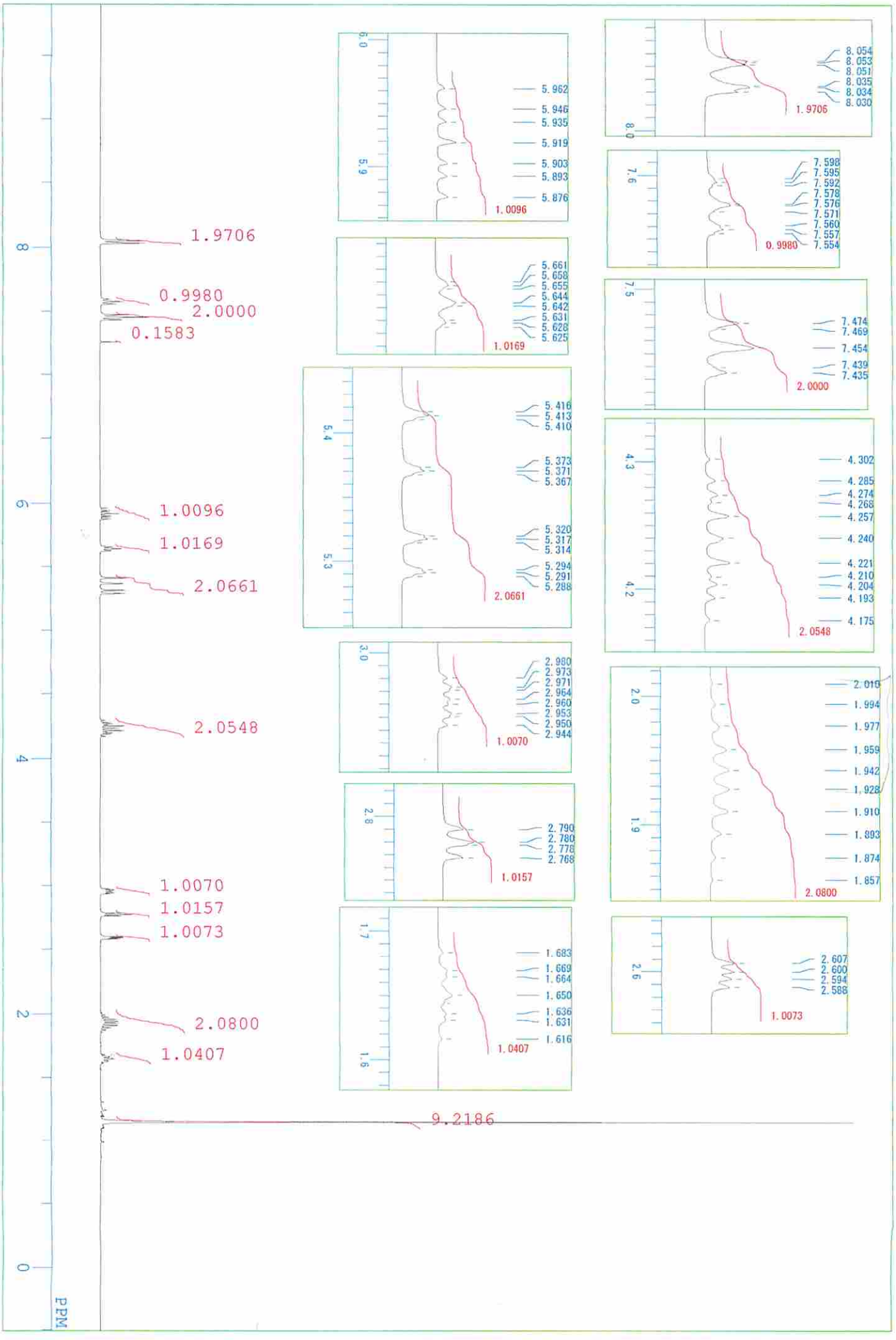
To a solution of **6** (521.7 mg, 1.09 mmol) in pyridine (11 mL) was added TsCl (2.08 g, 10.9 mmol) at 0°C, and the mixture was stirred at rt for 14.5 h. To the reaction mixture was re-added TsCl (0.209 g, 1.09 mmol), and the mixture was stirred at rt for further 1 h. To the mixture was added sat. NH_4Cl aq. at 0°C, and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 20/1-10/1) to give (3*R*,4*R*,5*S*)-3-benzoyloxy-5-[(*tert*-butyldimethylsilyl)oxy]-4-[(2-pivaloyloxy)ethyl]-6-(tosyloxy)hex-1-ene (662.5 mg, 1.05 mmol, 96%) as a colorless oil.

$[\alpha]_D^{19}$ +22.6 (c 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.053 (s, 3H), -0.028 (s, 3H), 0.84 (s, 9H), 1.16 (s, 9H), 1.65 (dddd, *J* = 6.1, 6.3, 6.6, 12.7 Hz, 1H), 1.79 (dddd, *J* = 7.1, 7.3, 7.6, 12.7 Hz, 1H), 2.08 (dddd, *J* = 6.3, 6.3, 7.1, 8.1 Hz, 1H), 2.43 (s, 3H), 3.99 (dd, *J* = 6.8, 10.3 Hz, 1H), 4.03-4.16 (m, 4H), 5.30 (ddd, *J* = 0.98, 1.2, 10.3 Hz, 1H), 5.38 (ddd, *J* = 0.98, 1.2, 17.1 Hz, 1H), 5.43 (dddd, *J* = 0.98, 0.98, 6.3, 7.1 Hz, 1H), 5.85 (ddd, *J* = 7.1, 10.3, 17.1 Hz, 1H), 7.30-7.32 (m, 2H), 7.45-7.48 (m, 2H), 7.57-7.61 (m, 1H), 7.77-7.79 (m, 2H), 8.02-8.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.11, -4.32, 18.0, 21.6, 25.0, 25.8 (3C), 27.2 (3C), 38.6, 42.0, 62.8, 69.9, 71.3, 75.5, 119.3, 127.8 (2C), 128.4 (2C), 129.5 (2C), 129.7 (2C), 130.0, 132.7, 133.0, 134.2, 144.8, 165.1, 178.2; IR (neat) 1468, 1379, 1258 cm^{-1}. ESI-HRMS calcd for $C_{33}H_{48}O_8SSi$ ($[M+Na]^+$) 655.2731, found 655.2715.

To a solution of the above tosylated product (237.6 mg, 0.375 mmol) in THF (4 mL) was added TBAF (1 M solution in THF, 0.60 mL, 0.60 mmol) at 0°C, and the mixture was stirred at rt for 2 h. To the mixture was added sat. NH_4Cl aq. at 0°C, and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column

chromatography on silica gel (hexane/EtOAc = 10/1) to give **7** (103.7 mg, 0.299 mmol, 80%) as a colorless oil.

$[\alpha]_D^{22}$ +33.3 (c 1.02, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 9H), 1.90 (dddd, *J* = 6.6, 6.8, 6.8, 13.9 Hz, 1H), 1.97 (dddd, *J* = 6.3, 6.6, 6.8, 13.9 Hz, 1H), 2.60 (dd, *J* = 2.7, 4.9 Hz, 1H), 2.78 (dd, *J* = 3.9, 4.9 Hz, 1H), 2.96 (ddd, *J* = 2.7, 3.9, 8.1 Hz, 1H), 4.21 (ddd, *J* = 6.6, 6.8, 11.2 Hz, 1H), 4.27 (ddd, *J* = 6.6, 6.8, 11.2 Hz, 1H), 5.30 (ddd, *J* = 0.98, 1.2, 10.5 Hz, 1H), 5.39 (ddd, *J* = 0.98, 1.2, 17.1 Hz, 1H), 5.64 (dddd, *J* = 0.98, 0.98, 6.3, 6.8 Hz, 1H), 5.92 (ddd, *J* = 6.3, 10.5, 17.1 Hz, 1H), 7.44-7.47 (m, 2H), 7.55-7.60 (m, 1H), 8.03-8.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2 (3C), 28.4, 38.7, 43.4, 46.7, 52.7, 62.2, 75.5, 118.4, 128.4 (2C), 129.5 (2C), 129.8, 133.1, 133.9, 165.2, 178.1; IR (neat) 1468, 1379, 1258 cm^{-1}. ESI-HRMS calcd for $C_{20}H_{26}O_5$ ($[M+Na]^+$) 369.1672, found 369.1675.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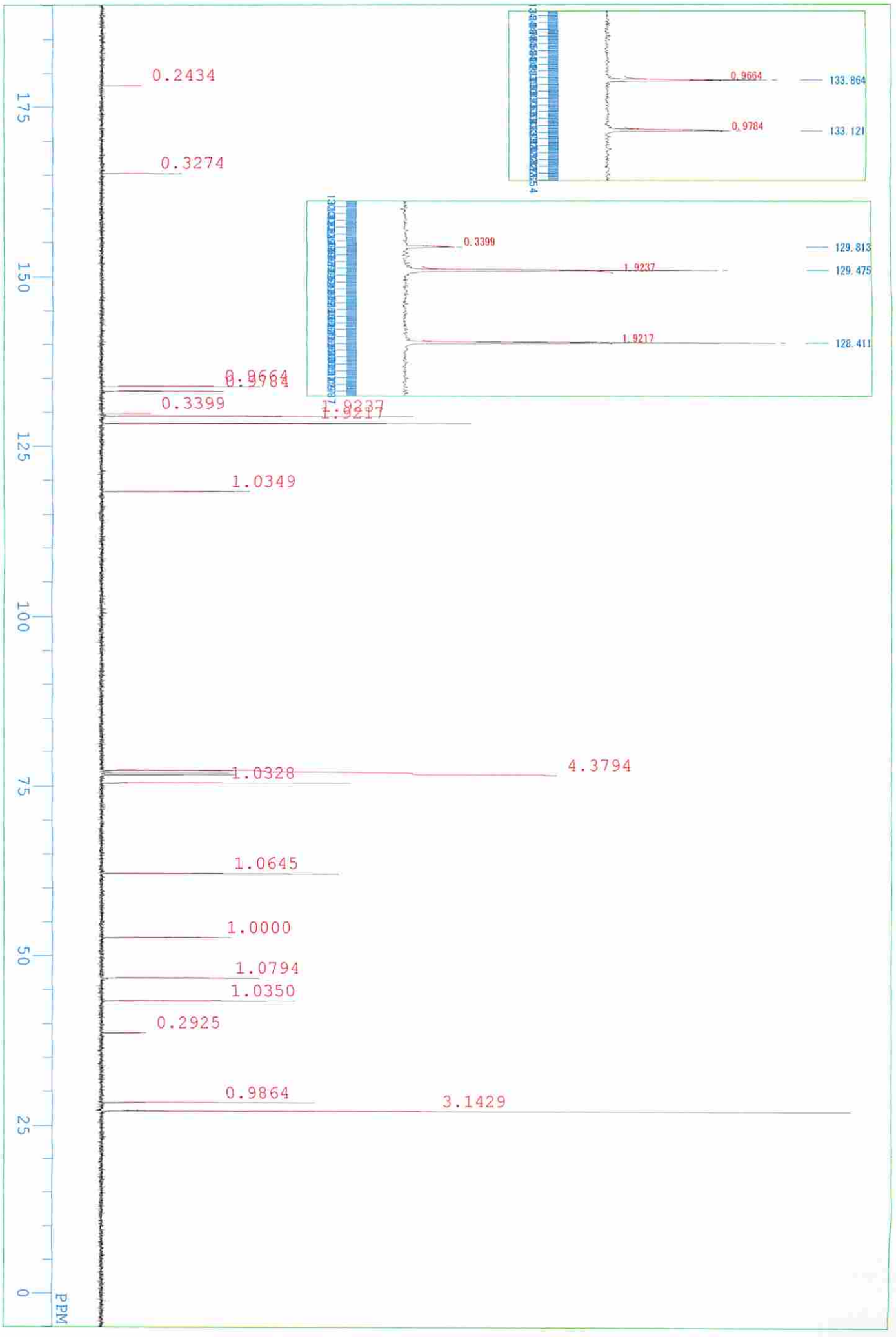

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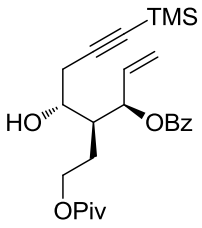
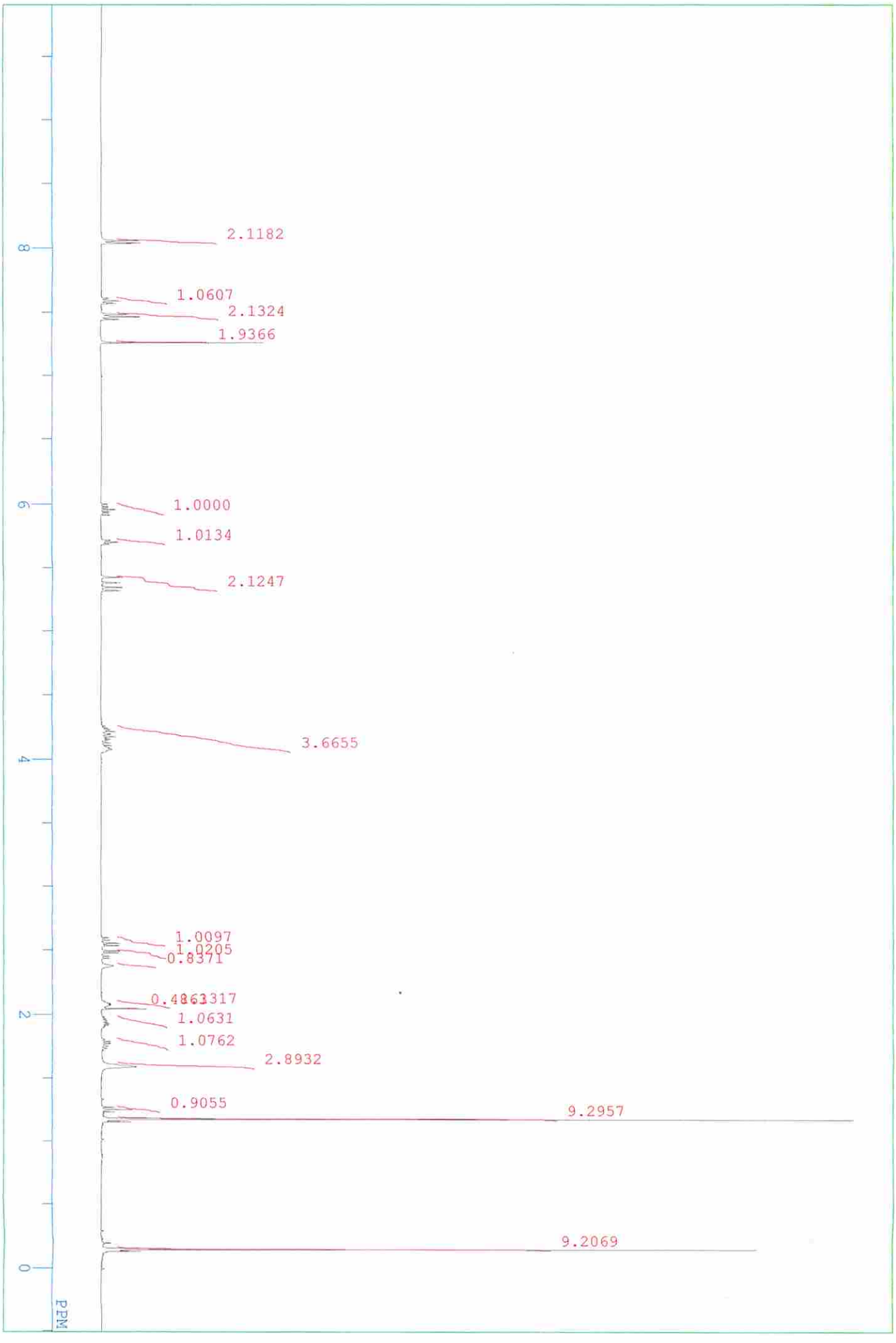
17

(4*R*,5*S*,6*R*)-6-Benzoyloxy-5-[2-(pivaloyloxy)ethyl]-1-(trimethylsilyl)oct-7-en-1-yn-4-ol (8).



To a solution of TMS-acetylene (0.15 mL, 1.06 mmol) in THF (2 mL) was added n-BuLi (1.65 M solution in hexane, 0.54 mL, 0.896 mmol) at -78°C, and the mixture was stirred at the same temperature for 1 h. To the mixture was added a solution of **7** (103.5 mg, 0.299 mmol) in THF (2 mL) at -78°C, and the mixture was allowed to warm to rt over 2 h. To the mixture was added sat. NH_4Cl aq. at 0°C, and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 10/1) to afford **8** (103.5 mg, 0.233 mmol, 78%) as a colorless oil.

$[\alpha]_D^{20}$ +29.2 (c 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14 (s, 9H), 1.17 (s, 9H), 1.76 (dddd, *J* = 6.3, 6.6, 7.1, 14.6 Hz, 1H), 1.94 (dddd, *J* = 4.4, 7.1, 7.3, 14.6 Hz, 1H), 2.08 (dddd, *J* = 2.7, 4.4, 5.6, 7.1 Hz, 1H), 2.42 (br, 1H), 2.47 (dd, *J* = 6.8, 16.8 Hz, 1H), 2.57 (dd, *J* = 7.1, 16.8 Hz, 1H), 4.08 (ddd, *J* = 2.7, 6.8, 7.1 Hz, 1H), 4.16 (ddd, *J* = 6.6, 7.3, 11.0 Hz, 1H), 4.22 (ddd, *J* = 6.3, 7.1, 11.0 Hz, 1H), 5.32 (ddd, *J* = 1.2, 1.2, 10.5 Hz, 1H), 5.40 (ddd, *J* = 0.98, 1.2, 17.1 Hz, 1H), 5.69 (dddd, *J* = 0.98, 1.2, 5.6, 6.1 Hz, 1H), 5.95 (ddd, *J* = 6.1, 10.5, 17.1 Hz, 1H), 7.43-7.47 (m, 2H), 7.55-7.59 (m, 1H), 8.03-8.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.065 (3C), 24.2, 26.8, 27.2 (3C), 38.7, 42.6, 63.1, 69.3, 71.1, 76.1, 87.7, 102.8, 128.4 (2C), 129.5 (2C), 129.8, 133.2, 134.3, 165.6, 178.2; IR (neat) 3510, 2175, 1725 cm^{-1}. ESI-LRMS m/z 467 ($[M+Na]^+$), 323, 149, 131. ESI-HRMS calcd for $C_{25}H_{36}O_5Si$ ($[M+Na]^+$) 467.2224, found 467.2228.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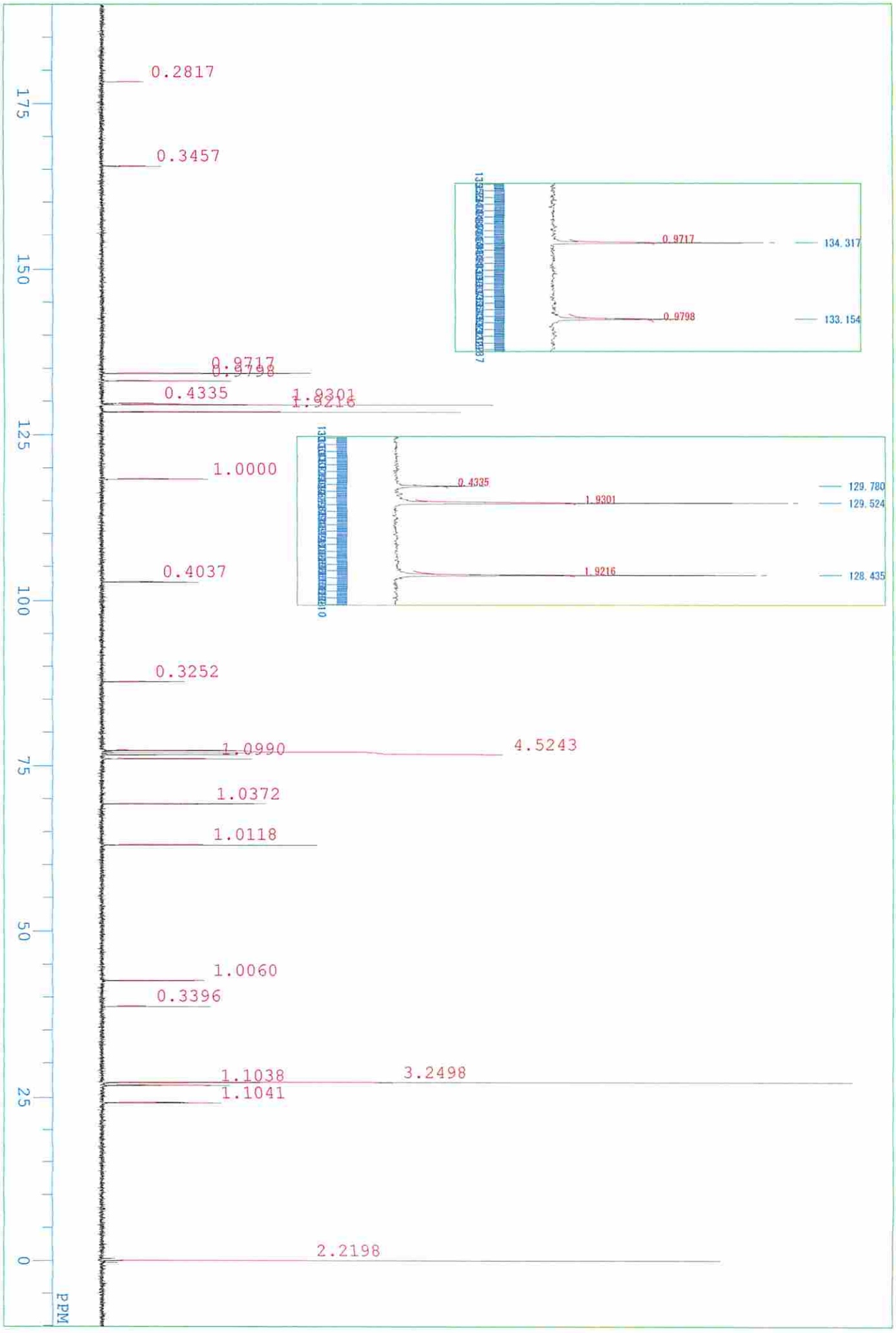

