Low pH-triggering Changes in Peptide Secondary Structures

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General.

Optical rotations $[\alpha]^{rt}_{D}$ were measured with a Jasco DIP-370 polarimeter using a 0.5 dm cell. Infrared spectra (IR) were recorded on a Shimadzu IR Affinity-1 spectrometer for conventional measurement (KBr or neat), or using the solution ($CDCl_3$) method with a 0.1 mm path-length of NaCl cell. ^{1}H NMR and ^{13}C NMR spectra were determined at JEOL AL 400 and Varian NMR System 500PS SN type spectrometers. FAB-MS spectra, DART-MS spectra, and MALDI-TOF-MS spectra were recorded with JEOL JMS-700N, JEOL JMS-T1000TD, and Bruker Ultrax spectrometers, respectively. X-ray crystallographic analyses were measured with Rigaku Varimax Saturn/1200S instrument.

Abbreviations.

Ac: acetyl; Cbz: benzyloxycarbonyl; dAA: α,α-disubstituted α-amino acid; *c*-Hex: cyclohexyl; CD: circular dichroism; dr: diastereomeric ratio; DIPEA: diisopropylamine; FTIR: Fourier transform infrared; HATU: *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HBTU: 1-[bis(dimethylamino)methylene]-1*H*-benzotriazolium 3-oxide hexafluorophosphate; HMDS: 1,1,1,3,3,3-hexamethyldisilazane; Hms: α-hydroxymethylserine; HOAt: 1-hydroxy-7-azabenzotriazole; HOBt: 1-hydroxybenzotriazole; Ipr: isopropyl; Leu: leucine; MALDI-TOF-MS: matrix-assisted laser desorption-ionization time-of-flight mass spectrometry; MCMM: Monte Carlo multiple minimum; Men: menthone; NOESY: nuclear Overhauser effect correlated spectroscopy; TFA: trifluoroacetic acid; TFE: 2,2,2-trifluoroethanol ; TMSOTf: trimethylsilyl trifluoromethanesulfonate

Synthesis of amino acids and peptides.

***N*-α-(Benzyloxcarbonyl)-*O,O*-cyclohexylidine-α-hydroxymethylserine Methyl Ester [Cbz-Hms(*c*-Hex)-OMe, 1b]**. 1,1,1,3,3,3-Hexamethyldisilazane (HMDS; 1.2 mL, 18 mmol) and trimethylsilyl trifluoromethanesulfonate (TMSOTf; 101 μL, 1.8 mmol) were added to a stirred solution of **2** (0.80 g, 9.1 mmol) in THF (30 mL). The reaction mixture was stirred at 0 °C for 90 min. The mixture was then diluted with Et_2O, washed with ice-cold water, and dried with MgSO4. The solvent was removed to give crude **TMS-2** (1.2 g, 96 %), which was used in the next reaction without further purification.

TMSOTf (1.7 μL, 9.2 μmol) was added to a stirred solution of **TMS-2** (98 mg, 0.23 mmol) and cyclohexanone (28 μL, 0.25 mmol) in CH_2Cl_2 (5 mL) at –78 °C, and the mixture was stirred at –78 °C for 18 h. NaOH (2 % in MeOH; 3 mL) was then added, and the mixture was stirred at room temperature for 2 h. The mixture was diluted with ice-cold water, and extracted with Et_2O. The combined organic extracts were washed with H_2O and dried with $MgSO_4$. The solvent was removed, and the residue was purified by column chromatography (70 % EtOAc in hexane) to give Cbz-Hms(*c*-Hex)-OMe (**1b**) (43 mg, 52%) as colorless crystals. M.p. 85–86 ˚C; IR (KBr) 3314, 3203, 3156, 3136, 2928, 2886, 2847, 2704, 2430, 2372, 2345, 2207, 1994, 1925, 1898, 1528, 1450, 1377, 1342, 1234, 1196, 1169, 1119, 1072, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.37 (m, 5H), 5.76 (br s, 1H), 5.10 (s, 2H), 4.24 (d, J = 12 Hz, 2H), 3.93 (d, J = 12 Hz, 2H), 3.74 (s, 3H), 1.85–1.92 (m, 2H), 1.41–1.65 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 155.1, 136.0, 128.5, 128.2, 128.1, 98.9, 67.0, 63.0, 56.6, 52.6, 52.5, 37.4, 26.8, 25.4, 22.4, 22.3; HRMS ($DART^+$) calcd for $C_{19}H_{26}NO_6$ $[M + H]^+$ 364.1760, found 364.1757.