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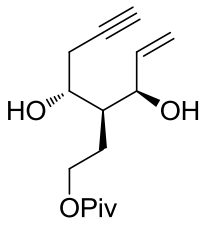
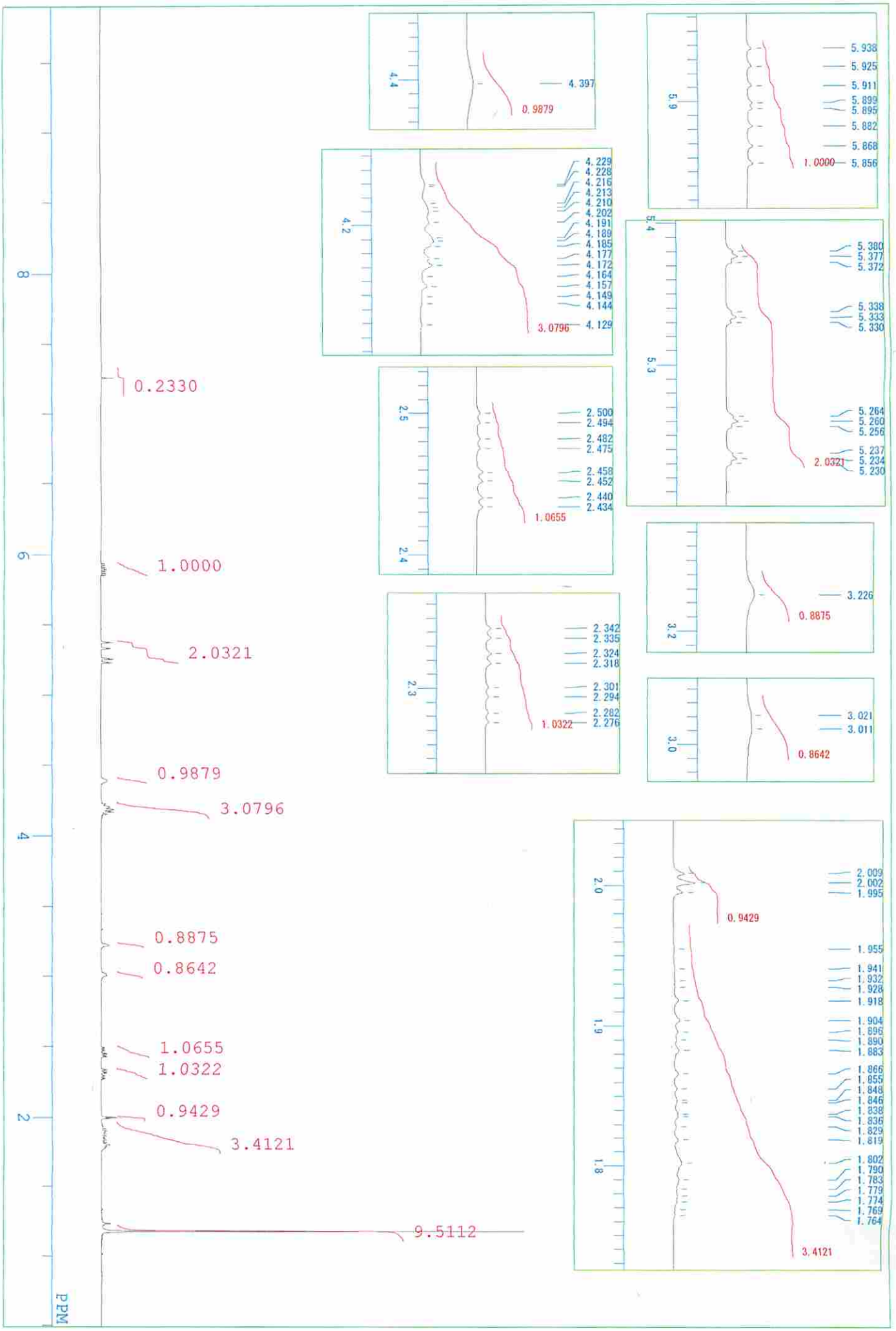
(3*R*,4*S*,5*R*)-4-[2-(pivaloyloxy)ethyl]oct-1-en-7-yne-3,5-diol (9).



To a solution of **8** (148.9 mg, 0.335 mmol) in MeOH (4 mL) was added K_2CO_3 (92.8 mg, 0.671 mmol) at 0°C, and the mixture was stirred at rt for 1.5 h. To the mixture was added sat. NH_4Cl aq. at 0°C, and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 5/1) to give **9** (63.8 mg, 0.238 mmol, 71%) as a colorless oil.

$[\alpha]_D^{20}$ +3.50 (c 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.79-1.89 (m, 2H), 1.95 (dddd, *J* = 2.2, 3.4, 5.6, 9.0 Hz, 1H), 2.02 (dd, *J* = 2.7, 2.7 Hz, 1H), 2.37 (ddd, *J* = 2.7, 6.8, 16.6 Hz, 1H), 2.50 (ddd, *J* = 2.7, 6.3, 16.6 Hz, 1H), 2.50 (d, *J* = 4.9 Hz, 1H), 2.91 (d, *J* = 2.7 Hz, 1H), 4.15-4.25 (m, 3H), 4.43 (ddddd, *J* = 1.5, 1.7, 2.7, 3.4, 4.9 Hz, 1H), 5.28 (ddd, *J* = 1.5, 1.5, 10.5 Hz, 1H), 5.38 (ddd, *J* = 1.5, 1.7, 17.1 Hz, 1H), 5.95 (ddd, *J* = 4.9, 10.5, 17.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 24.4, 27.2 (3C), 38.8, 41.9, 62.7, 69.7, 70.6, 73.8, 80.7, 115.7, 139.3, 178.5; IR (neat) 3424, 3307, 2120, 1725 cm^{-1}. ESI-LRMS m/z 291 ($[M+Na]^+$), 279, 233, 201, 171. ESI-HRMS calcd for $C_{15}H_{24}O_4$ ($[M+Na]^+$) 291.1567, found 291.1560.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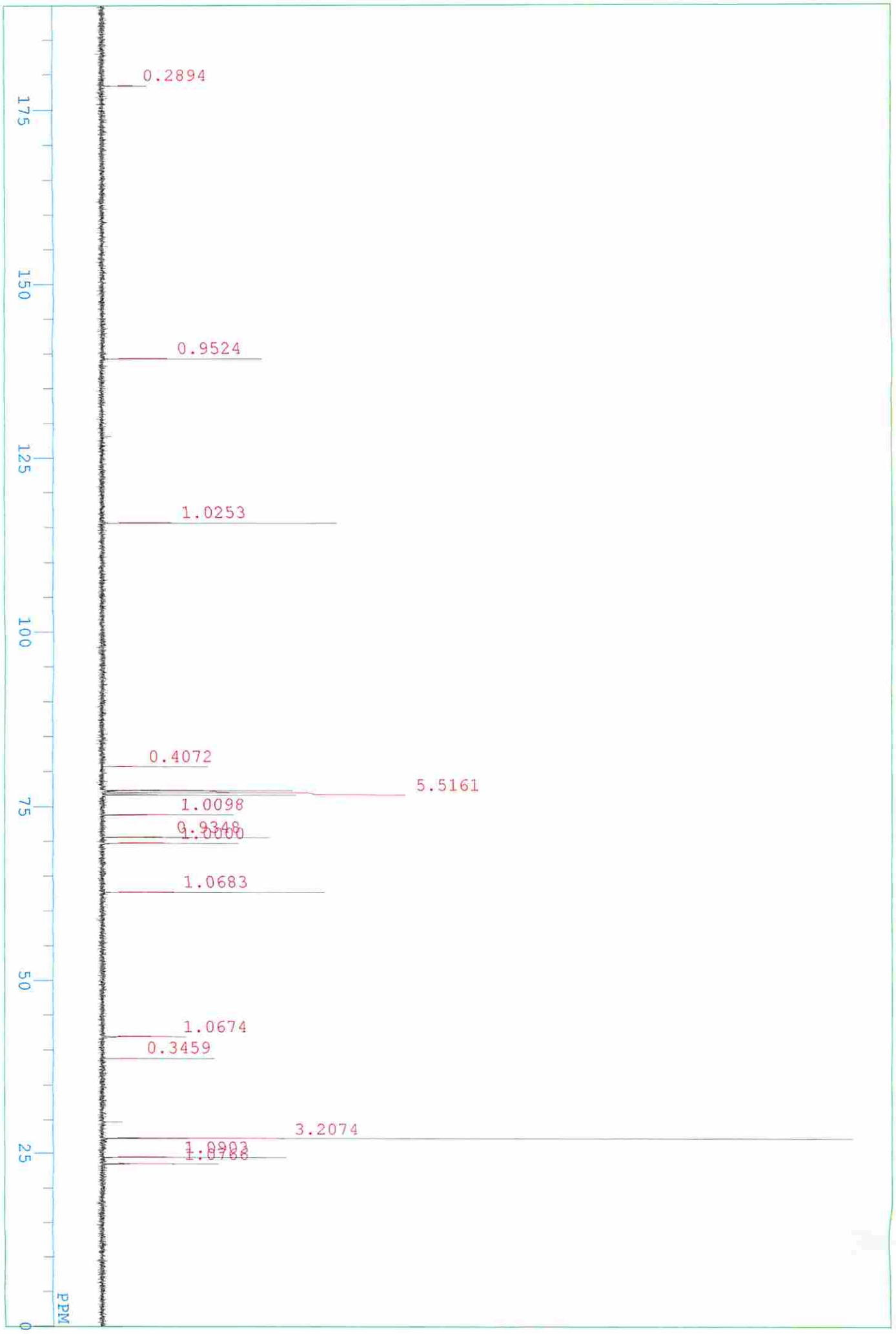
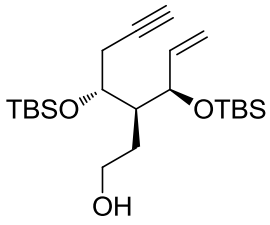


(3*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)allyl]hept-6-yn-1-ol (10).[2]

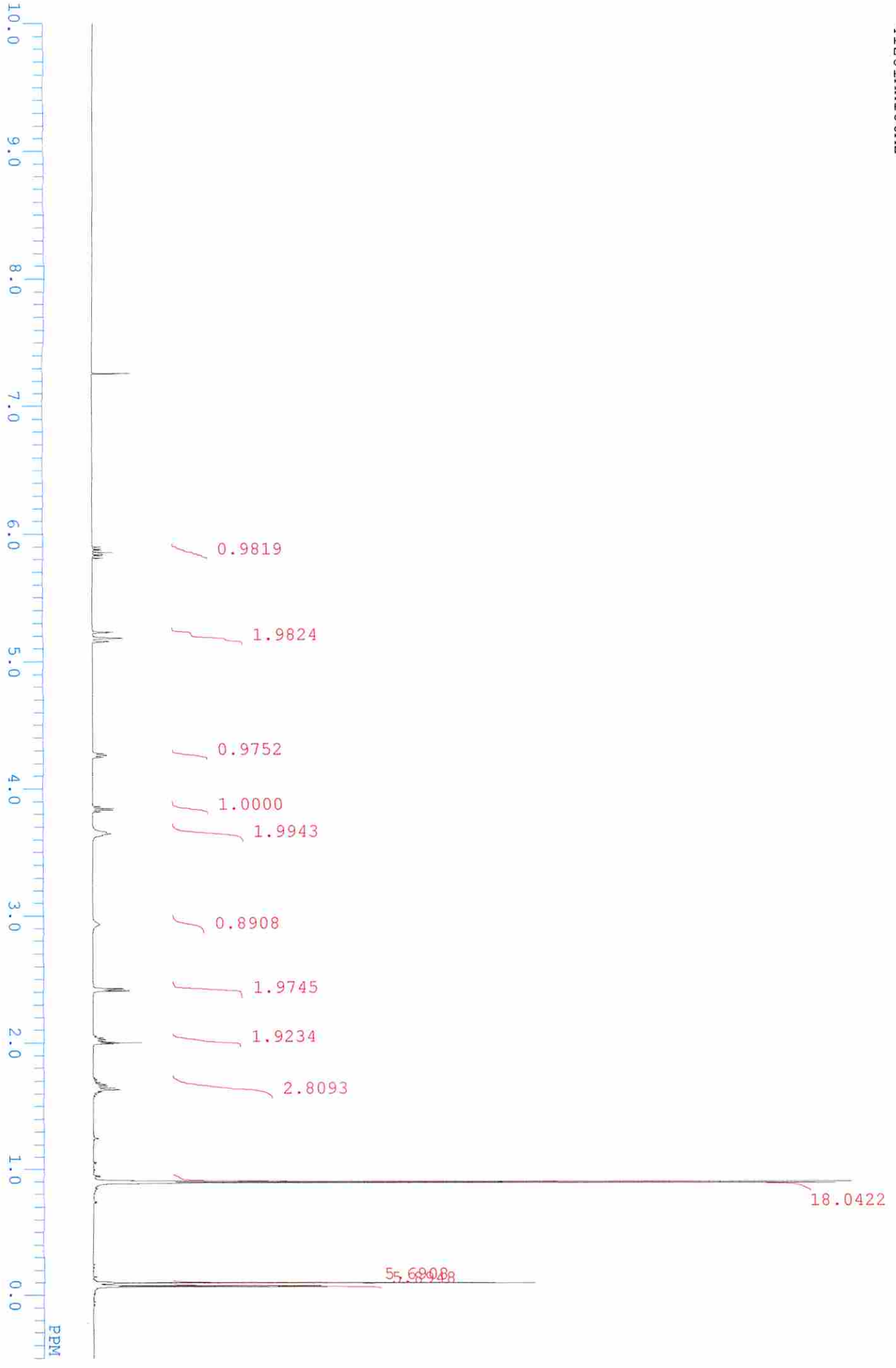


To a solution of **9** (47.0 mg, 0.175 mmol) in CH_2Cl_2 (5 mL) were added 2,6-lutidine (0.06 mL, 0.516 mmol) and TBSOTf (0.10 mL, 0.438 mmol) at 0°C, and the mixture was stirred at rt for 17 h. To the mixture was added sat. NH_4Cl aq. at 0°C, and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 100/1) to obtain (3*R*,4*S*,5*R*)-3,5-bis(*tert*-butyldimethylsilyloxy)-4-[2-(pivaloyloxy)ethyl]oct-1-en-7-yne (80.5 mg, 0.162 mmol, 93%) as a colorless oil.

$[\alpha]_D^{21}$ +0.29 (c 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.034 (s, 3H), 0.061 (s, 3H), 0.069 (s, 3H), 0.093 (s, 3H), 0.89 (s, 9H), 0.89 (s, 9H), 1.19 (s, 9H), 1.57-1.75 (m, 2H), 1.95 (dddd, *J* = 3.9, 5.4, 6.8, 6.8 Hz, 1H), 1.96 (t, *J* = 2.7 Hz, 1H), 2.39 (dd, *J* = 2.7, 6.1 Hz, 2H), 3.97 (ddd, *J* = 3.9, 6.1, 6.1 Hz, 1H), 4.04-4.18 (m, 3H), 5.14 (ddd, *J* = 0.98, 0.98, 10.3 Hz, 1H), 5.20 (ddd, *J* = 0.98, 1.2, 17.1 Hz, 1H), 5.82 (ddd, *J* = 7.1, 10.3, 17.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.58, -4.46, -4.03, -3.70, 18.1, 18.2, 25.1, 25.9 (3C), 26.0 (3C), 26.4, 27.3 (3C), 38.7, 45.9, 64.2, 70.4, 71.0, 75.6, 81.4, 116.2, 139.2, 178.4; IR (neat) 3314, 2121, 1729 cm^{-1}. ESI-HRMS calcd for $C_{27}H_{52}O_4Si_2$ ($[M+Na]^+$) 519.3296, found 519.3286.

To a solution of the above *O*-protected product (94.0 mg, 0.189 mmol) in CH_2Cl_2 (5 mL) was added DIBAL-H (1.01 M solution in toluene, 0.38 mL, 0.383 mmol) at -78°C, and the mixture was stirred at the same temperature for 2.5 h. To the reaction mixture were added Et_2O (10 mL) and sat. Rochell Salt aq. (10 mL) at -78°C, and the mixture was stirred for 1 h at rt. After separation and extraction from the aqueous layer with Et_2O, the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel

(hexane/EtOAc = 20/1) to give the known compound **10** (73.8 mg, 0.179 mmol, 95%) as a colorless oil.[2]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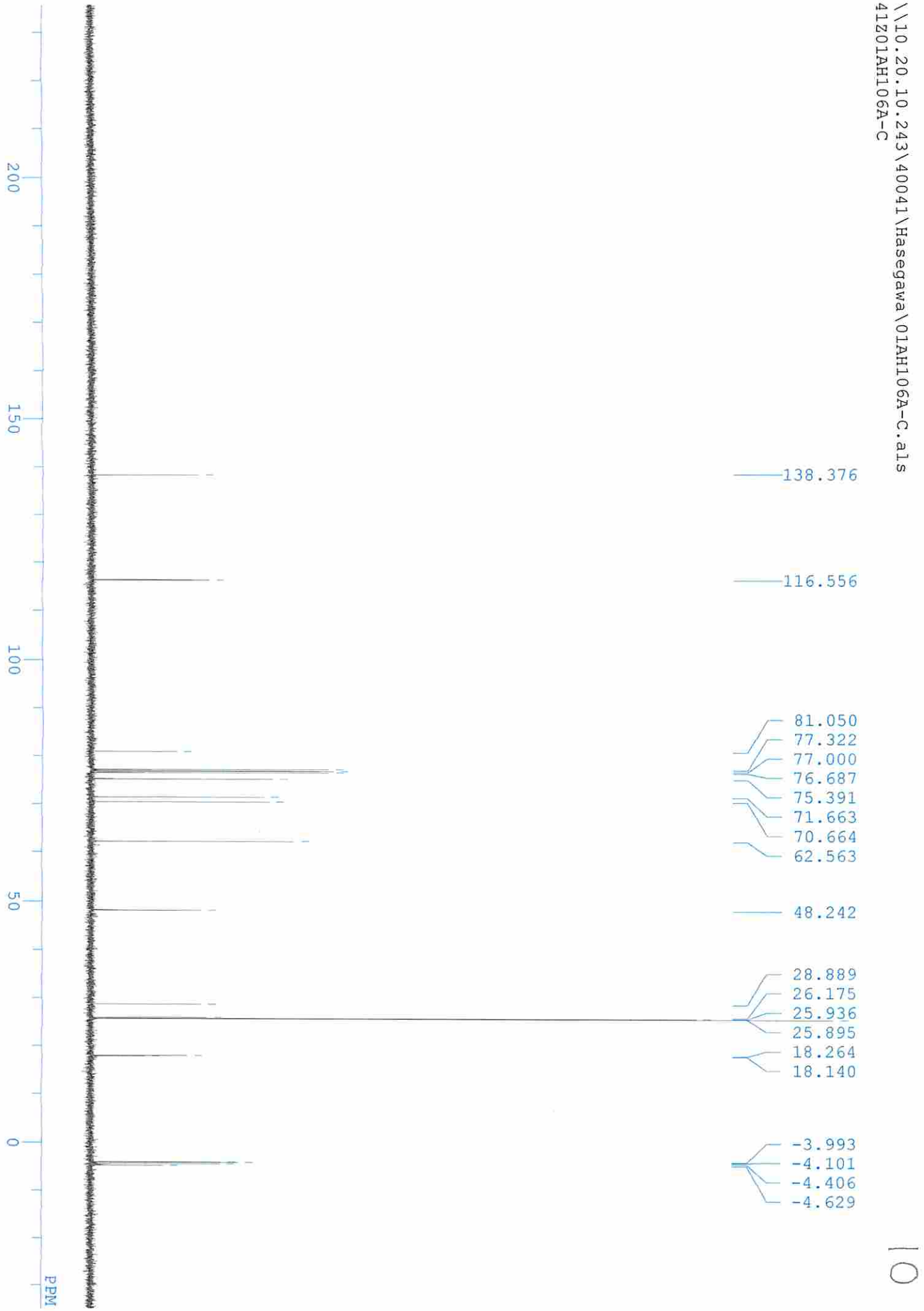
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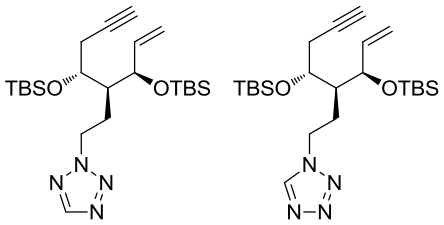
PPM

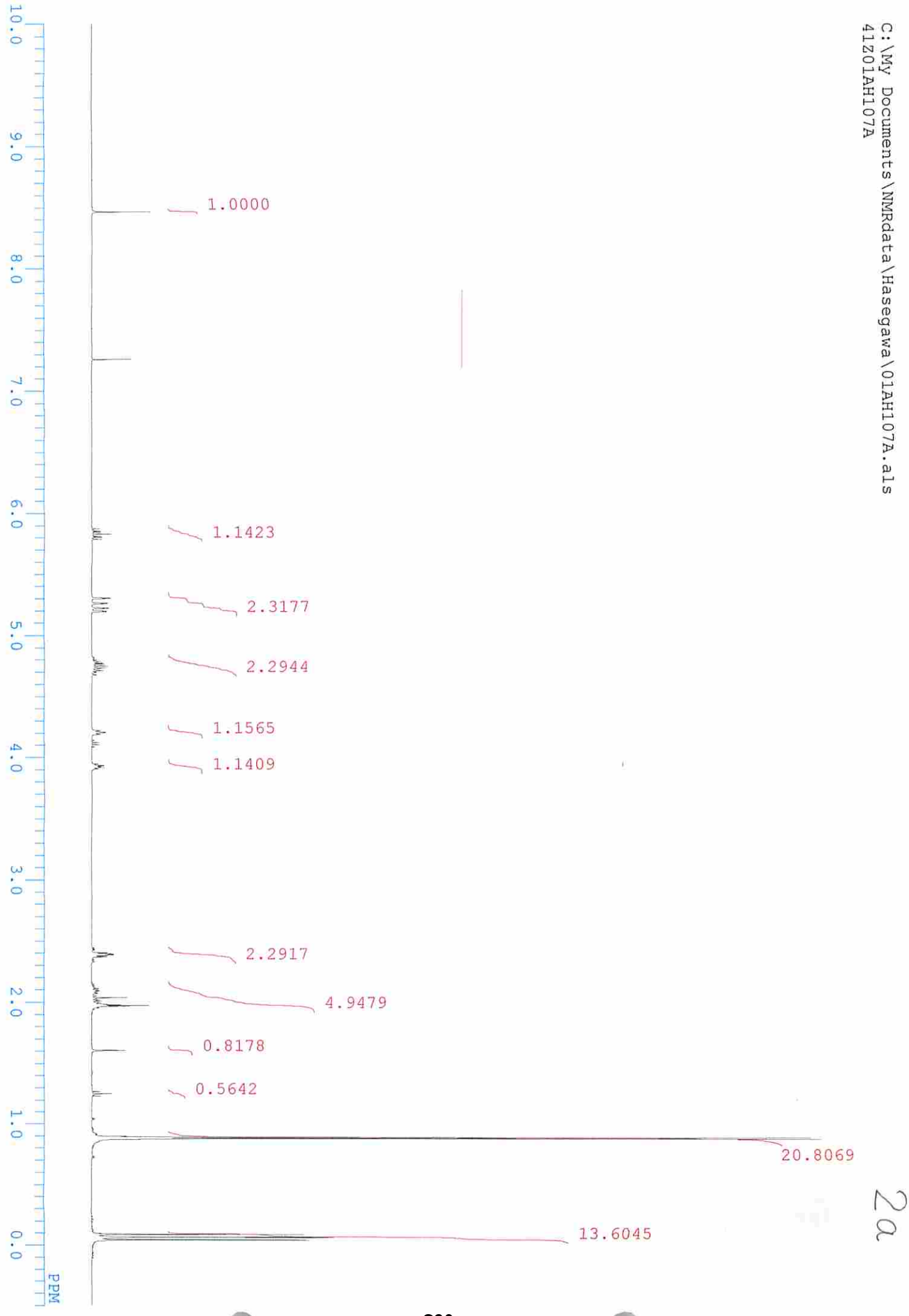
(3*R*,4*S*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-4-[2-(2*H*-tetrazol-2-yl)ethyl]oct-1-en-7-yne (2a) and **(3*R*,4*S*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-4-[2-(1*H*-tetrazol-1-yl)ethyl]oct-1-en-7-yne (2b)**



To a solution of **10** (238.5 mg, 0.578 mmol) in THF (6 mL) were added PPh_3 (304 mg, 1.17 mmol), 1*H*-tetrazole (60.7 mg, 0.867 mmol) and DIAD (1.9 M solution in toluene, 0.62 mL, 1.17 mmol) at 0°C, and the mixture was stirred at the same temperature for 1 h. The mixture was concentrated, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 40/1-5/1) to give **2a** (216.8 mg, 0.467 mmol, 81%) and **2b** (49.7 mg, 0.107 mmol, 19%) each as a colorless oil.

2a: $[\alpha]_D^{21}$ -4.70 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.067 (s, 3H), 0.071 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.99-2.15 (m, 3H), 2.33-2.45 (m, 2H), 3.93 (dt, *J* = 6.8, 4.6 Hz, 1H), 4.21 (dd, *J* = 6.6, 5.4 Hz, 1H), 4.68-4.82 (m, 2H), 5.21 (d, *J* = 10.5 Hz, 1H), 5.28 (d, *J* = 17.1 Hz, 1H), 5.83 (ddd, *J* = 17.1, 10.3, 6.6 Hz, 1H), 8.46 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.61, -4.45, -4.14, -3.92, 18.1, 18.2, 25.9 (3C), 26.0 (3C), 26.1, 26.5, 46.5, 53.0, 70.86, 70.89, 75.2, 80.4, 116.7, 138.2, 152.6; IR(neat) 3312, 3144, 3079, 2708, 2124, 1740, 1647, 1471, 1406, 1389, 1362, 1283, 1256 cm^{-1}. ESI-HRMS calcd for $C_{23}H_{44}N_4O_2Si_2$ ($[M+Na]^+$) 487.2895, found 487.2874.

2b: $[\alpha]_D^{24}$ -5.08 (c 0.99, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.10 (s, 3H), 0.89 (s, 18H), 1.94-2.00 (m, 3H), 2.35-2.48 (m, 2H), 3.88 (dt, *J* = 6.8, 4.4 Hz, 1H), 4.47-4.64 (m, 2H), 5.22 (d, *J* = 10.5 Hz, 1H), 5.28 (d, *J* = 17.1 Hz, 1H), 5.78 (ddd, *J* = 17.1, 10.5, 6.1 Hz, 1H), 8.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.63, -4.43, -4.19, -4.09, 18.1, 18.2, 25.9, 26.0, 26.61, 26.62, 46.4, 48.2, 70.9, 71.3, 75.0, 80.2, 116.8, 137.8, 142.1; IR(neat) 3312, 3134, 3078, 1732, 1472, 1443, 1406, 1389, 1362, 1256 cm^{-1}. ESI-HRMS calcd for $C_{23}H_{44}N_4O_2Si_2$ ($[M+Na]^+$) 487.2895, found 487.2892.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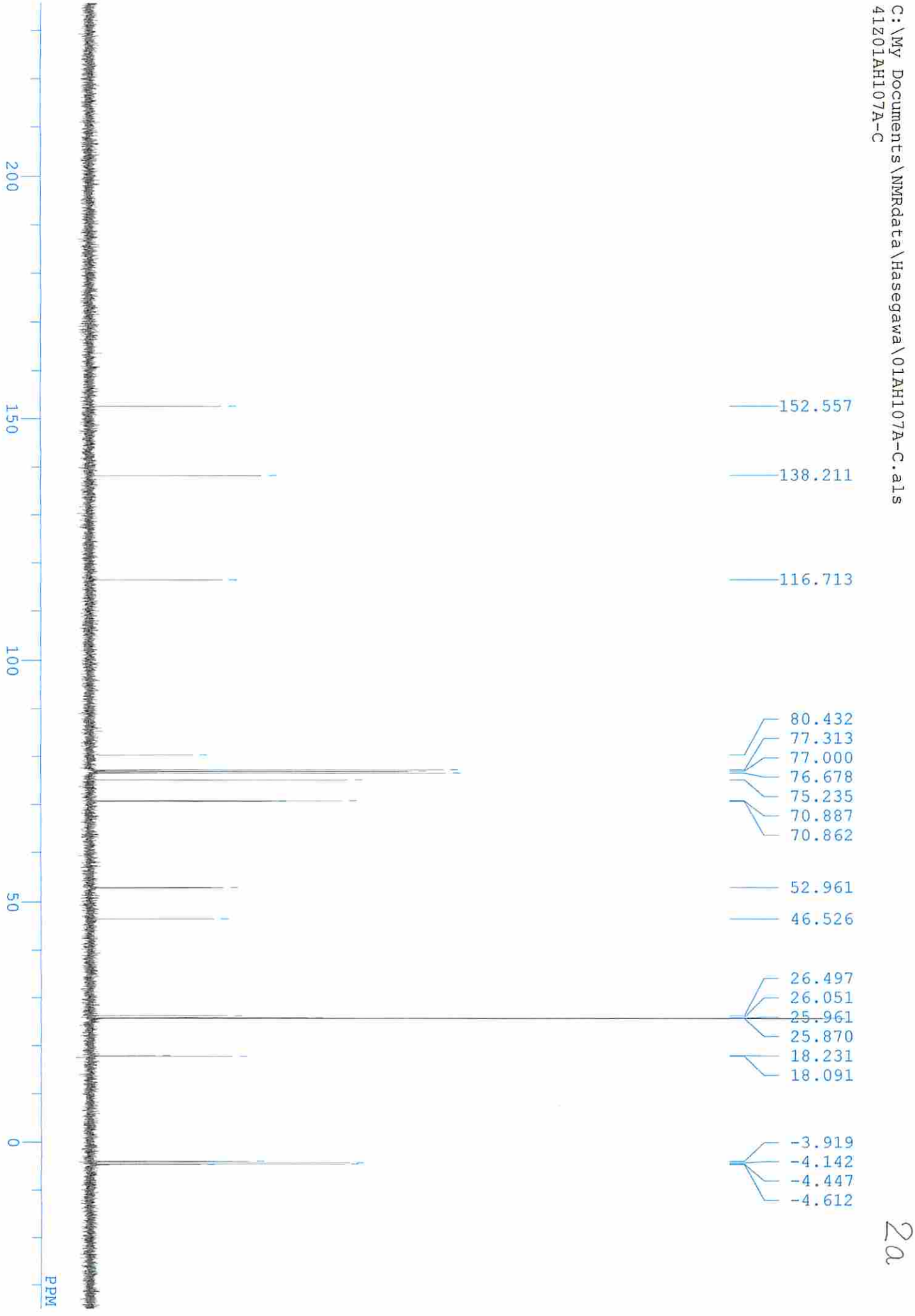
2a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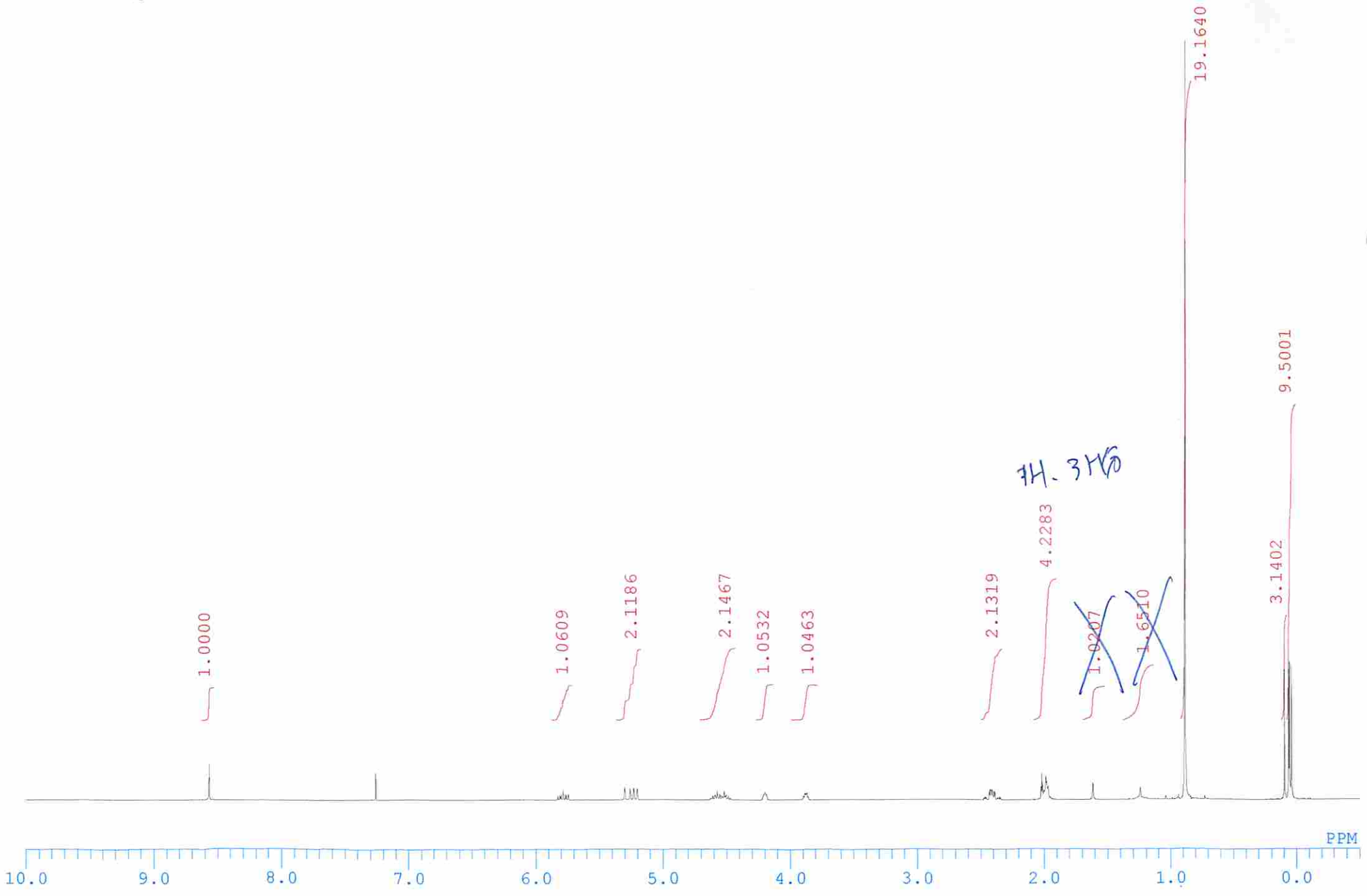
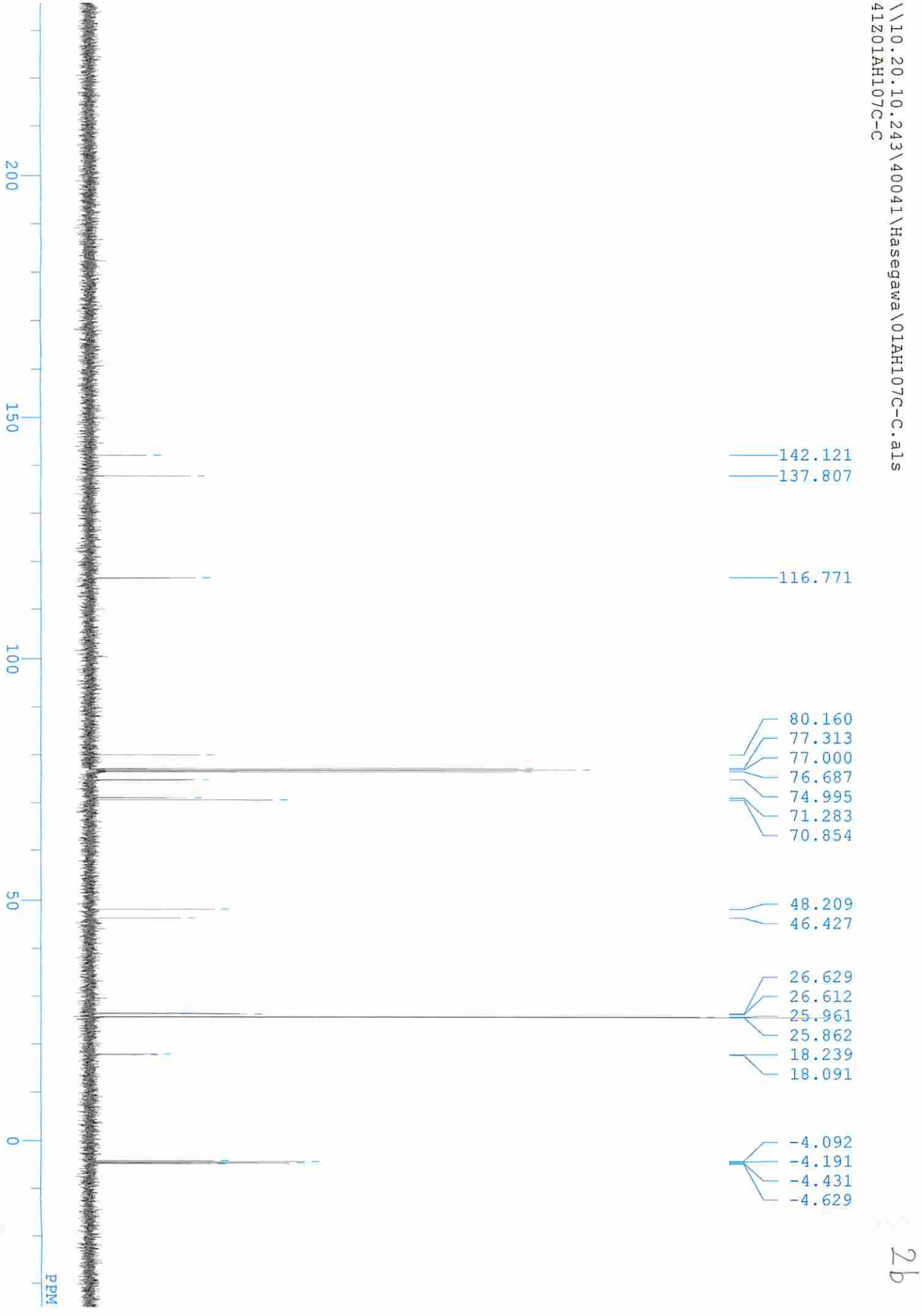
2b

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150
100
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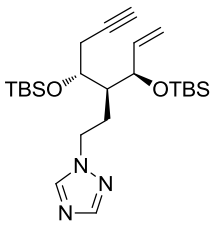
0
PPM

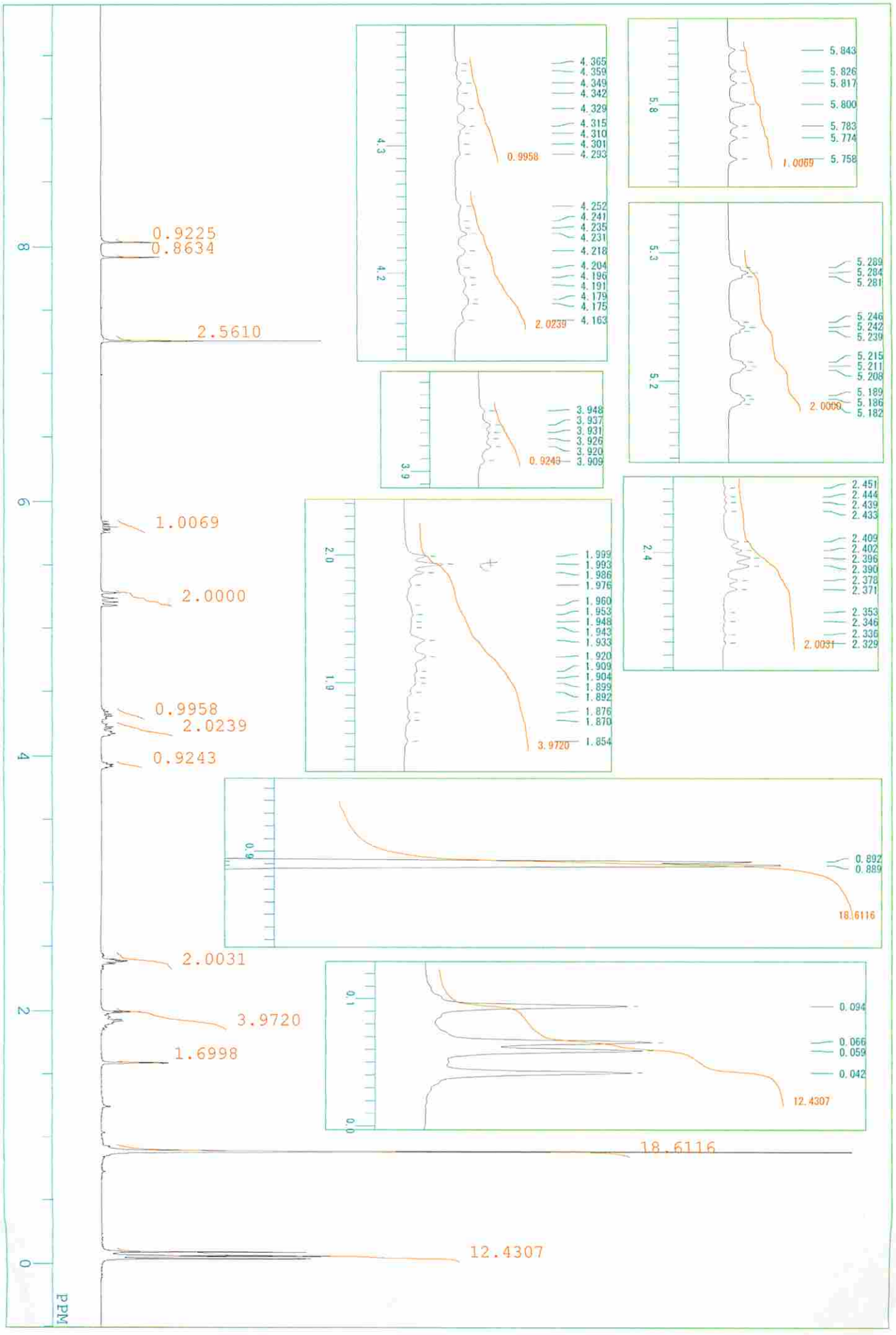
2b

(3*R*,4*S*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-4-[2-(1,2,4-triazole-2-yl)ethyl]oct-1-en-7-yne (2c).



To a solution of **10** (65.0 mg, 0.157 mmol) in THF (3 mL) were added PPh_3 (83.6 mg, 0.319 mmol), 1,2,4-triazole (17.3 mg, 0.250 mmol) and DIAD (1.9 M solution in toluene, 0.17 mL, 0.315 mmol) at 0°C, and the mixture was stirred at the same temperature for 3 h. The mixture was concentrated, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 20/1-10/1) to give **2c** (68.1 mg, 0.147 mmol, 94%) as a colorless oil.