Cbz-Hms(Ipr)-(L-Leu)$_2$-OMe (4a). The amine H-(L-Leu)$_2$-OMe (65 mg, 0.10 mmol) was added to a stirred solution of carboxylic acid **5a** (51 mg, 0.16 mmol), HATU (49 mg, 0.13 mmol), HOAt

(18 mg, 0.13 mmol), and DIEA (52 μL, 0.31 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 48 h, then the solvent was evaporated. EtOAc was added, and the mixture was washed with saturated $NaHCO_3$ aqueous solution and brine, and dried with $MgSO_4$. Removal of the solvent gave a white solid, which was purified by column chromatography on silica gel (80% EtOAc in hexane) to geive tripeptide **4a** (80 mg, 86%) as colorless crystals. M.p 102–104 °C; $[\alpha]^{22}_D$ = –18.8 (c 0.86 $CHCl_3$); IR (KBr) 3336, 3283, 3136, 3067, 3032, 2955, 2870, 2762, 2723, 2646, 2627, 2372, 2345, 2276, 2218, 1628, 1609, 1524, 1373, 1315, 1265, 1242, 1204, 1172, 1150, 1096, 1045, 1030, 976, 937, 833, 806, 741 cm^{-1}.; ^1H NMR (400 MHz, $CDCl_3$) 7.50 (d, *J* = 4 Hz, 1H), 7.32–7.38 (m, 5H), 6.86 (d, *J* = 4 Hz, 1H), 6.01 (br s, 1H), 5.09 (s, 2H), 4.58–4.63 (m, 2H), 4.49–4.52 (m, 2H), 3.95–3.99 (m, 2H), 3.70 (s, 3H), 1.63 (s, 3H), 1.53–1.82 (m, 6H), 1.49 (s, 3H), 0.91–0.96 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) 173.1, 171.5, 170.8, 155.1, 135.9, 128.6, 128.3, 127.9, 99.1, 66.9, 62.5, 62.2, 60.4, 53.9, 52.2, 50.6, 41.3, 40.1, 31.5, 24.9, 23.0, 22.6, 21.8, 21.6, 21.4, 21.0; HRMS (FAB^+) calcd for $C_{28}H_{43}N_3O_8$ $[M + H]^+$ 572.2948, found 572.2962.

Cbz-Hms(*c*-Hex)-(L-Leu)$_2$-OMe (4b). Tripeptide **4b** was prepared from **3b** and H-(L-Leu)$_2$-OMe in a manner similar to that described for the preparation of tripeptide **4a**. Yield 94%. Colorless oil. $[\alpha]^{21}_D$ = –6.87 (c 1.3 $CHCl_3$); IR ($CDCl_3$): 3367, 2956, 1734, 1683, 1558, 1314, 1155, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.1 Hz, 1H), 7.33–7.39 (m, 5H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.08 (s, 1H), 5.09 (s, 2H), 4.57–4.66 (m, 2H), 4.48–4.53 (m, 2H), 3.91–3.95 (m, 2H), 3.71 (s, 3H), 1.44–1.81 (m, 16H), 0.91–0.96 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 171.4, 170.8, 154.9, 135.7, 128.3, 128.0, 127.6, 99.0, 66.6, 61.4, 61.2, 60.1, 53.9, 52.0, 50.3, 41.0, 40.5, 34.8, 29.6, 25.2, 24.7, 24.6, 22.8, 22.6, 22.3, 22.1, 21.6, 21.5; HRMS (FAB^+) calcd for $C_{31}H_{47}N_3O_8Na$ $[M + Na]^+$ 612.3261, found 612.3216.