$[\alpha]_D^{20}$ -2.78 (c 1.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.026 (s, 3H), 0.044 (s, 3H), 0.050 (s, 3H), 0.078 (s, 3H), 0.87 (s, 9H), 0.87 (s, 9H), 1.83-1.99 (m, 3H), 1.98 (t, *J* = 2.7 Hz, 1H), 2.35 (ddd, *J* = 2.7, 6.8, 17.l Hz, 1H), 2.40 (ddd, *J* = 2.7, 4.6, 17.l Hz, 1H), 3.96 (ddd, *J* = 4.2, 4.6, 6.8 Hz, 1H), 4.15-4.36 (m, 3H), 5.18 (ddd, *J* = 0.73, 0.98, 10.3 Hz, 1H), 5.25 (ddd, *J* = 0.98, 1.2, 17.1 Hz, 1H), 5.78 (ddd, *J* = 6.6, 10.3, 17.1 Hz, 1H), 7.90 (s, 1H), 8.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.62, -4.46, -4.17, -3.95, 18.1, 18.2, 25.9 (3C), 25.9 (3C), 26.4, 26.5, 46.4, 49.4, 70.9, 71.0, 75.3, 80.5, 116.5, 138.4, 142.6, 151.6; IR (neat) 3312, 3121, 3078, 2120 cm^{-1}. ESI-LRMS *m*/*z* 464 ($[M+H]^+$), 313, 219, 130. ESI-HRMS calcd for $C_{24}H_{45}N_3O_2Si_2$ ($[M+H]^+$) 464.3123, found 464.3120.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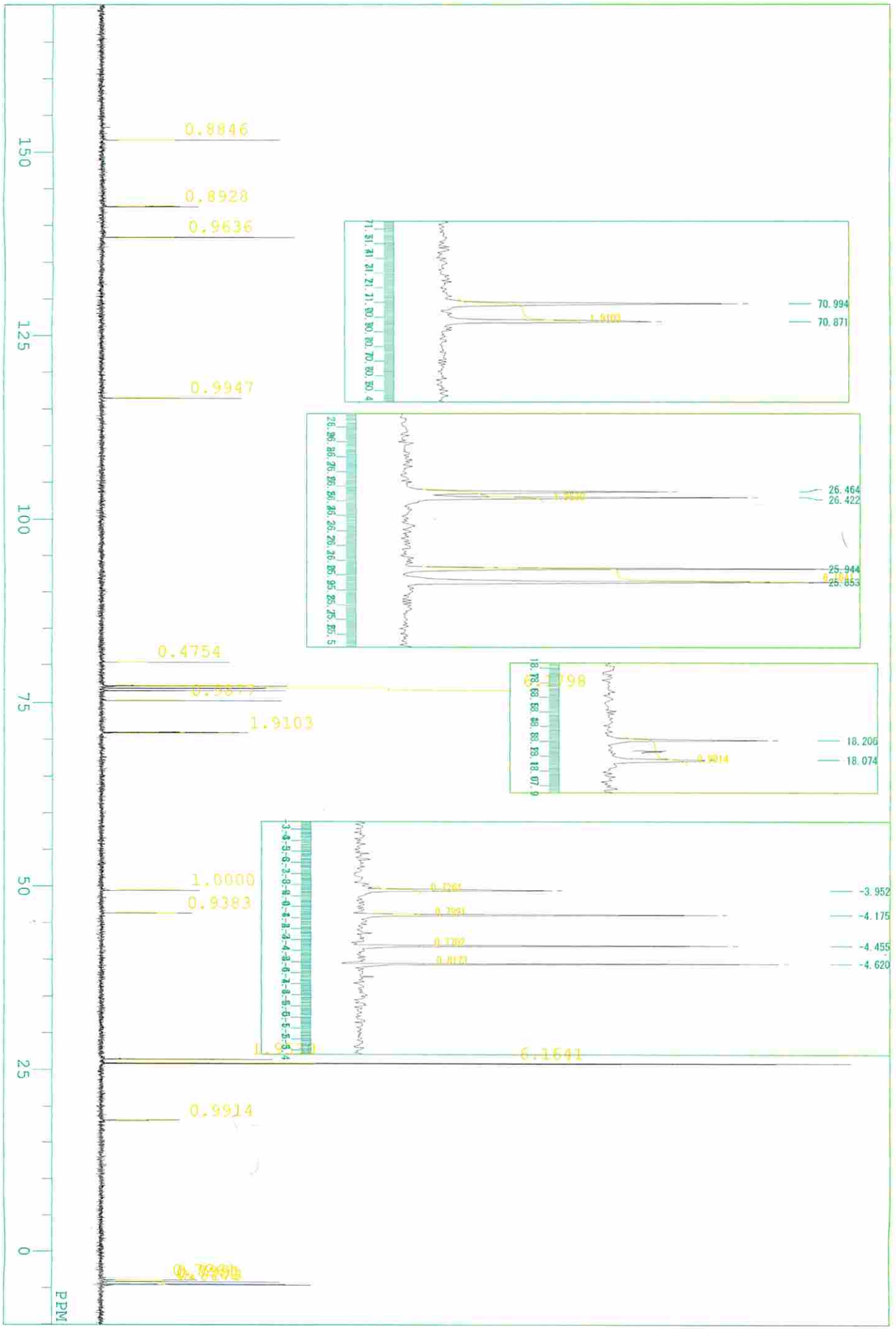
2c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50
25
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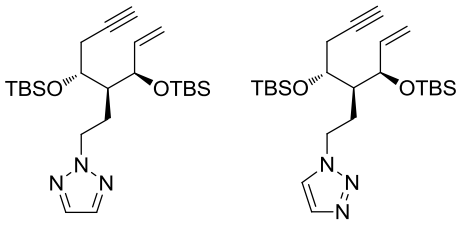
PPM

(3*R*,4*S*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-4-[2-(2*H*-1,2,3-triazole-2-yl)ethyl]oct-1-en-7-yne (2d) and **(3*R*,4*S*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-4-[2-(1*H*-1,2,3-triazole-1-yl)ethyl]oct-1-en-7-yne (2e).**

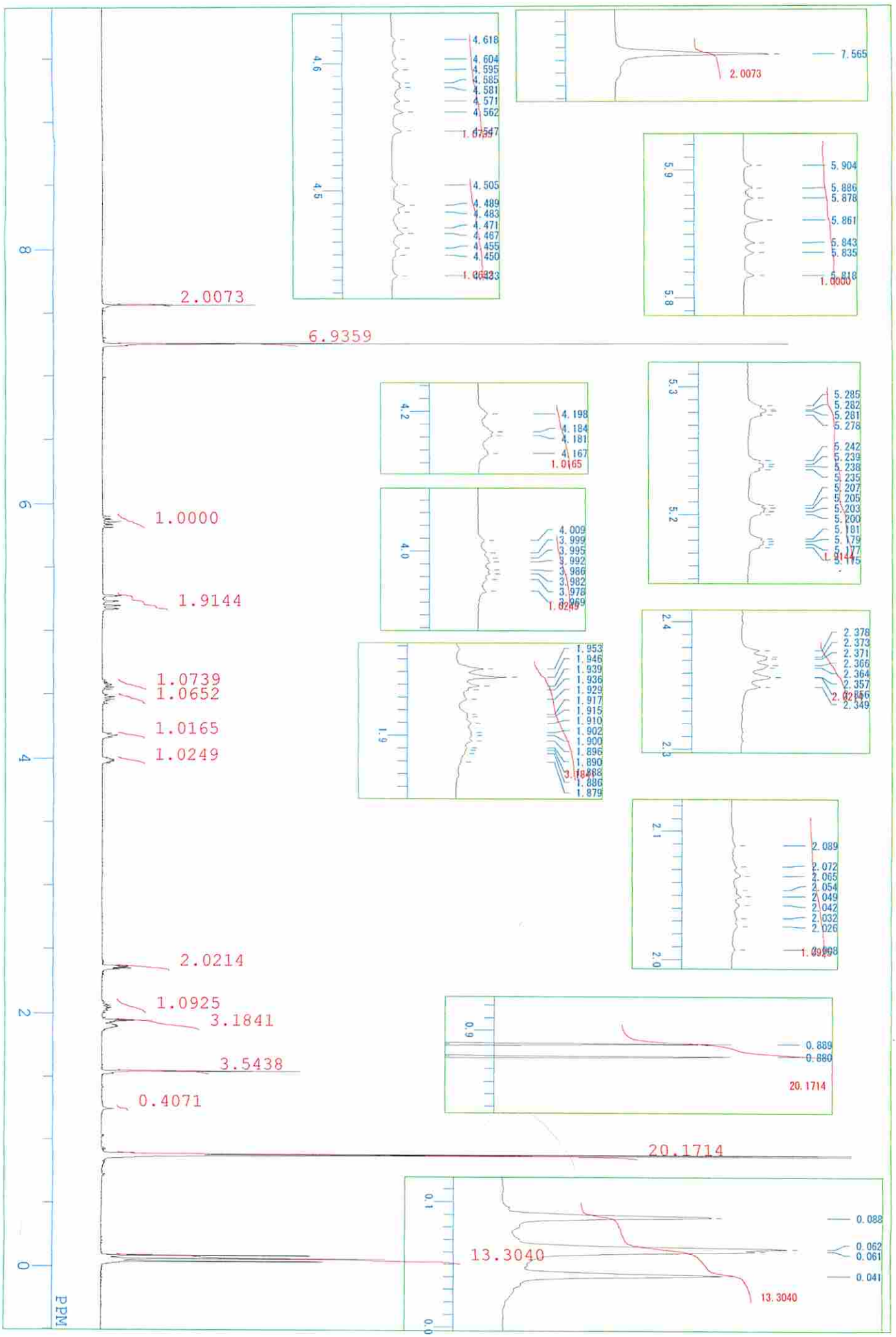


To a solution of **10** (58.0 mg, 0.141 mmol) in THF (3 mL) were added PPh_3 (75.5 mg, 0.288 mmol), 1,2,3-triazole (13.0 μL, 0.224 mmol) and DIAD (1.9 M solution in toluene, 0.15 mL, 0.282 mmol) at 0°C, and the mixture was stirred at the same temperature for 3.5 h. The mixture was concentrated and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 120/1-20/1-5/1) to give **2d** (55.6 mg, 0.120 mmol, 85%) and **2e** (9.7 mg, 0.021 mml, 15%) each as a colorless oil.

2d: $[\alpha]_D^{26}$ -0.78 (c 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.041 (s, 3H), 0.061 (s, 3H), 0.062 (s, 3H), 0.088 (s, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 1.88-1.95 (m, 2H), 1.95 (t, *J* = 2.7 Hz, 1H), 2.01-2.10 (m, 1H), 2.34 (ddd, *J* = 2.7, 6.8, 16.8 Hz, 1H), 2.39 (ddd, *J* = 2.7, 5.6, 16.8 Hz, 1H), 3.99 (ddd, *J* = 3.7, 5.6, 6.8 Hz, 1H), 4.18 (dddd, *J* = 0.98, 1.2, 5.9, 6.8 Hz, 1H), 4.46 (ddd, *J* = 6.6, 8.8, 13.4 Hz, 1H), 4.58 (ddd, *J* = 6.1, 9.5, 13.4 Hz, 1H), 5.19 (ddd, *J* = 0.98, 0.98, 10.3 Hz, 1H), 5.26 (ddd, *J* = 0.98, 1.2, 17.1 Hz, 1H), 5.86 (ddd, *J* = 6.8, 10.3, 17.1 Hz, 1H), 7.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.58, -4.42, -4.10, -3.71, 18.1, 18.2, 25.9 (3C), 26.0 (3C), 26.3, 26.3, 46.6, 54.5, 70.4, 71.1, 75.5, 81.1, 116.4, 133.6 (2C), 138.9; IR (neat) 3313, 3077, 2121 cm^{-1}. ESI-LRMS *m*/*z* 464 ($[M+H]^+$), 332, 200, 131, 83. ESI-HRMS calcd for $C_{24}H_{45}N_3O_2Si_2$ ($[M+H]^+$) 464.3123, found 464.3121.

2e: $[\alpha]_D^{24}$ -0.39 (c 0.76, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.045 (s, 3H), 0.066 (s, 3H), 0.066 (s, 3H), 0.096 (s, 3H), 0.89 (s, 9H), 0.89 (s, 9H), 1.89-2.01 (m, 3H), 2.00 (t, *J* = 2.7 Hz, 1H), 2.37 (ddd, *J* = 2.7, 6.8, 16.8 Hz, 1H), 2.43 (ddd, *J* = 2.7, 4.6, 16.8 Hz, 1H), 3.93 (ddd, *J* = 4.4, 4.6, 6.8 Hz, 1H), 4.20 (dddd, *J* = 0.98, 1.2, 6.1, 6.6 Hz, 1H), 4.44 (ddd, *J* = 6.1, 9.0, 13.7 Hz, 1H), 4.54 (ddd, *J* = 6.1, 9.3, 13.7 Hz, 1H), 5.20 (ddd, *J* = 0.98, 1.7, 10.3 Hz, 1H), 5.27 (ddd, *J* = 1.2, 1.7, 17.1 Hz, 1H), 5.81 (ddd, *J* = 6.6,

10.3, 17.1 Hz, 1H), 7.52 (d, *J* = 0.98 Hz, 1H), 7.68 (d, *J* = 0.98 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.59, -4.41, -4.15, -3.92, 18.1, 18.2, 25.9 (3C), 26.0 (3C), 26.6, 27.1, 46.7, 49.9, 70.0 (2C), 75.2, 80.6, 116.6, 122.9, 133.5, 138.3; IR (neat) 3312, 3077, 2120 cm^{-1}. ESI-LRMS *m/z* 464 ($[M+H]^+$), 290, 219. ESI-HRMS calcd for $C_{24}H_{45}N_3O_2Si_2$ ($[M+H]^+$) 464.3123, found 464.3125.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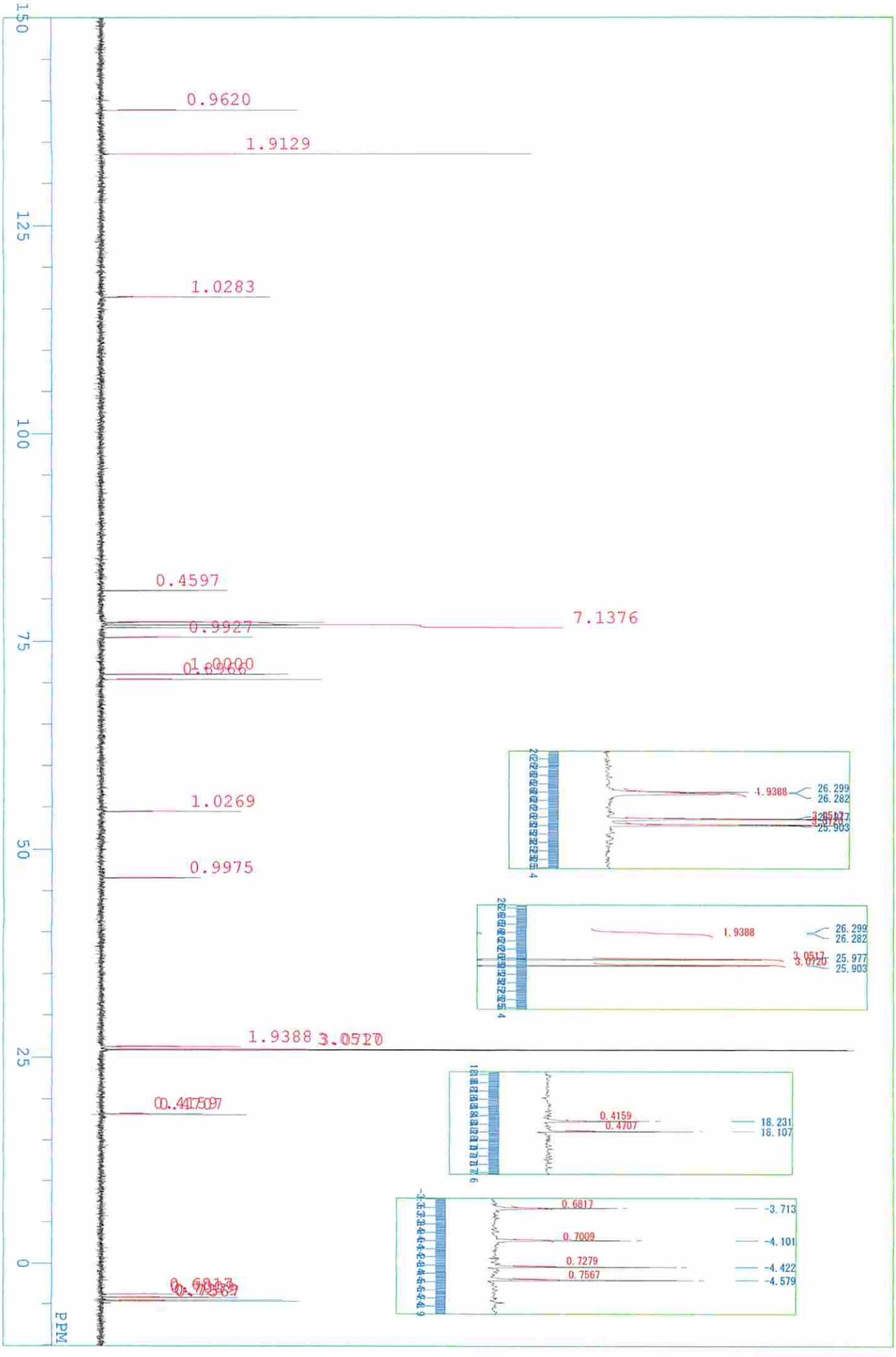
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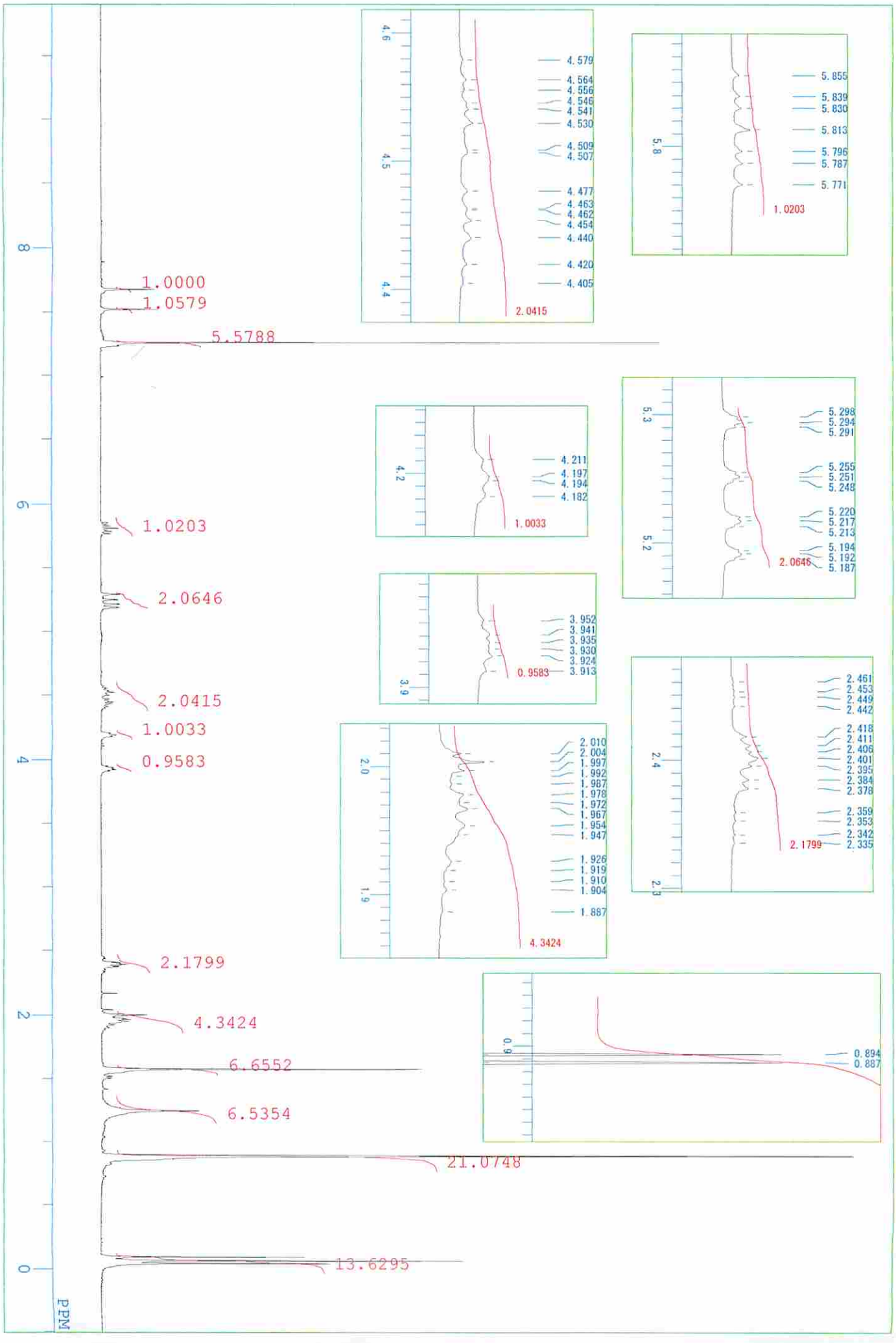
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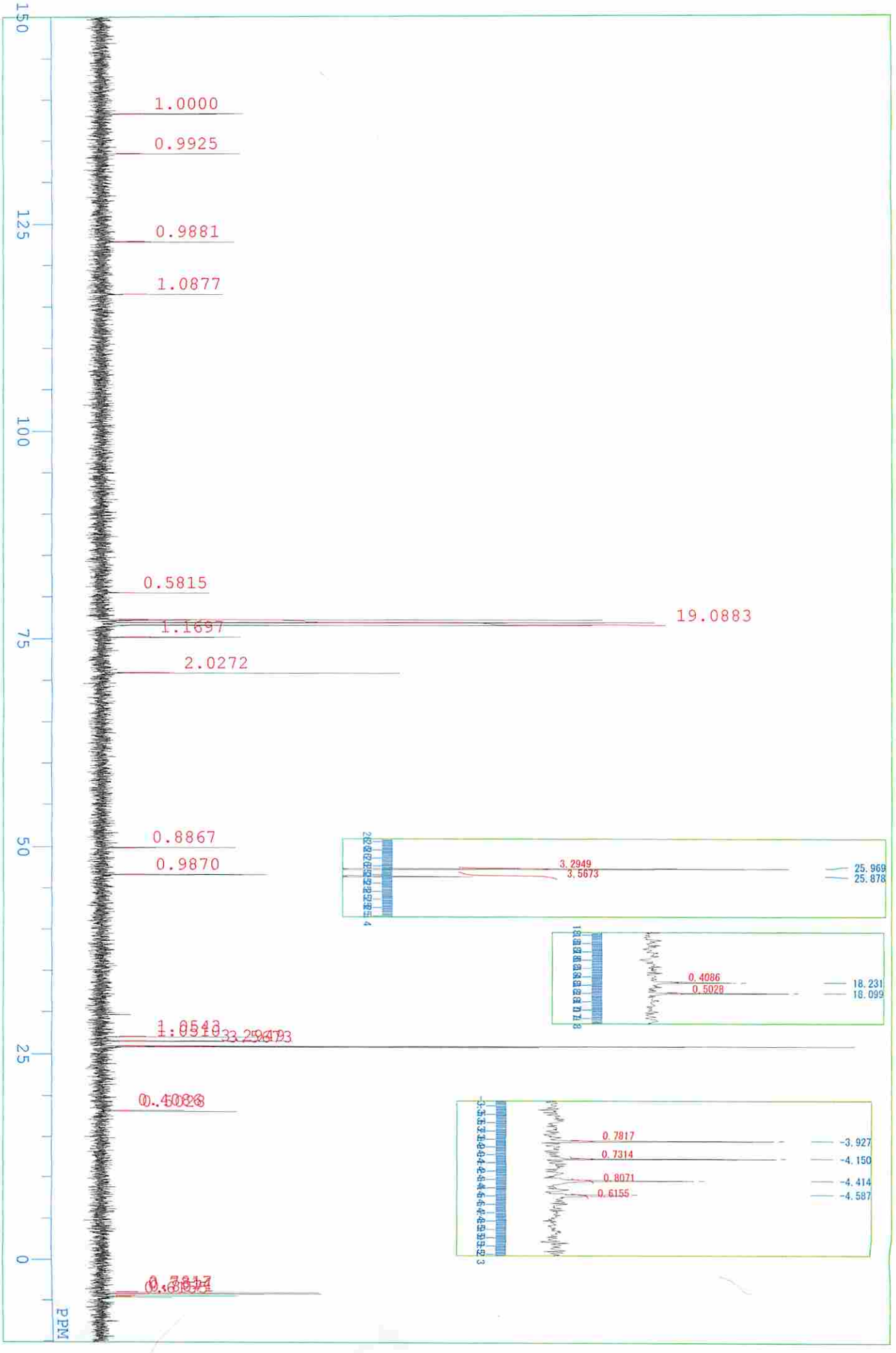
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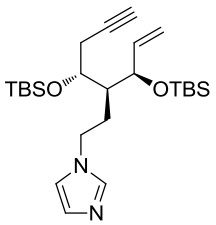
(3*R*,4*S*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-4-[2-(imidazole-1-yl)ethyl]oct-1-en-7-yne (2f).

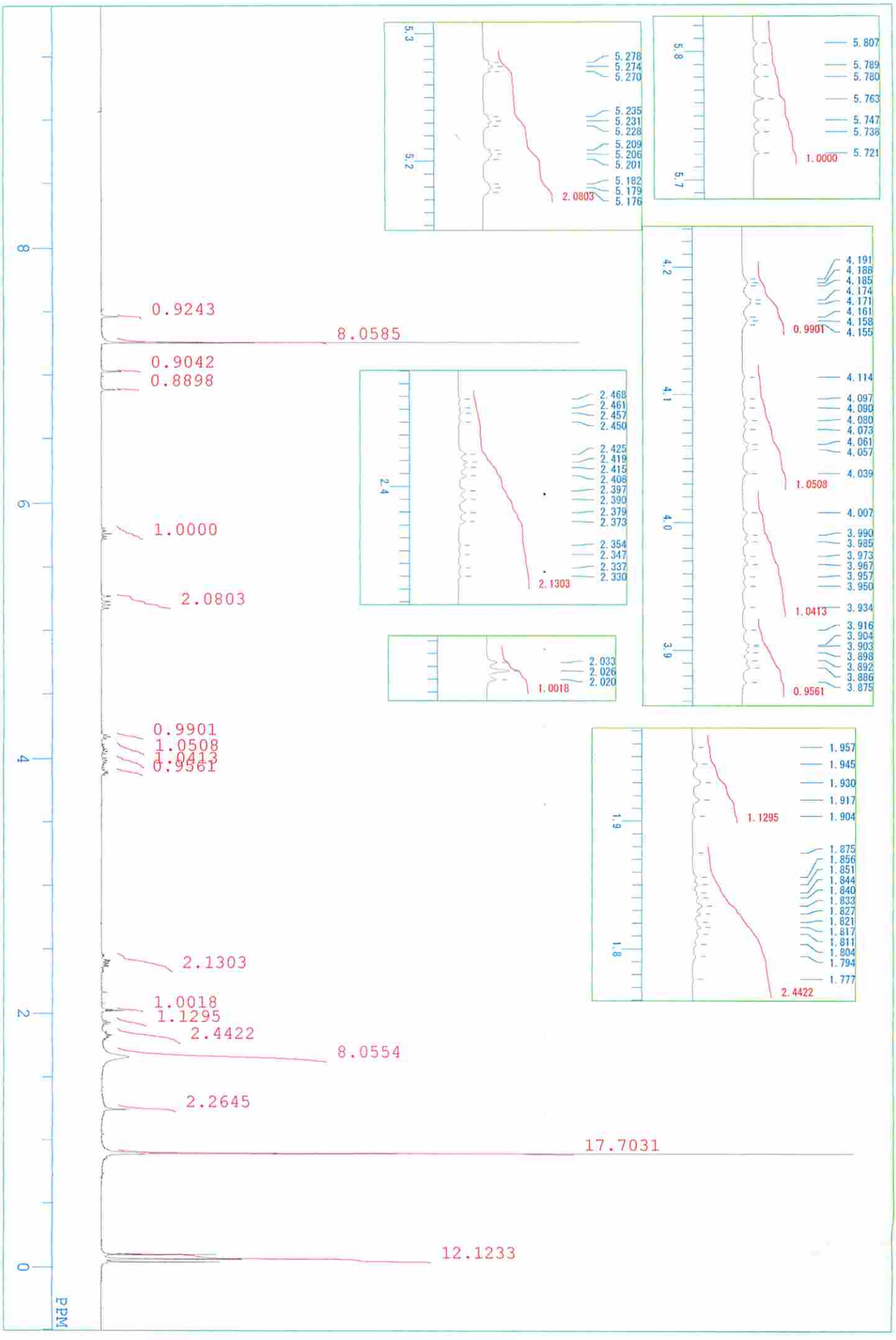


To a solution of **10** (13.1 mg, 0.0317 mmol) in CH_2Cl_2 (5 mL) were added Et_3N (0.055 mL, 0.395 mmol) and MsCl (0.025 mL, 0.317 mmol) at 0°C, and the mixture was stirred at rt for 2 h. To the mixture was added brine at 0°C, and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 30/1) to give (3*R*,4*S*,5*R*)-3,5-bis(*tert*-butyldimethylsilyloxy)-4-[2-(mesyloxy)-ethyl]oct-1-en-7-yne (14.1 mg, 0.0287 mmol, 91%) as a colorless oil. $[\alpha]_D^{24}$ +0.16 (c 0.77, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.042 (s, 3H), 0.070 (s, 3H), 0.078 (s, 3H), 0.096 (s, 3H), 0.89 (s, 9H), 0.90 (s, 9H), 1.71-1.89 (m, 2H), 1.94-1.99 (m, 1H), 2.00 (t, *J* = 2.7 Hz, 1H), 2.38 (ddd, *J* = 2.7, 6.8, 17.1 Hz, 1H), 2.42 (ddd, *J* = 2.7, 5.1, 17.1 Hz, 1H), 2.98 (s, 3H), 3.94 (ddd, *J* = 4.6, 5.1, 6.8 Hz, 1H), 4.15 (dddd, *J* = 1.2, 1.5, 5.6, 6.6 Hz, 1H), 4.24 (ddd, *J* = 6.3, 9.0, 15.6 Hz, 1H), 4.38 (ddd, *J* = 6.3, 9.0, 15.6 Hz, 1H), 5.18 (ddd, *J* = 1.2, 1.5, 10.3 Hz, 1H), 5.24 (ddd, *J* = 1.5, 1.5, 17.1 Hz, 1H), 5.79 (ddd, *J* = 6.6, 10.3, 17.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.60, -4.45, -4.08, -3.84, 18.1, 18.2, 25.6, 25.9 (3C), 25.9 (3C), 26.4, 37.4, 45.7, 70.1, 70.7, 70.8, 75.2, 80.7, 116.6, 138.4; IR (neat) 3312, 2120, 1360, 1176 cm^{-1}. ESI-LRMS *m*/*z* 514 ($[M+Na]^+$), 491, 359. ESI-HRMS calcd for $C_{23}H_{46}O_5SSi_2$ ($[M+Na]^+$) 513.2497, found 513.2494.

Imidazole (59.2 mg, 0.870 mmol) and NaH (60% in oil, 37.4 mg, ca. 0.935 mmol) were suspended in THF (1 mL) at 0°C, and the mixture was stirred at rt for 1 h. To the mixture was added a solution of the above obtained mesylate (14.1 mg, 0.0287 mmol) in THF (1 mL) at 0°C, and the mixture was refluxed for 17 h. Imidazole (61.5 mg, 0.903 mmol) and NaH (60% in oil, 38.0 mg, ca. 0.950 mmol) were suspended in THF (1 mL) at 0°C, and the mixture was stirred at rt for 1 h. The mixture was re-added to the

above reaction mixture at rt, and refluxed for 42 h. To the mixture was added sat. NH_4Cl aq. at 0°C, and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 30/1-1/1) to give **2f** (9.4 mg, 0.0203 mmol, 71%) as a colorless oil.

$[\alpha]_D^{26}$ +0.096 (c 1.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.042 (s, 3H), 0.064 (s, 3H), 0.066 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 0.90 (s, 9H), 1.78-1.88 (m, 2H), 1.90-1.96 (m, 1H), 2.03 (t, *J* = 2.7 Hz, 1H), 2.36 (ddd, *J* = 2.7, 6.8, 16.8 Hz, 1H), 2.44 (ddd, *J* = 2.7, 4.4, 16.8 Hz, 1H), 3.90 (ddd, *J* = 4.4, 5.1, 6.8 Hz, 1H), 3.97 (ddd, *J* = 6.6, 9.0, 13.7 Hz, 1H), 4.08 (ddd, *J* = 6.8, 9.5, 13.7 Hz, 1H), 4.17 (dddd, *J* = 1.2, 1.5, 5.4, 6.6 Hz, 1H), 5.19 (ddd, *J* = 1.2, 1.5, 10.3 Hz, 1H), 5.25 (ddd, *J* = 1.5, 1.5, 17.1 Hz, 1H), 5.76 (ddd, *J* = 6.6, 10.3, 17.1 Hz, 1H), 6.89 (s, 1H), 7.03 (s, 1H), 7.46 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.57, -4.39, -4.16, -3.94, 18.1, 18.2, 25.9 (3C), 26.0 (3C), 26.6, 27.9, 46.7, 47.0, 70.9, 71.0, 75.0, 80.5, 116.5, 118.4, 129.1, 136.8, 138.3; IR (neat) 3312, 3077, 2120 cm^{-1}. ESI-LRMS *m*/*z* 463 ($[M+H]^+$), 441, 414. ESI-HRMS calcd for $C_{25}H_{46}N_2O_2Si_2$ ($[M+H]^+$) 463.3171, found 463.3182.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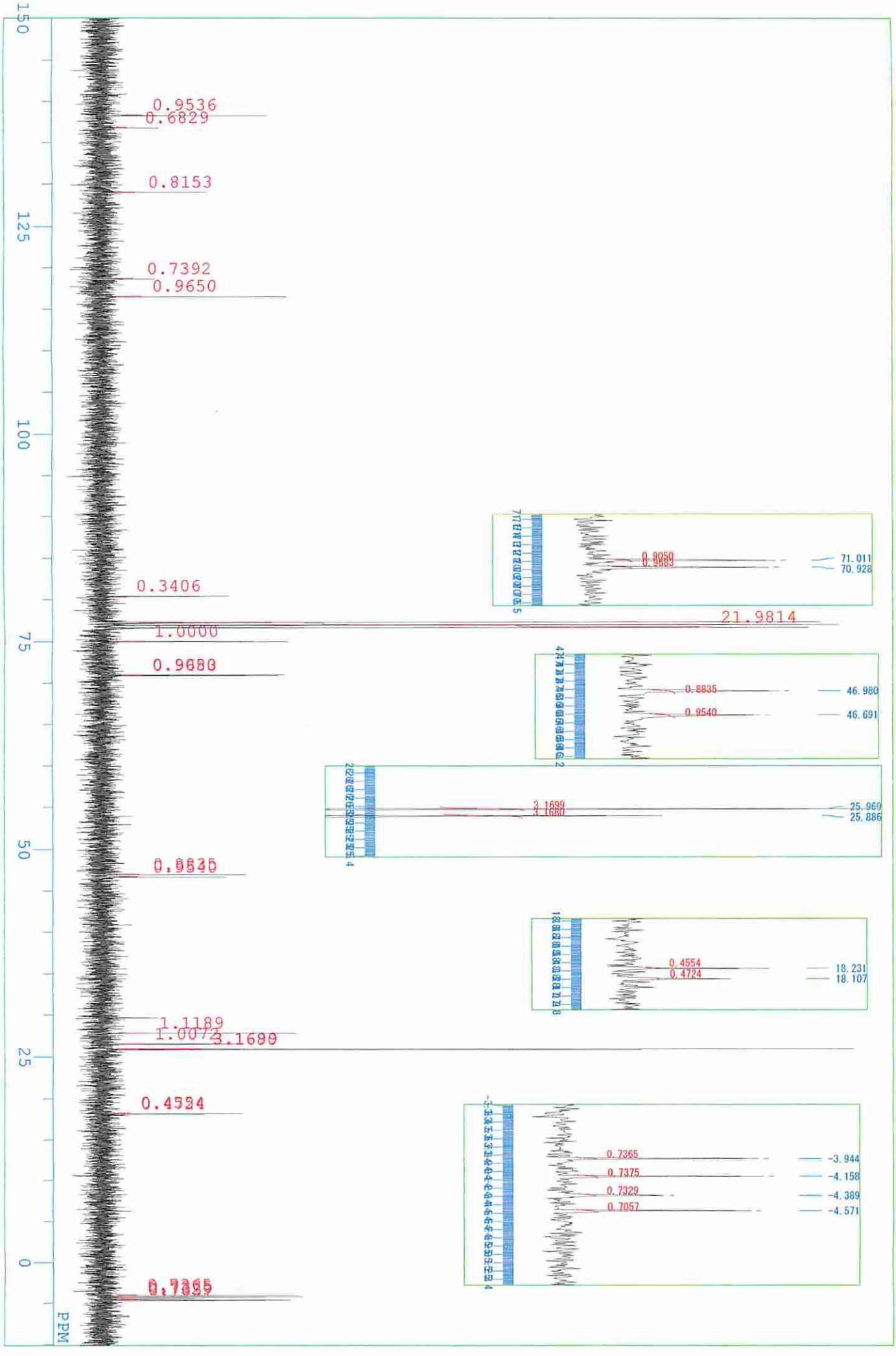
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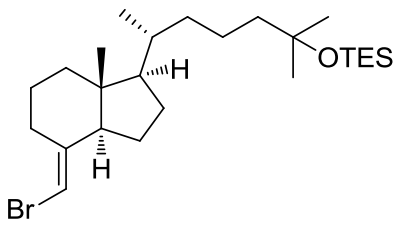
(4*E*)-(1*R*,3a*R*,7a*R*)-1-[(2*R*)-6-(Triethylsilyloxy)-6-methylheptan-2-yl]-4-bromomethylene-7a-methyloctahydro-1*H*-indene (12).



(1*R*,3a*R*,7a*R*)-1-((*R*)-6-hydroxy-6-methylheptan-2-yl)-7a-methylhexahydro-1*H*-inden-4(2*H*)-one[3] (203.2 mg, 0.725 mmol) was dissolved in DMF (2.4 mL), and imidazole (123 mg, 1.81 mmol) and TESCl (0.15 mL, 0.870 mmol) were added to the solution at 0°C. The mixture was stirred at rt for 1.5 h and partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 40/1) to yield 233.6 mg of (1*R*,3a*R*,7a*R*)-1-[(2*R*)-6-(triethylsilyloxy)-6-methylheptan-2-yl]-7a-methylhexahydro-1*H*-inden-4(2*H*)-one as a colorless oil (82%).

$[\alpha]_D^{23}$ +4.38 (c 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.56 (q, *J* = 7.8 Hz, 6H), 0.64 (s, 3H), 0.94 (t, *J* = 7.8 Hz, 9H), 0.95 (d, *J* = 7.8 Hz, 3H), 1.19 (s, 6H), 1.22-1.62 (m, 10H), 1.67-1.78 (m, 1H), 1.84-1.95 (m, 2H), 1.96-2.04 (m, 1H), 2.12 (ddd, *J* = 13.2, 3.9, 2.6 Hz, 1H), 2.17-2.31 (m, 2H), 2.45 (dd, *J* = 11.7, 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.87 (3C), 7.18 (3C), 12.5, 18.8, 19.1, 20.8, 24.1, 27.6, 29.9, 30.0, 35.5, 36.3, 39.0, 41.0, 45.5, 50.0, 56.4, 62.0, 73.4, 211.9; IR(neat) 1717, 1460, 1416, 1379, 1364, 1236 cm^{-1}. ESI-HRMS calcd for $C_{24}H_{46}O_2Si$ ($[M+Na]^+$) 417.3159, found 417.3143.

$(PPh_3P^+CH_2Br)Br^-$ (1.29 g, 2.96 mmol) was suspended in THF (4 mL), and NaHMDS (1 M solution in THF, 2.9 mL, 2.9 mmol) was added at 0°C with stirring. After 1 h, a solution of the above *O*-protected product (233.6 mg, 0.592 mmol) in THF (2 mL) was added to the suspension at 0°C. The mixture was stirred at the same temperature for 3 h, and then at rt for 2.5 h. The reaction mixture was partitioned between sat. NH_4Cl aq. and EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column

chromatography (hexane/EtOAc = 100/1-5/1) to yield 125.6 mg of **12** as a colorless oil (45%).

$[\alpha]_D^{20}$ +67.7 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.561 (q, *J* = 8.0 Hz, 6H), 0.563 (s, 3H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.94 (t, *J* = 8.0 Hz, 9H), 1.19 (s, 6H), 1.22-1.69 (m, 15H), 1.87-1.93 (m, 1H), 1.95-2.04 (m, 2H), 2.85-2.91 (m, 1H), 5.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.90 (3C), 7.21 (3C), 11.9, 18.9, 20.9, 22.1, 22.7, 27.7, 29.9, 30.1, 31.1, 36.1, 36.5, 39.9, 45.5, 45.6, 55.89, 55.95, 73.4, 97.2, 145.1; IR(neat) 1460, 1414, 1379, 1364, 1236, 1215 cm^{-1}. EI-HRMS calcd for $C_{25}H_{47}OBrSi$ $(M)^+$ 470.2580, found 470.2593.

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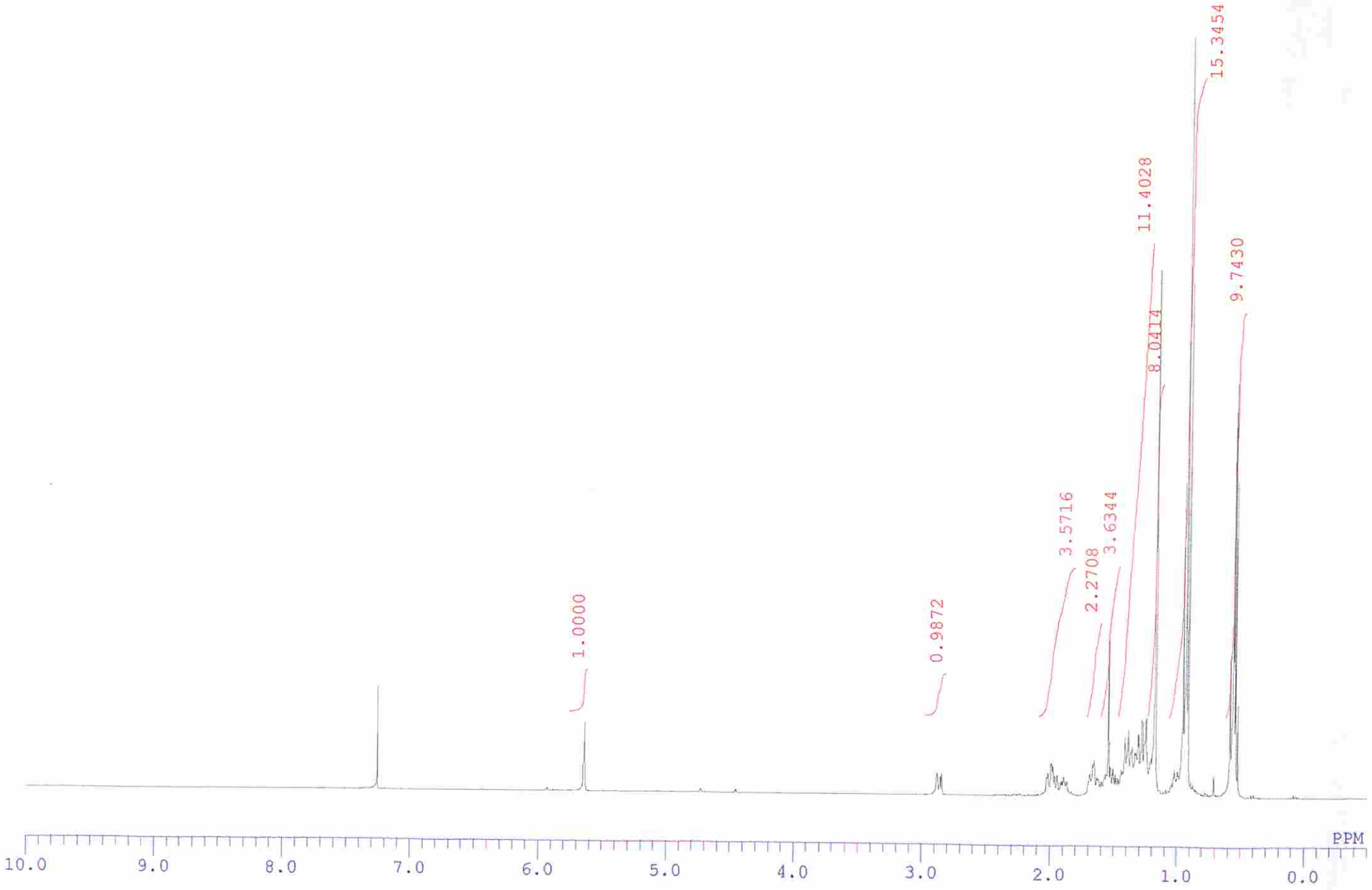
01AH085A