Cbz-(L-Leu)$_2$-Hms(Ipr)-(L-Leu)$_2$-OMe (5a). A mixture of Cbz-Hms(Ipr)-(L-Leu)$_2$-OMe **4a** (2.4 g, 4.4 mmol) and Pd/C (5%; 1.3 g) in MeOH (30 mL) was vigorously stirred for 3 h, the Pd/C catalyst was removed by filtration, and the filtrate was evaporated in vacuo to give crude **4a**-amine (1.7 g, 96%). The crude **4a**-amine (0.90 g, 2.2 mmol) was added to a stirred solution of carboxylic acid Cbz-(L-Leu)$_2$-OH (1.1 g, 3.0 mmol), HBTU (1.2 g, 3.3 mmol), HOBt (0.51 g, 3.8 mmol), and DIEA (1.1 mL, 6.6 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred at room temperature for 48 h, then the solvent was evaporated. EtOAc was added, and the mixture was washed with saturated $NaHCO_3$ aqueous solution, and brine, and dried with $MgSO_4$. Removal of the solvent gave a white solid, which was purified by column chromatography on silica gel (50% EtOAc in hexane) to give pentapeptide **5a** (1.2 g, 74%) as colorless crystals. M.p. 100–102 ˚C; $[\alpha]^{22}_D$ = –226 (c 1.05 $CHCl_3$); IR (KBr) 3329, 3036, 2959, 2870, 2766, 2723, 2646, 2608, 2573, 2372, 2345, 2276, 2203, 1994, 1636, 1524, 1439, 1373, 1265, 1227, 1204, 1169, 1123, 1096, 1042, 983, 937, 833, 756, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 6.9 Hz, 1H), 7.50 (d, *J* = 6.9 Hz, 1H), 7.27–7.40 (m, 6H), 7.20 (br s, 1H), 6.23 (br s, 1H), 5.11–5.22 (m, 2H), 4.39–4.49 (m, 2H), 4.29–4.37 (m, 2H), 4.09–4.21 (m, 2H), 3.94–4.04 (m, 2H), 3.63 (s, 3H), 1.55–1.86 (m, 12H), 1.50 (s, 3H), 1.37 (s, 3H), 0.79–1.00 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 174.3, 173.4, 173.1, 171.4, 157.2, 135.9, 128.5, 128.3, 128.2, 98.9, 67.5, 64.1, 62.3, 55.2, 54.1, 53.1, 52.4, 51.1, 40.2, 40.0, 39.7, 39.5, 24.9, 24.81, 24.75, 24.7, 23.2, 23.0, 22.9, 22.8, 21.8, 21.7, 21.6, 21.3, 21.0; HRMS (FAB$^+$) calcd for $C_{40}H_{66}N_5O_{10}$ $[M + H]^+$ 776.4804, found 776.4814.

Cbz-(L-Leu)$_2$-Hms(*c*-Hex)-(L-Leu)$_2$-OMe (5b). Pentapeptide **5b** was prepared from tripeptide **4b** and Cbz-(L-Leu)$_2$-OH in a manner similar to that described for the preparation of pentapeptide **5a**. Yield 53%. Colorless crystals. M.p 150–152 ˚C; $[\alpha]^{21}_D$ = –55.4 (c 0.42, $CHCl_3$); IR ($CDCl_3$): 3429, 3348, 2959, 1734, 1681, 1506, 1253, 1217 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.34–7.39 (m, 6H), 7.22 (d, J = 8.3 Hz, 1H), 7.13 (br s, 1H), 6.68 (d, J = 5.8 Hz, 1H), 5.29 (d, J = 5.8 Hz, 1H), 5.15 (s, 2H), 4.52–4.54 (m, 1H), 4.39–4.43 (m, 2H), 4.07–4.27 (m, 5H), 3.68 (s, 3H), 1.40–1.93 (m, 22H), 0.87–0.96 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 172.5, 171.1, 170.1, 156.8, 135.8, 128.6, 128.5, 128.3, 98.8, 67.6, 63.1, 61.2, 56.9, 54.6, 53.8, 52.4, 52.1, 50.9, 40.4, 40.3, 40.2, 40.0, 29.8, 25.5, 25.0, 24.8, 24.73, 24.65, 23.3, 22.99, 22.93, 22.88, 22.81, 22.4, 21.9, 21.8, 21.7, 21.6, 21.2; HRMS (FAB$^+$) calcd for $C_{43}H_{69}N_5O_{10}Na$ [M^++Na] 838.4942, found 838.4948.