12



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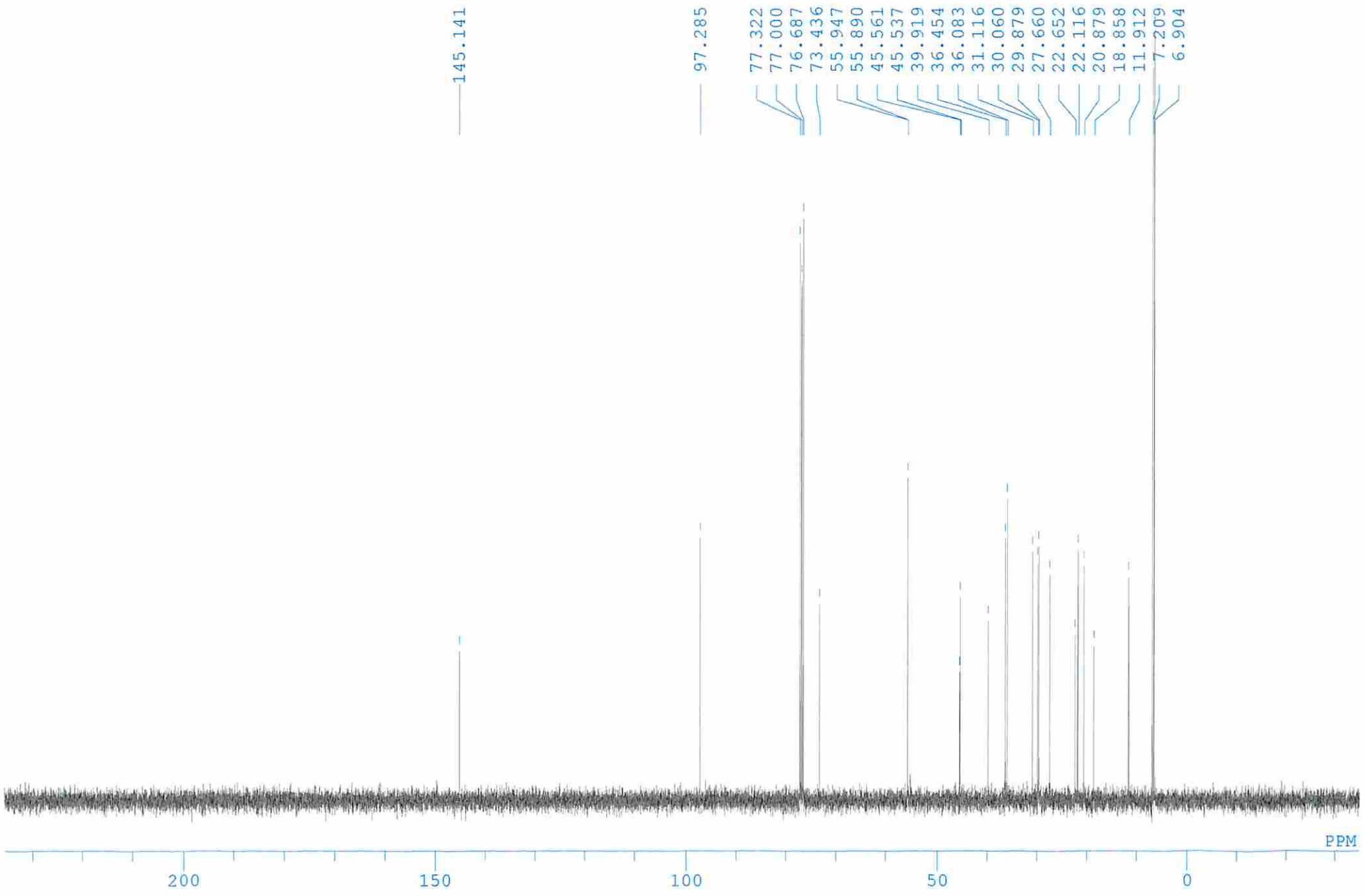
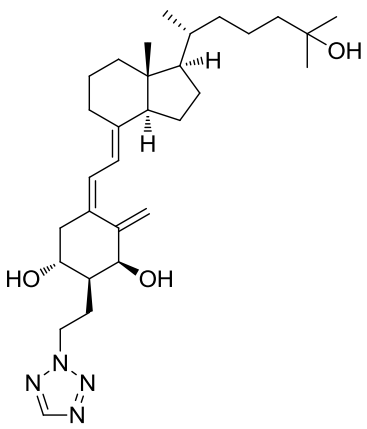
12



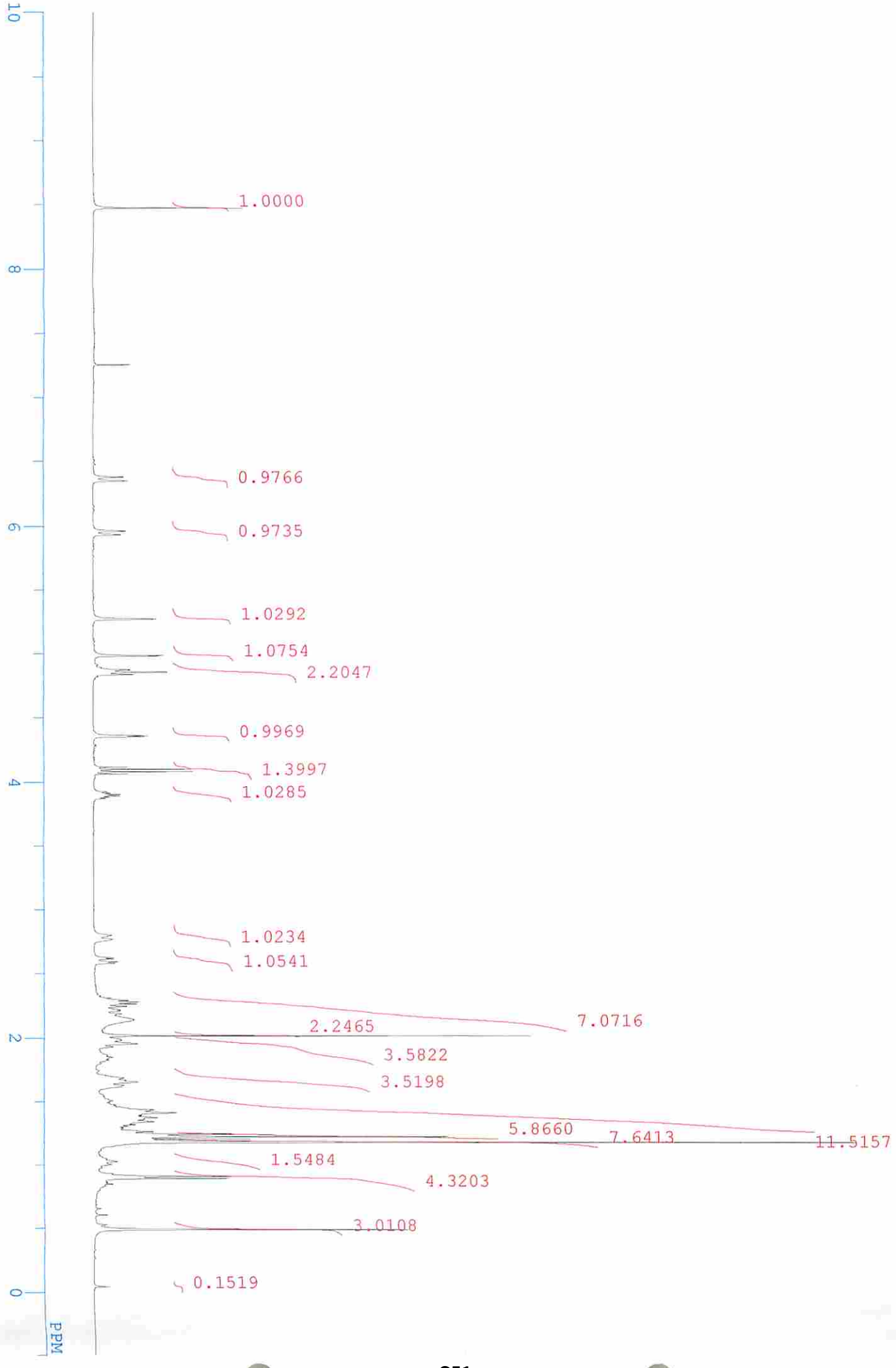
1α,25-Dihydroxy-2α-[2-(2*H*-tetrazol-2-yl)ethyl]vitamin D_3 (1a).



To a solution of enyne **2a** (104 mg, 0.225 mmol) and bromoolefin **12** (141 mg, 0.300 mmol) in toluene/Et_3N (10 mL, toluene/Et_3N = 1/1) was added $Pd(PPh_3)_4$ (78.0 mg, 0.0675 mmol) at rt, and the mixture was heated at 110°C for 1 h. After cooling, the reaction mixture was filtered through a Celite pad (EtOAc). Concentration followed by column chromatography on silica gel (hexane/EtOAc = 50/1) gave the crude protected coupling product (103 mg, oil), which was used in the next step without further purification.

To the solution of the coupling product (103 mg) in THF (2.5 mL) was added TBAF (1 M solution in THF, 0.60 mL, 0.60 mmol) at 0°C, and the mixture was stirred at rt overnight. To the mixture was added sat. NH_4Cl aq. at 0°C, and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 1/1) to give 46.0 mg of **1a** as a colorless oil (40% for two steps). The product was further purified by preparative HPLC (YMC-Pack ODS-A 250 × 20 mm, CH_3CN/H_2O= 9/1, 10 mL/min) for biological evaluations.

$[\alpha]_D^{23}$ +15.8 (c 1.14, $CHCl_3$); UV (EtOH) λ_{max} 268 nm, λ_{min} 227 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.52 (s, 3H), 0.85-1.88 (m, 25H), 1.96-2.05 (m, 4H), 2.17-2.40 (m, 5H), 2.64 (dd, *J* = 13.2, 4.4 Hz, 1H), 2.81 (d, *J* = 12.8 Hz, 1H), 3.93 (ddd, *J* = 8.8, 8.7, 4.4 Hz, 1H), 4.38 (d, *J* = 2.8 Hz, 1H), 4.90 (t, *J* = 7.2 Hz, 2H), 5.02 (d, *J* = 1.6 Hz, 1H), 5.30 (s, 1H), 5.97 (d, *J* = 11.4 Hz, 1H), 6.41 (d, *J* = 11.4 Hz, 1H), 8.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 18.8, 20.9, 22.3, 23.6, 27.7, 28.3, 29.1, 29.2, 29.4, 36.1, 36.4, 40.5, 44.4, 44.7, 45.9, 46.4, 51.9, 56.3, 56.5, 70.3, 71.1, 74.1, 114.4, 116.7, 125.0, 131.8, 143.6, 145.7, 152.6; IR (neat) 3596, 3407, 1647, 1447, 1377, 1289, 1215 cm^{-1}. ESI-HRMS calcd for $C_{30}H_{48}N_4O_3$ ($[M+Na]^+$) 535.3619, found 535.3623.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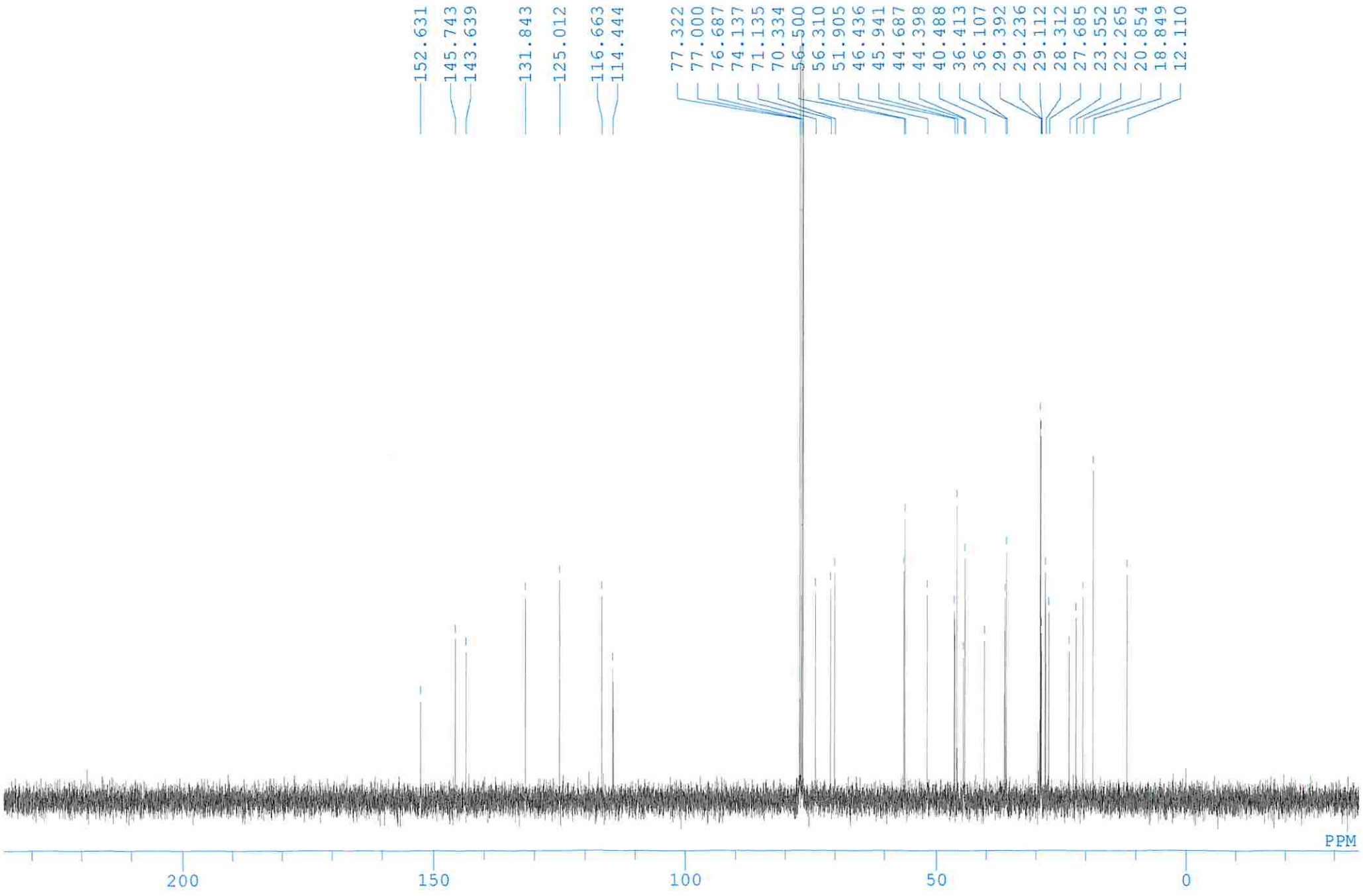
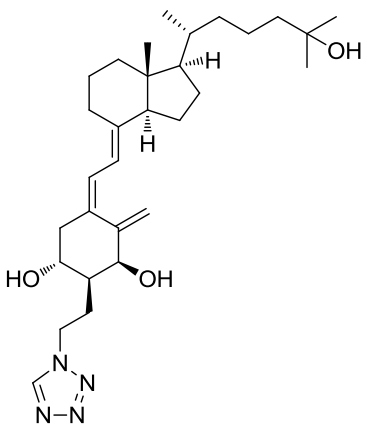
1a



1α,25-Dihydroxy-2α-[2-(1*H*-tetrazole-1-yl)ethyl]vitamin D_3 (1b)



The title compound **1b** (10.4 mg) was obtained according to the similar procedure described above for **1a**, starting from enyne **2b** (25.8 mg, 0.0555 mmol) and bromoolefin **12** (42.6 mg, 0.0903 mmol), as a colorless oil (37% for two steps).

$[\alpha]_D^{22}$ +48.7 (c 0.40, $CHCl_3$); UV (EtOH) λ_{max} 269 nm, λ_{min} 227 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 1.04-1.72 (m, 25H), 1.86-2.02 (m, 3H), 2.22-2.28 (m, 3H), 2.62 (dd, *J* = 4.2, 13.4 Hz, 1H), 2.81 (dd, *J* = 3.9, 12.2 Hz, 1H), 3.94 (dddd, *J* = 4.2, 4.4, 8.8, 9.0 Hz, 1H), 4.33 (dd, *J* = 3.2, 3.4 Hz, 1H), 4.69 (t, *J* = 7.3 Hz, 2H), 5.03 (d, *J* = 1.5 Hz, 1H), 5.29 (d, *J* = 1.2 Hz, 1H), 5.95 (d, *J* = 11.4 Hz, 1H), 6.41 (d, *J* = 11.4 Hz, 1H), 8.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 18.8, 20.8, 22.2, 23.5, 27.7, 29.1, 29.2, 29.3, 29.7, 36.1, 36.4, 40.5, 44.4, 44.8, 46.0, 46.0, 47.2, 56.3, 56.5, 70.5, 71.1, 74.6, 114.7, 116.6, 125.3, 131.5, 142.7, 144.1, 145.7; IR (neat) 3582, 3412, 1643 cm^{-1}. ESI-HRMS calcd for $C_{30}H_{48}N_4O_3$ ($[M+Na]^+$) 535.3619, found 535.3616.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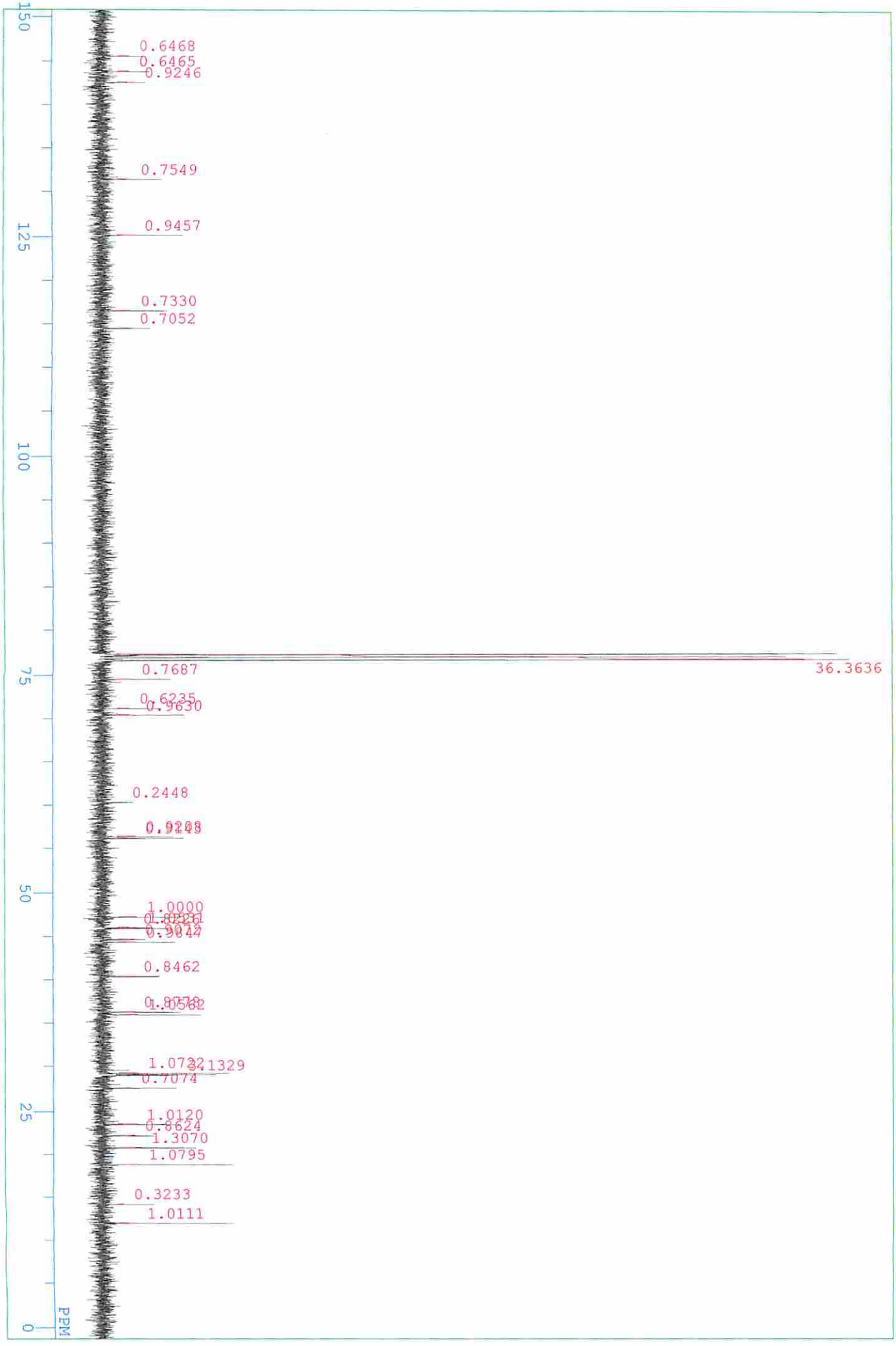
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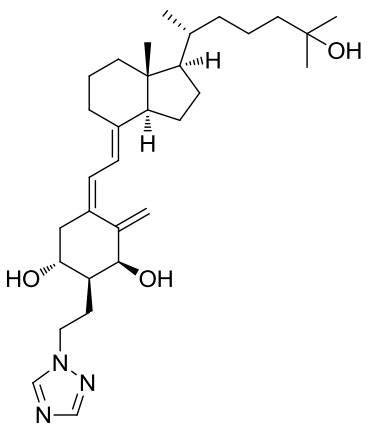
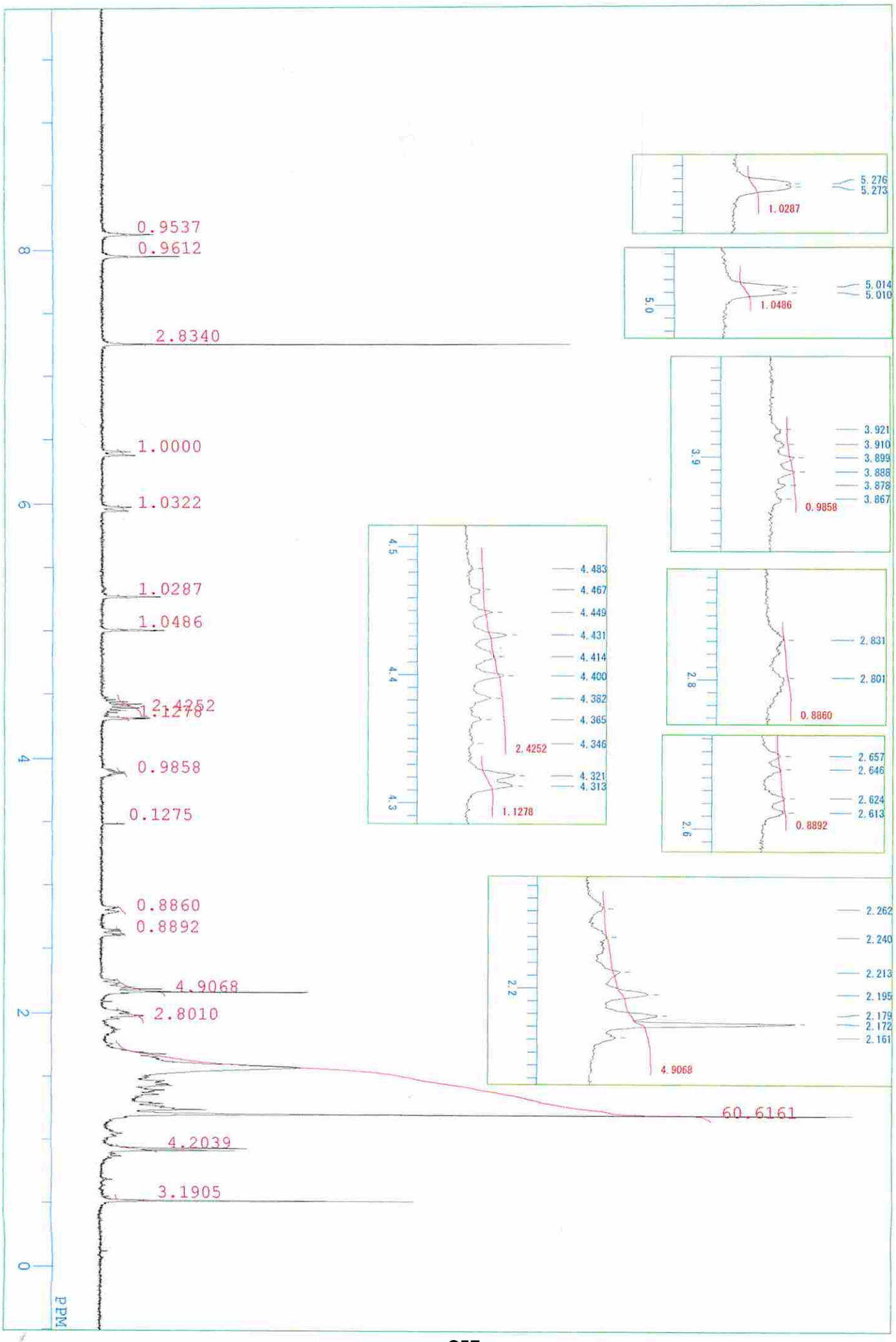
1α,25-Dihydroxy-2α-[2-(1,2,4-triazole-2-yl)ethyl]vitamin D_3 (1c).