Cbz-Hms(Ipr)-(L-Leu)$_2$-Hms(Ipr)-(L-Leu)$_2$-OMe (6a). A mixture of Cbz-(L-Leu)$_2$-Hms(Ipr)-(L-Leu)$_2$-OMe **5a** (275 mg, 0.35 mmol) and Pd/C (10%; 132 mg) in MeOH (15 mL) was vigorously stirred for 2 h, the Pd/C catalyst was removed by filtration, and the filtrate was evaporated in vacuo to give crude **5a**-amine (215 mg, 97%). The crude **5a**-amine (65 mg, 0.10 mmol) was added to a stirred solution of carboxylic acid **3a** (51 mg, 0.16 mmol), HATU (49 mg, 0.13 mmol), HOAt (18 mg, 0.13 mmol), and DIEA (52 μL, 0.31 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 48 h, then the solvent was evaporated. EtOAc was added, and the mixture was washed with saturated $NaHCO_3$ aqueous solution, and brine, and dried with $MgSO_4$. Removal of the solvent gave a white solid, which was purified by column chromatography on silica gel (80% EtOAc in hexane) to give hexapeptide **6a** (80 mg, 86%) as colorless crystals. M.p. 102–104 ˚C; $[\alpha]^{22}_D$ = +9.79 (c 1.32, $CHCl_3$); IR (KBr) 3336, 3283, 3136, 3067, 3032, 2955, 2870, 2762, 2723, 2646, 2627, 2372, 2345, 2276, 2218, 1628, 1609, 1524, 1373, 1315, 1265, 1242, 1204, 1172, 1150, 1096, 1045, 1030, 976, 937, 833, 806, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.34–7.41 (m, 7H), 7.21 (d, J = 7.0 Hz, 1H), 7.06 (s, 1H), 7.05 (brs, 1H), 6.00 (s, 1H), 5.10–5.21 (m, 2H), 4.48–4.52 (m, 2H), 4.34–4.40 (m, 2H), 4.00–4.28 (m, 6H), 3.93–3.98 (m, 1H), 3.86–3.91 (m, 1H), 3.68 (s, 3H), 1.59–1.88 (m, 12H), 1.51 (s, 6H), 1.47 (s, 3H), 1.32 (s, 3H),

0.86–0.98 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$): 174.11, 174.08, 174.0, 173.0, 171.4, 156.7, 135.4, 128.7, 128.5, 127.8, 99.3, 98.4, 67.6, 64.9, 64.7, 62.2, 61.6, 57.6, 52.9, 52.3, 51.1, 39.8, 39.3, 25.04, 25.01, 24.8, 24.6, 23.3, 23.1, 22.9, 22.7, 21.6, 21.4, 21.2, 21.0; HRMS (FAB$^+$) calcd for $C_{47}H_{77}N_6O_{13}$ $[M + H]^+$ 933.5543, found 933.5544.

Cbz-Hms(*c*-Hex)-(L-Leu)$_2$-Hms(*c*-Hex)-(L-Leu)$_2$-OMe (6b). Hexapeptide **6b** was prepared from pentapeptide **5b** and carboxylic acid **3b** in a manner similar to that described for the preparation of hexapeptide **6a**. Yield 40%. Colorless crystals. M.p 217–218 ˚C; $[\alpha]^{22}_D = -20.0$ (c 0.52, $CHCl_3$); IR ($CDCl_3$) 3336, 2958, 1749, 1670, 1521, 1256 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (brs, 1H), 7.33–7.41 (m, 6H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.19 (brs, 1H), 7.07 (s, 1H), 6.11 (s, 1H), 5.08–5.20 (m, 2H), 4.47–4.52 (m, 3H), 4.36–4.39 (m, 2H), 4.24–4.27 (m, 1H), 4.03–4.19 (m, 4H), 3.89–3.96 (m, 2H), 3.66 (s, 3H), 1.38–2.08 (m, 32H), 0.85–0.98 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 173.4, 173.1, 172.9, 156.4, 135.4, 128.6, 128.5, 127.6, 99.5, 98.2, 67.5, 64.2, 64.0, 61.4, 60.7, 58.2, 56.5, 54.9, 54.4, 52.3, 51.9, 51.0, 40.1, 40.0, 39.7, 39.4, 37.3, 27.6, 25.5, 25.3, 25.1, 25.0, 24.9, 24.5, 23.4, 23.1, 22.9, 22.7, 22.4, 22.33, 22.31, 21.6, 21.5, 21.2, 20.9; HRMS (FAB$^+$) calcd for $C_{53}H_{84}N_6O_{13}Na$ $[M + Na]^+$ 1035.5994, found 1013.6174.