The title compound **1c** (4.3 mg) was obtained according to the similar procedure described above for **1a**, starting from enyne **2c** (13.6 mg, 0.0293 mmol) and bromoolefin **12** (19.2 mg, 0.0407 mmol), as a colorless oil (29% for two steps).

$[\alpha]_D^{23}$ +38.8 (c 0.83, $CHCl_3$); UV (EtOH) λ_{max} 268 nm, λ_{min} 227 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3H), 0.93 (d, *J* = 6.3 Hz, 3H), 1.21-1.76 (m, 25H), 1.96-2.01 (m, 3H), 2.16-2.26 (m, 3H), 2.64 (dd, *J* = 4.2, 13.4 Hz, 1H), 2.82 (d, *J* = 12.0 Hz, 1H), 3.89 (ddd, *J* = 4.4, 8.5, 8.8 Hz, 1H), 4.32 (d, *J* = 3.2 Hz, 1H), 4.41 (ddd, *J* = 7.1, 13.7, 14.1 Hz, 1H), 4.42 (ddd, *J* = 7.1, 13.7, 14.2 Hz, 1H), 5.01 (d, *J* = 1.7 Hz, 1H), 5.27 (d, *J* = 0.98 Hz, 1H), 5.96 (d, *J* = 11.2 Hz, 1H), 6.40 (d, *J* = 12.0 Hz, 1H), 7.95 (s, 1H) , 8.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 18.9, 20.9, 22.3, 23.6, 27.7, 28.9, 29.1, 29.3, 29.4, 36.1, 36.4, 40.5, 44.4, 44.5, 45.9, 46.4, 48.4, 56.3, 56.5, 70.3, 71.1, 74.3, 114.0, 116.7, 124.8, 132.2, 143.0, 143.4, 146.0, 151.6; IR (neat) 3583, 3399, 1645 cm^{-1}. ESI-HRMS calcd for $C_{31}H_{49}N_3O_3$ ($[M+H]^+$) 512.3847, found 512.3853.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0.1275
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2.8010
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4.2039
3.1905
PPM
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5.010
1.0486
3.921
3.910
3.899
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3.878
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0.9858
4.483
4.467
4.449
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4.400
4.382
4.365
4.346
4.321
4.313
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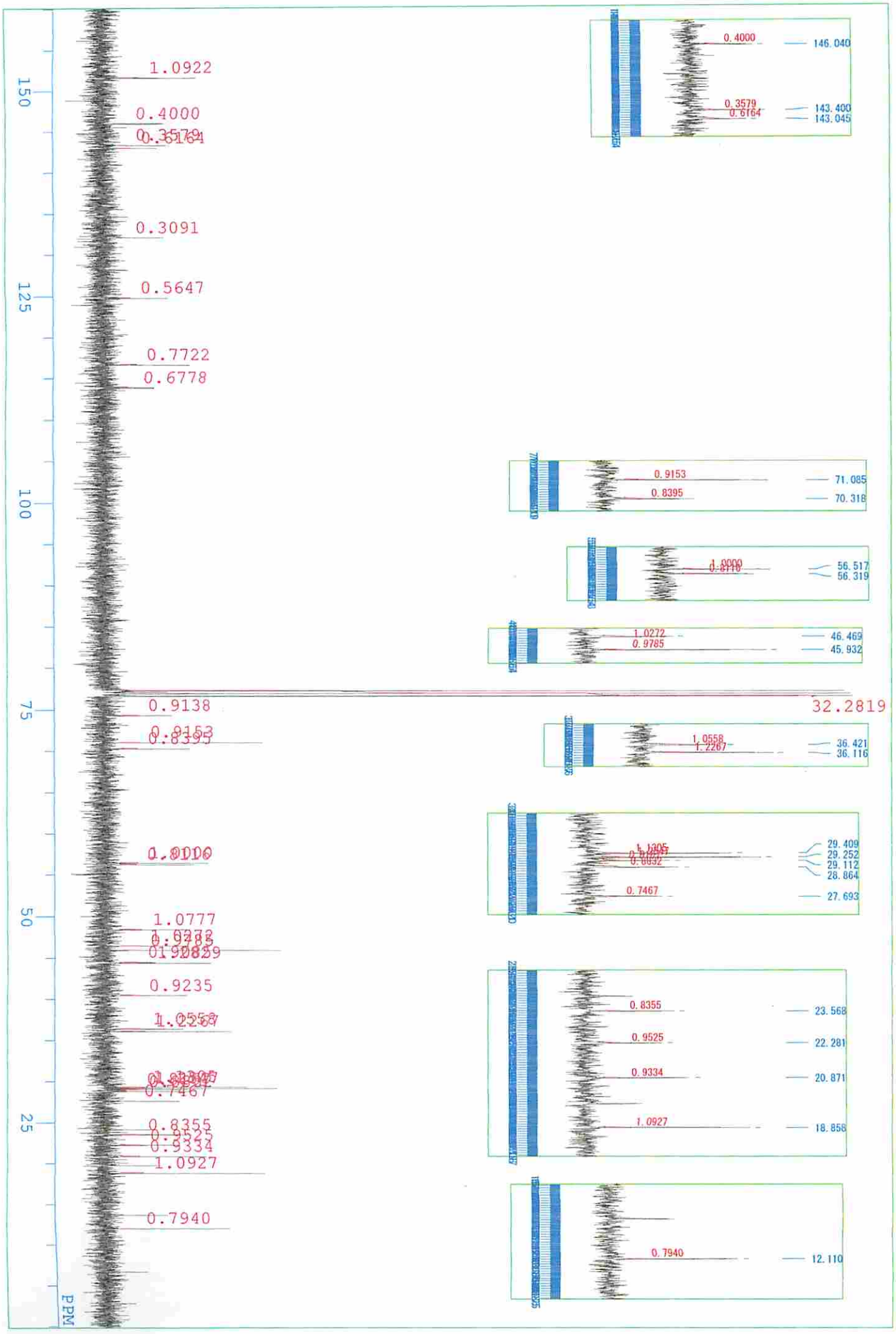
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1.0927
0.7940
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0.9153
0.8395
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1.0272
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46.469
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0.6032
0.7467
29.409
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27.693
0.8355
0.9525
0.9334
1.0927
23.568
22.281
20.871
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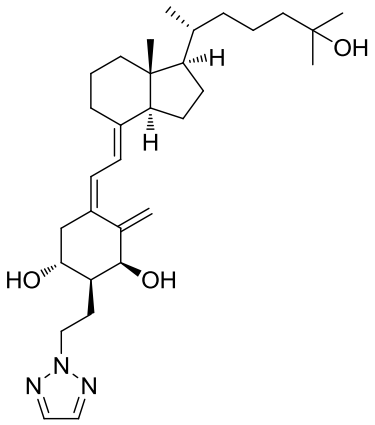
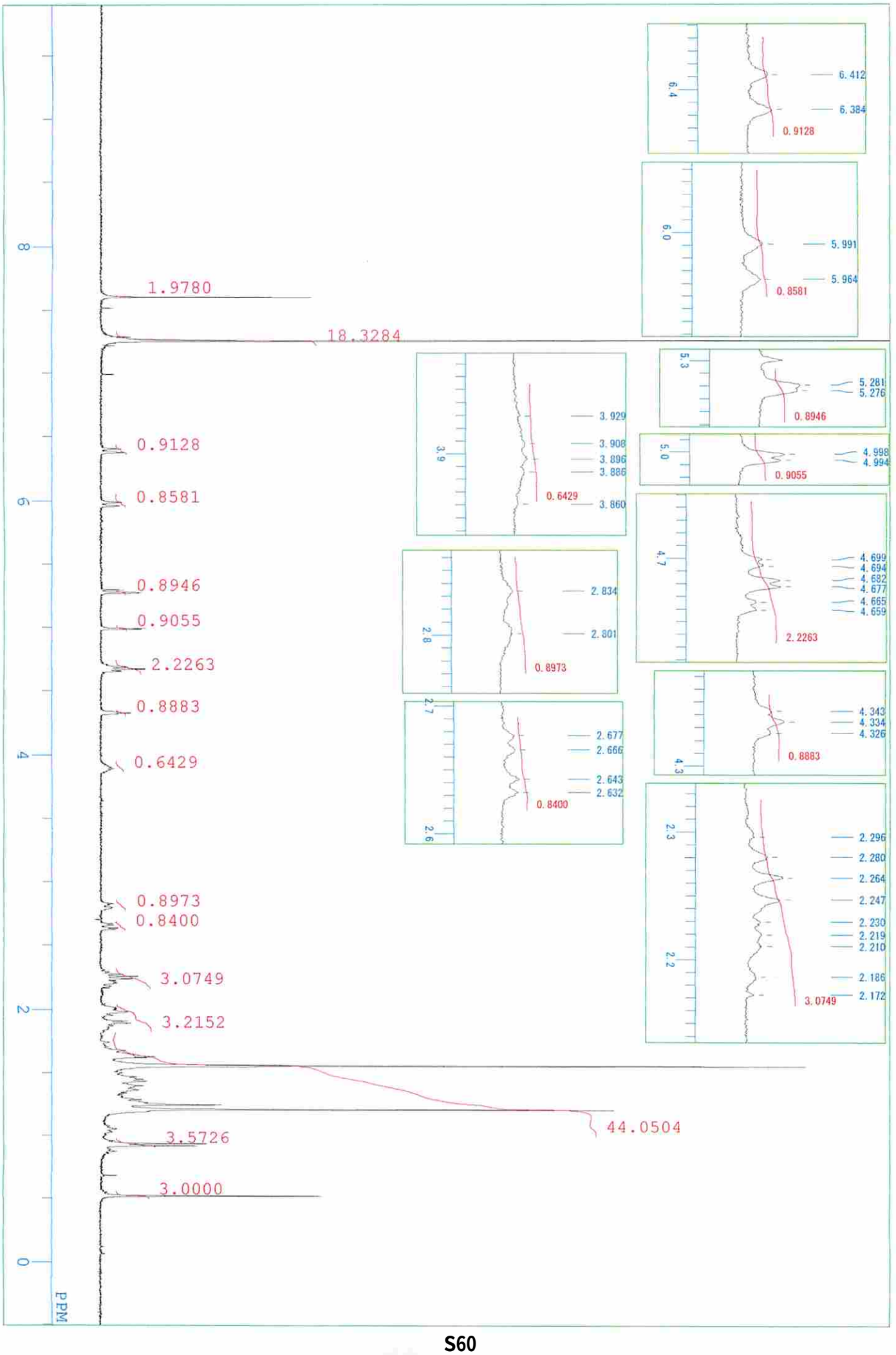
0.7940
12.110

1α,25-Dihydroxy-2α-[2-(2*H*-1,2,3-triazole-2-yl)ethyl]vitamin D_3 (1d).



The title compound **1d** (4.9 mg) was obtained according to the similar procedure described above for **1a**, starting from enyne **2d** (16.6 mg, 0.0358 mmol) and bromoolefin **12** (23.4 mg, 0.0496 mmol), as a colorless oil (27% for two steps).

$[\alpha]_D^{22}$ +31.5 (c 0.72, $CHCl_3$); UV (EtOH) λ_{max} 269 nm, λ_{min} 235 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 1.21-1.75 (m, 25H), 1.88-1.98 (m, 3H), 2.17-2.30 (m, 3H), 2.65 (dd, *J* = 4.2, 13.4 Hz, 1H), 2.82 (d, *J* = 13.2 Hz, 1H), 3.86-3.93 (m, 1H), 4.34 (t, *J* = 3.4 Hz, 1H), 4.68 (td, *J* = 2.0, 6.6 Hz, 2H), 5.00 (d, *J* = 1.7 Hz, 1H), 5.28 (d, *J* = 1.7 Hz, 1H), 5.98 (d, *J* = 11.0 Hz, 1H), 6.40 (d, *J* = 11.0 Hz, 1H), 7.60 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 18.9, 20.9, 22.3, 23.6, 27.7, 28.2, 29.1, 29.3, 29.4, 36.1, 36.4, 40.5, 44.4, 44.6, 45.9, 46.7, 53.4, 56.3, 56.5, 70.4, 71.1, 74.1, 114.0, 116.8, 124.8, 132.2, 133.8 (2C), 143.4, 146.0; IR (neat) 3585, 3399, 1645 cm^{-1}. ESI-HRMS calcd for $C_{31}H_{49}N_3O_3$ ($[M+H]^+$) 512.3847, found 512.3845.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PPM
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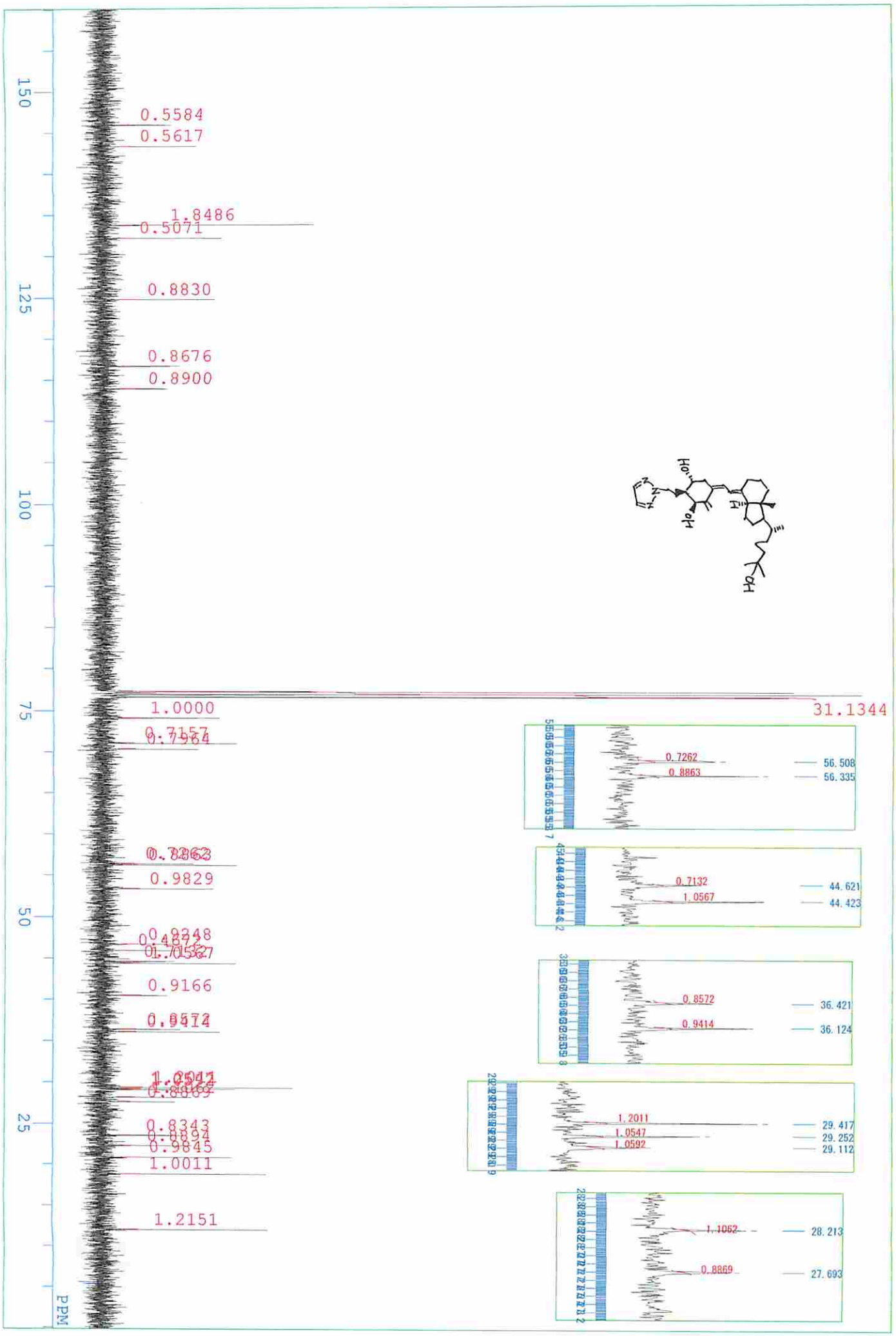
1d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0.9845
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36.124
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1.1062
0.8869
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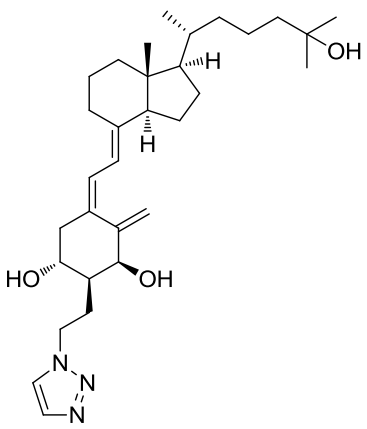
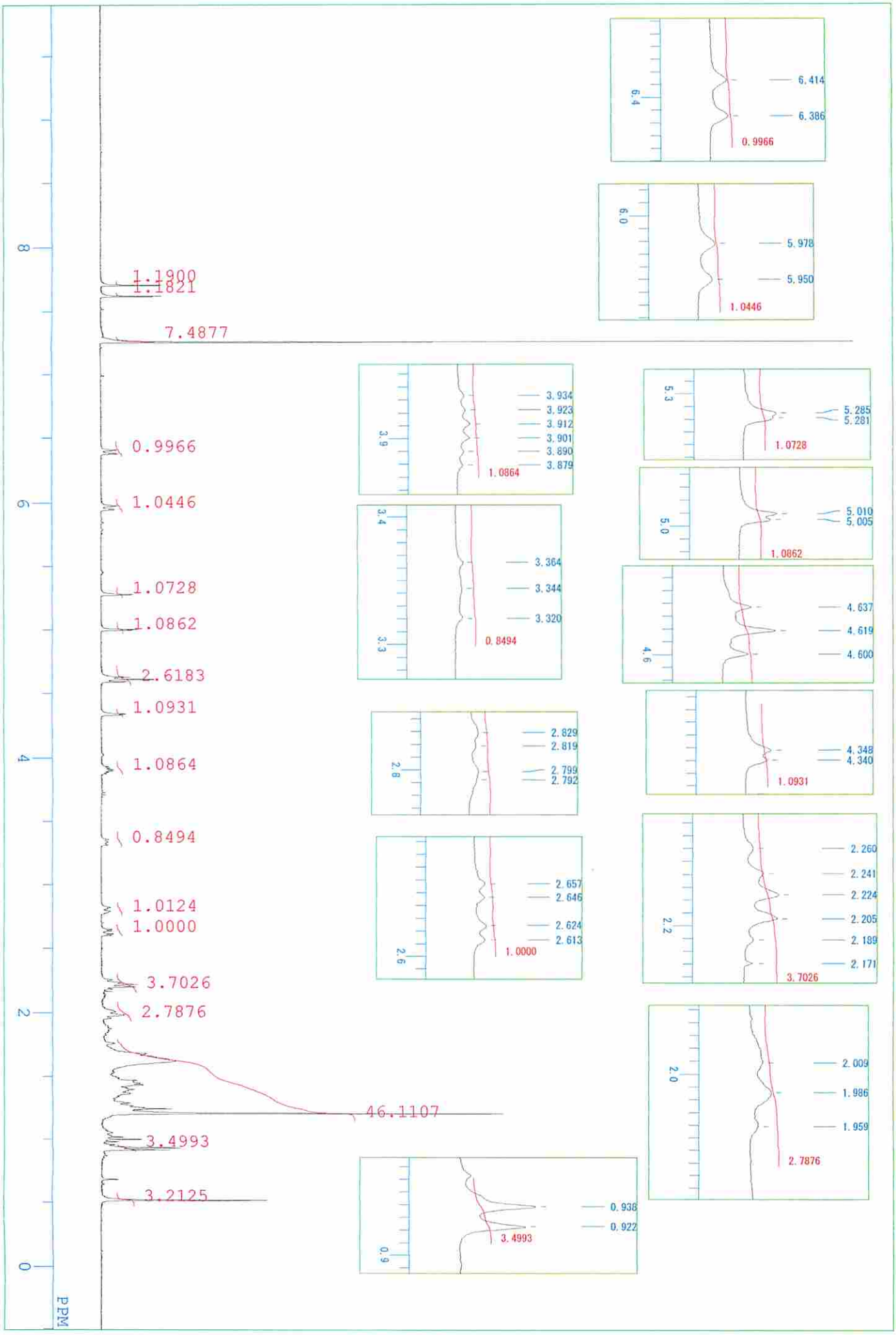
C 31
1d

1α,25-Dihydroxy-2α-[2-(1*H*-1,2,3-triazole-1-yl)ethyl]vitamin D_3 (1e).



The title compound **1e** (6.8 mg) was obtained according to the similar procedure described above for **1a**, starting from enyne **2e** (12.5 mg, 0.0270 mmol) and bromoolefin **12** (17.7 mg, 0.0375 mmol), as a colorless oil (49% for two steps).