Cbz-(L-Leu)$_2$-Hms(Ipr)-(L-Leu)$_2$-Hms(Ipr)-(L-Leu)$_2$-OMe (7). Cbz-Hms(Ipr)-(L-Leu)$_2$-Hms(Ipr)-(L-Leu)$_2$-OMe **6a** (80 mg, 90 μmol) and Pd/C (10%; 26 mg) in MeOH (5 mL) was vigorously stirred for 5 h, the Pd/C catalyst was removed by filtration, and the filtrate was evaporated in vacuo to give crude **6a**-amine (64 mg, 93%). The crude **6a**-amine (162 mg, 0.20 mmol) was added to a stirred solution of Cbz-(L-Leu)$_2$-OH (231 mg, 0.61 mmol), HATU (232 mg, 0.61 mmol), HOAt (83 mg, 0.61 mmol), and DIEA (106 μL, 0.61 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred at room temperature for 18 h, then the solvent was evaporated.

EtOAc was added, and the mixture was washed with saturated $NaHCO_3$ aqueous solution, and brine, and dried with $MgSO_4$. Removal of the solvent gave a white solid, which was purified by column chromatography on silica gel (X% EtOAc in hexane) to give octapeptide **7** (58 mg, 25%) as colorless crystals. M.p 232–234 ˚C; $[\alpha]^{22}_D$ = –1.85 (c 1.26, CH_3OH); IR ($CDCl_3$) 3421, 3325, 2958, 1663, 1528, 1265 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 8.30 (d, J = 5.9 Hz, 1H), 7.88 (d, J = 4.2 Hz, 1H), 7.60 (s, 1H), 7.55 (d, J = 5.9 Hz, 1H), 7.48–7.50 (m, 2H),7.30–7.40 (m, 6H), 7.09 (d, J = 2.6 Hz, 1H), 5.09–5.24 (m, 2H), 3.93–4.53 (m, 14H), 3.62 (s, 3H), 1.50–2.02 (m, 18H), 1.47 (s, 3H), 1.44 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H), 0.78–1.08 (m, 36H); HRMS (FAB^+) calcd for $C_{59}H_{98}N_8O_{15}Na$ $[M + Na]^+$ 1181.7049, found 1181.7061.

Ac-(L-Leu)$_2$-Hms(Ipr)-(L-Leu)$_2$-Hms(Ipr)-(L-Leu)$_2$-OMe (8). Octapeptide **8** was prepared from hexapeptide **6a** and Ac-(L-Leu)$_2$-OH in a manner similar to that described for the preparation of octapeptide **7**. Yield 20%. Colorless crystals. M.p 264–265 ˚C; $[\alpha]^{22}_D$ = –0.87 (c 0.23, CH_3OH); IR ($CDCl_3$) 3429, 3321, 2959, 1723, 1658, 1535, 1253 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 8.28 (br s, 1H), 7.96 (br s, 1H), 7.88 (d, J = 3.6 Hz, 1H), 7.65 (d, J = 5.6 Hz, 1H), 7.49–7.52 (m, 2H), 7.37-7.41 (m, 1H), 7.30 (br s, 1H), 3.91–4.49 (m, 14H), 3.63 (s, 3H), 1.29-1.90 (m, 33H), 0.83–1.00 (m, 36H); HRMS (FAB^+) calcd for $C_{53}H_{94}N_8O_{14}Na$ $[M + Na]^+$ 1089.6787, found 1089.6787.