$[\alpha]_D^{24}$ +42.5 (c 0.12, $CHCl_3$); UV (EtOH) λ_{max} 271 nm, λ_{min} 229 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.52 (s, 3H), 0.93 (d, *J* = 6.3 Hz, 3H), 1.21-1.76 (m, 25H), 1.96-2.01 (m, 3H), 2.17-2.26 (m, 3H), 2.63 (dd, *J* = 4.2, 13.4 Hz, 1H), 2.82 (dd, *J* = 4.2, 12.2 Hz, 1H), 3.91 (td, *J* = 4.4, 8.8 Hz, 1H), 4.34 (d, *J* = 3.2 Hz, 1H), 4.62 (t, *J* = 7.3 Hz, 2H), 5.01 (d, *J* = 2.0 Hz, 1H), 5.28 (d, *J* = 1.5 Hz, 1H), 5.96 (d, *J* = 11.2 Hz, 1H), 6.40 (d, *J* = 11.2 Hz, 1H), 7.62 (s, 1H) , 7.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 18.9, 20.9, 22.3, 23.6, 27.7, 29.1, 29.3, 29.4, 29.7, 36.1, 36.4, 40.5, 44.4 (2C), 46.0, 46.4, 48.8, 56.3, 56.5, 70.4, 71.1, 74.3, 114.4, 116.7, 123.3, 125.0, 131.8, 133.8, 143.7, 145.8; IR (neat) 3583, 3390, 1644 cm^{-1}. ESI-HRMS calcd for $C_{31}H_{49}N_3O_3$ ($[M+H]^+$) 512.3847, found 512.3832.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1.0931
1.0864
0.8494
1.0124
1.0000
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2.7876
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3.2125
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0.9966
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5.950
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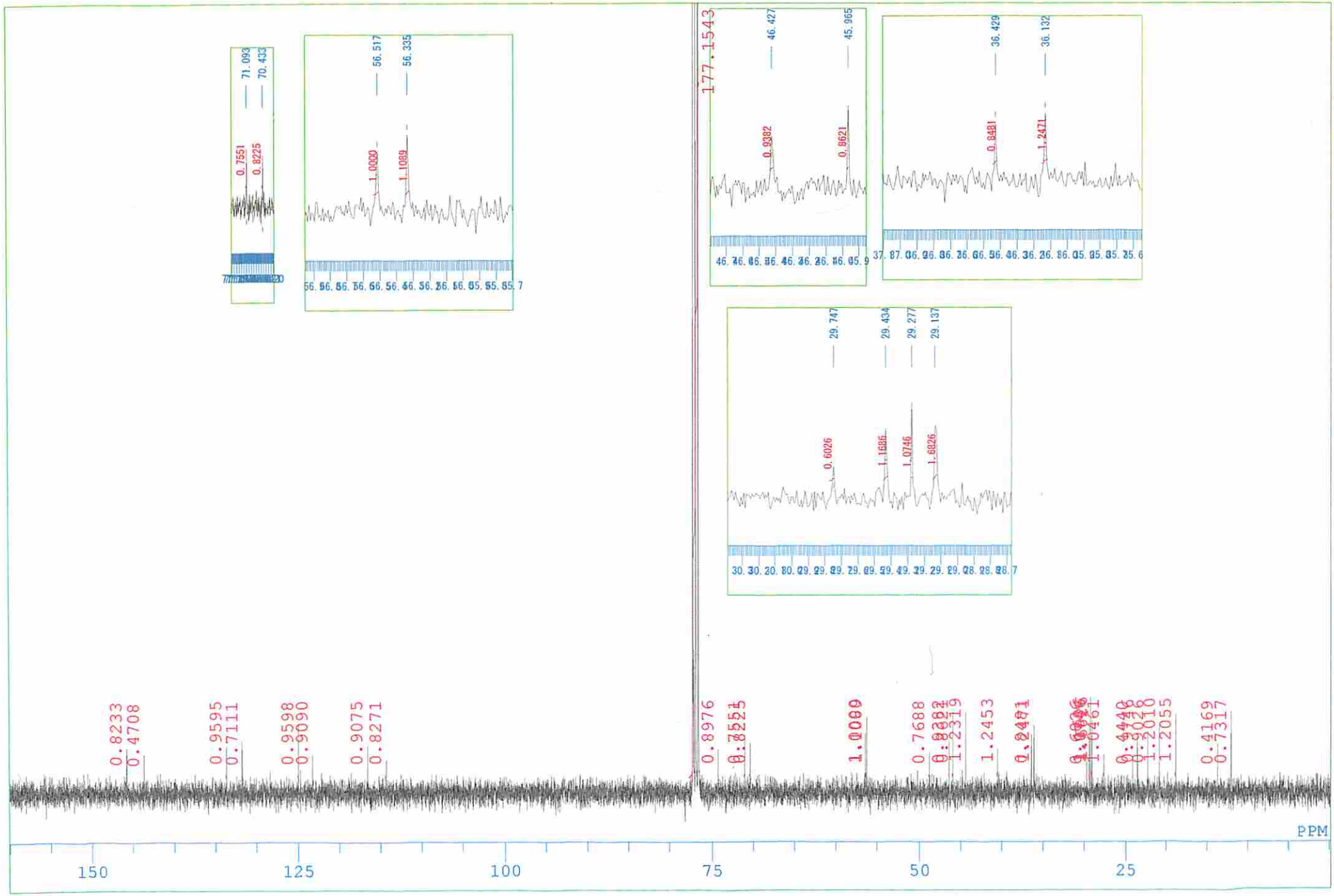
1e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PPM
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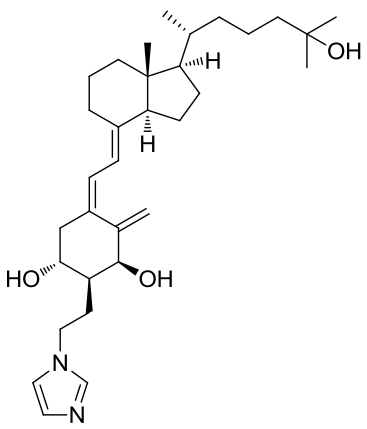
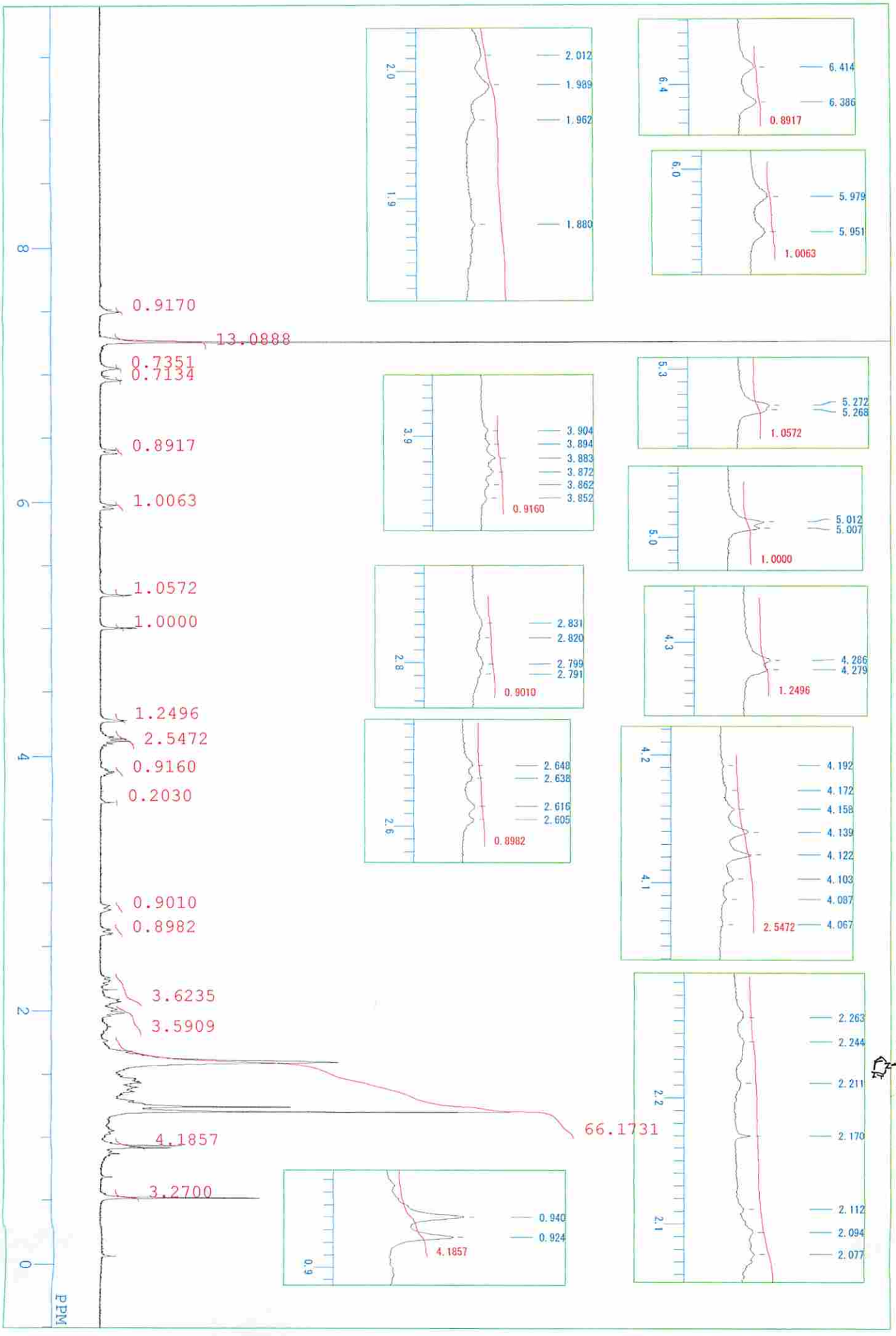
125
100
75
50
25

1α,25-Dihydroxy-2α-[2-(imidazole-1-yl)ethyl]vitamin D_3 (1f).



The title compound **1f** (5.7 mg) was obtained according to the similar procedure described above for **1a**, starting from enyne **2f** (10.8 mg, 0.0233 mmol) and bromoolefin **12** (18.1 mg, 0.0384 mmol), as a colorless oil (48% for two steps).

$[\alpha]_D^{22}$ +9.44 (c 0.36, $CHCl_3$); UV (EtOH) λ_{max} 269 nm, λ_{min} 231 nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3H), 0.93 (d, *J* = 6.3 Hz, 3H), 1.21-1.78 (m, 25H), 1.88-2.01 (m, 3H), 2.08-2.26 (m, 3H), 2.62 (dd, *J* = 4.2, 13.0 Hz, 1H), 2.81 (dd, *J* = 3.2, 13.0 Hz, 1H), 3.88 (td, *J* = 4.2, 8.5 Hz, 1H), 4.13 (td, *J* = 7.8, 13.7 Hz, 2H), 4.28 (d, *J* = 2.9 Hz, 1H), 5.01 (d, *J* = 2.0 Hz, 1H), 5.27 (d, *J* = 1.5 Hz, 1H), 5.97 (d, *J* = 11.0 Hz, 1H), 6.40 (d, *J* = 11.0 Hz, 1H), 6.96 (s, 1H), 7.05 (s, 1H), 7.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 18.9, 20.9, 22.3, 23.6, 27.7, 29.1, 29.3, 29.4, 29.7, 36.1, 36.4, 40.5, 44.4 (2C), 45.8, 45.9, 46.6, 56.3, 56.5, 70.2, 71.1, 73.9, 114.0, 114.0, 116.7, 116.8, 124.9, 132.2, 133.8, 143.5, 146.1; IR (neat) 3583, 3390, 1645 cm^{-1}. ESI-HRMS calcd for $C_{32}H_{50}N_2O_3$ ($[M+H]^+$) 511.3894, found 511.3891.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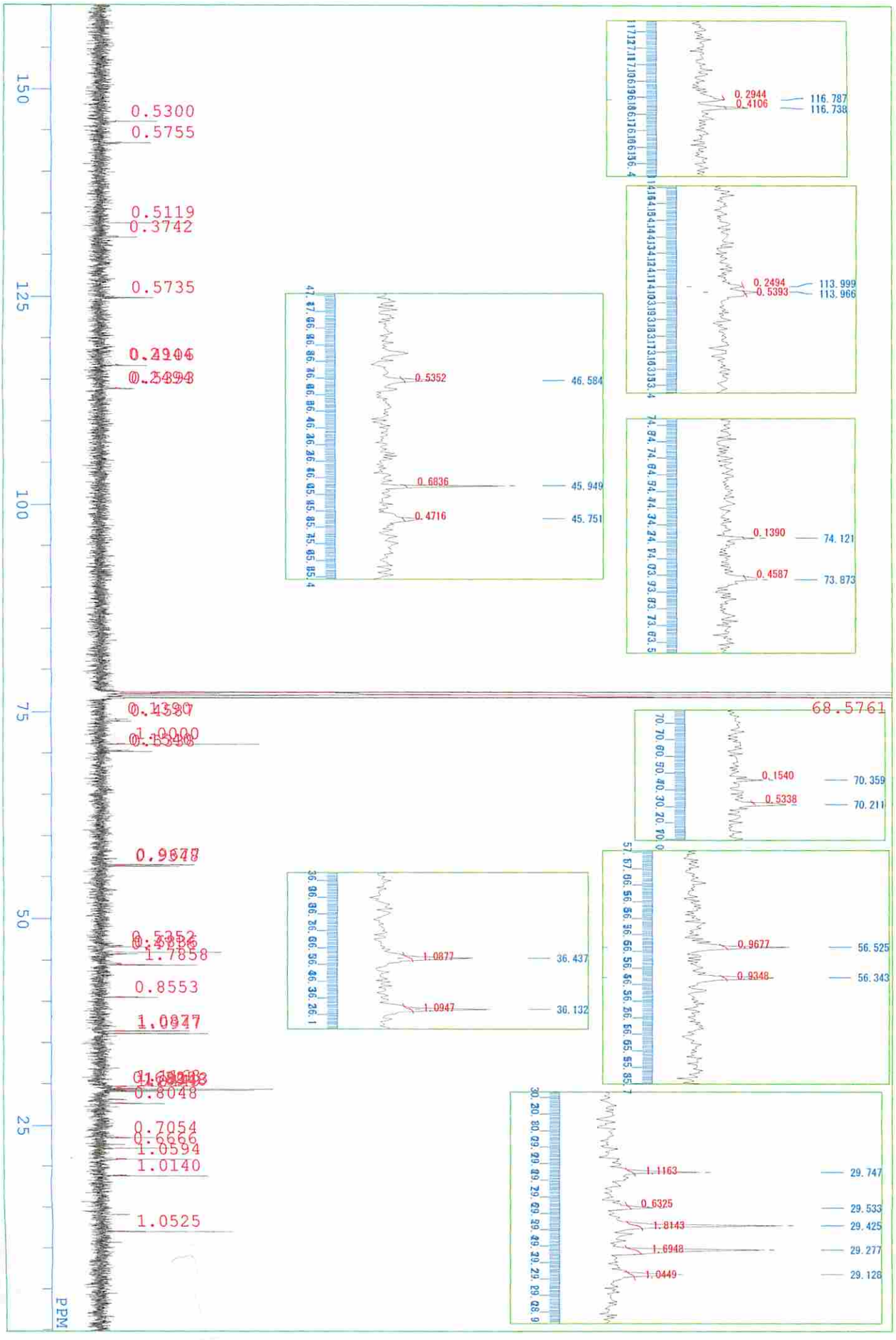
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0.8553
1.0877
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1.1163
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0.6325
29.533
1.8143
29.425
1.6948
29.277
1.0449
29.126

References for SI

(1) Honzawa, S.; Yamamoto, Y.; Hirasaka, K.; Takayama, H.; Kittaka, A. Synthesis of A-ring synthon of 2α-substituted vitamin D_3 analogues utilizing Grignard reaction towards methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside. *Heterocycles* **2003**, *61*, 327-338.

(2) Suhara, Y.; Nihei, K.; Kurihara, M.; Kittaka, A.; Yamaguchi, K.; Fujishima, T.; Konno, K.; Miyata, N.; Takayama, H. Efficient and versatile synthesis of novel 2α-substituted 1α,25-dihydroxyvitamin D_3 analogues and their docking to vitamin D receptors. *J. Org. Chem.* **2001**, *66*, 8760-8771.

(3) Maynard, D. F.; Trankle, W. G.; Norman, A. W.; Okamura, W. H. 14-Epi stereoisomers of 25-hydroxy- and lα,25-dihydroxyvitamin D_3: synthesis, isomerization to previtamins, and biological studies. *J. Med. Chem.* **1994**, *37*, 2387-2393.

human VDR binding assay

Binding affinity to hVDR was evaluated using a $1\alpha,25(OH)_2D_3$ assay kit (POLARSCREEN VITAMIN D RECEPTOR COMPETITOR ASSAY, RED, Cat. No. PV4569) purchased from Invitrogen. The solution of test compound (1 mM in EtOH) was diluted to 10 times with DMSO. The solution was diluted to 50 times with the assay buffer included in the kit more. The solution was defined as the compound solution. On the other hand, VDR/Fluoromone and VDR RED, both of which are included in the kit, were diluted with the assay buffer included in the kit so that the concentration of VDR/Fluoromone was 2.8 nM, and that of VDR RED was 2 nM in the mixture. The solution was defined as the VDR/Fluoromone and VDR RED complex. To a 384 well Black plate (Coring, #3677) was added the compound solution (10 μL), and the VDR/Fluoromone and VDR RED complex (10 μL) was added to each wells. The mixture was incubated under 20-25°C for 2 h. The polarized fluoresce in each wells was measured (384 nm, emission: 595 nm, excitation: 535 nm, time: 250 ms/well). All compounds were evaluated with N = 2 within the range from 10^{-6} M to 10^{-10} M. IC_{50} values were calculated by using the average of measured value. The activities of each compound were shown as relative value in which the activity of the natural hormone **1** was normalized to 100%.

Transactivation assay of human osteocalcin promoter

The human osteocalcin gene promoter fragment –838 / +10 was cloned into the reporter plasmid pGL3 (Promega) as reported. Human VDR and RXR gene were cloned into expression vector pcDNA3 (Invitrogen). Hos cells maintained in phenol red free DMEM (Invitrogen) containing 10% FCS (Invitrogen). Prior to transfections, the cells were plated in a 96 well plate at the density of 400,000 cells per well in the Opti-MEM (Invitrogen). The cells were transfected with human osteocalcin reporter vector (pGL3-hOc: 100 ng/well), human VDR and RXR expression vector (pcDNA-hVDR, pcDNA-hRXR: 10 ng/well) and phRL-TK (Promega: 25 ng/well) using 0.45 μL of Lipofectamine 2000 reagent (Invitrogen). After incubation at 37 °C for 3 h, the culture media were replaced to phenol red free DMEM containing 10% FCS. The cells were treated with ethanol vehicle or various concentrations of compounds (from 0.1 pM to 100 nM). After incubation at 37 °C for 24 h, the luciferase activity of the cells was quantitated by luminometer (Berthold) using Dual-Glo luciferase assay system (Promega).

X-ray co-crystallographic analysis

The human VDR LBD protein was the same construct and was purified and complexed by the same protocol as described in ref. 4. Crystallization experiments were performed using the hanging-drop vapor diffusion method. The ligand **1a** or **1b** was added to aliquots of the purified protein in a 5-fold molar excess. Crystallization conditions were similar conditions for the VDR LBD-1α,25$(OH)_2D_3$ complex crystals by mixing 1 μL of protein solution (10 mg/mL) with an equal volume of the reservoir solution, which contained 1.4 M ammonium sulfate with 0.1 M MES, pH 6.5 and equilibrating against 1 mL reservoir solution. Single crystals grew to suitable dimensions in 2-4 days. Crystals were cryo-protected in 30% glycerol and cooled at 79 K, and X-ray data were collected using beamline NW12 at the Photon Factory (PF). The data were processed using the HKL2000 software package (Otwinowski & Minor, 1997). We carried out molecular replacement using MOLREP (Vagin & Teplyakov, 1997) from CCP4 (Collaborative Computational Project, Number 4, 1994) with the coordinates of the VDR LBD-1α,25$(OH)_2D_3$ complex (PDB code 1DB1; the solvent molecules and 1α,25$(OH)_2D_3$ were removed) as the initial model. Refinement was carried out using the programs REFMAC (Murshudov et al., 1997). A sample containing a random 5% of the total reflections in the data set was excluded for R_{free} calculations. After rigid-body refinement, electron density for ligand **1a** or **1b** was clearly constructed using COOT (Emsley & Cowtan, 2004). Statistics of the data collection and final structure are summarized in Table 1. Figures were produced using DS Visualizer (Accelrys, http://accelrys.co.jp/).

Table 1. Data collection and refinement statistics

Values in parentheses are for the highest resolution shell.

Crystal data	hVDR LBD-**1a**	hVDR LBD-**1b**
PDB ID	4ITE	4ITF
Space group	$P2_12_12_1$	$P2_12_12_1$
Unit cell (Å) *a*	44.76	44.35
b	51.53	51.81
c	131.78	132.08
Data collection		
Beam line	NW12	NW12
Wavelength (Å)	1.0000	1.0000
Resolution (Å)	50.0-2.50	50.0-2.85
Total number of reflections	65685	53126
Unique reflections	11281	7647
R_{merge}[a] (%)	8.2(20.4)	12.0(34.4)
Completeness (%)	99.6(97.0)	99.8(100.0)
Multiplicity	3.2(2.9)	3.9(3.8)
Average I/σ (I)	21.3(5.77)	18.1(6.30)
Refined statistics		
R_{factor}[b] (%)	25.3	20.3
R_{free}[b] (%)	28.3	25.5
Ramachandran statistics		
Bond lengths (Å)	0.014	0.011
Bond angles (°)	1.69	1.52

[a] $R_{merge} = \Sigma\Sigma i | Ii - \langle I \rangle | / \Sigma \langle I \rangle$, where $\langle I \rangle$ is the mean intensity of N reflections with intensities Ii and common indices h, k and l.
[b] $R_{factor} = \Sigma_{hkl} || F_{obs} | - k | F_{calc} || / \Sigma_{hkl} | F_{obs} |$, where Fobs and F_{calc} are the observed and calculated structure factors, R_{free} is calculated for a randomly chosen 5% of reflections and R_{factor} is calculated for the remaining 95% of reflections.