Cbz-(L-Leu)$_2$-Hms(*c*-Hex)-(L-Leu)$_2$-Hms(*c*-Hex)-(L-Leu)$_2$-OMe (9). Octapeptide **9** was prepared from hexapeptide **6b** and Cbz-(L-Leu)$_2$-OH in a manner similar to that described for the preparation of octapeptide **7**. Yield 12%. Colorless crystals. M.p 260–262 ˚C; $[\alpha]^{22}_D$ = –10.3 (c 0.37, CH_3OH); IR ($CDCl_3$) 3429, 3337, 2959, 1659, 1531, 1261 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 8.30 (d, J = 3.4 Hz, 1H), 7.93 (d, J = 5.4 Hz, 1H), 7.79 (s, 1H), 7.68 (d, J = 3.8 Hz,

1H), 7.61 (d, J = 7.5 Hz, 1H), 7.38–7.40 (m, 5H), 7.23 (d, J = 7.5 Hz, 1H), 7.19 (s, 1H), 7.12 (d, J = 3.8 Hz, 1H), 5.10–5.27 (m, 2H), 3.80–4.51 (m, 14H), 3.62 (s, 3H), 1.28–2.00 (m, 38H), 0.78–1.03 (m, 36H); HRMS (FAB^+) calcd for $C_{65}H_{106}N_8O_{15}Na$ $[M + Na]^+$ 1261.7675, found 1261.7474.

Ac-(L-Leu)$_2$-Hms(*c*-Hex)-(L-Leu)$_2$-Hms(*c*-Hex)-(L-Leu)$_2$-OMe (10). Octapeptide **10** was prepared from hexapeptide **6b** and Ac-(L-Leu)$_2$-OH in a manner similar to that described for the preparation of octapeptide **7**. Yield 5%. Colorless crystals. M.p. 250–251 ˚C; $[\alpha]^{22}_D$ = +6.90 (c 1.3, CH_3OH); IR ($CDCl_3$) 3441, 3325, 2959, 1659, 1536, 1265 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.32 (d, J = 4.9 Hz, 1H), 7.99 (d, J = 4.2 Hz, 1H), 7.96 (s, 1H), 7.88 (d, J = 4.4 Hz, 1H), 7.65 (d, J = 5.4 Hz, 1H), 7.50 (d, J = 5.9 Hz, 1H), 7.38 (d, J = 8.3 Hz, 1H), 7.31 (s, 1H), 3.90–4.48 (m, 14H), 3.62 (s, 3H), 1.29–2.01 (m, 41H), 0.84–0.99 (m, 36H); HRMS (FAB^+) calcd for $C_{59}H_{102}N_8O_{14}Na$ $[M + Na]^+$ 1169.7413, found 1169.7430.

Ac-(L-Leu)$_2$-Hms-(L-Leu)$_2$-Hms-(L-Leu)$_2$-OMe (11). Octapeptide **8** (10.5 mg, 9 μmol) in 2 M HCl/MeOH (13.7 μL, 27 μmol) was stirred at room temperature for 30 min. Removal of the solvent gave a crude peptide, which was purified by HPLC (solvent A: 0.05% TFA in H_2O; solvent B: 0.05% in CH_3CN; from 95% to 5% solvent A over 30 min) to give octapeptide **11** (3.5 mg, 39%) as colorless crystals. M.p. 137–138 ˚C; $[\alpha]^{22}_D$ = –20.8 (c 0.83, CH_3OH); IR ($CDCl_3$) 3630, 3421, 3356, 2959, 2360, 1670, 1203, 1172 cm^{-1}; ^1H NMR (500 MHz, CD_3OH) δ 8.36 (d, J = 5.6 Hz, 1H), 8.32 (d, J = 5.6 Hz, 1H), 8.06 (d, J = 6.7 Hz, 1H), 7.97 (d, J = 6.7 Hz, 1H), 7.82 (d, J = 5.0 Hz, 1H), 7.61 (s, 1H), 7.49(d, J = 7.4 Hz, 1H), 7.39 (s, 1H), 3.16–4.42 (m, 14H), 3.69 (s, 3H), 2.81–2.90 (m, 4H), 1.99–2.03 (m, 3H), 1.55–1.90 (m, 18H), 0.86–1.02 (m, 36H); HRMS (FAB^+) calcd for $C_{47}H_{86}N_8O_{14}Na$ $[M + Na]^+$ 1009.6161, found 1009.6154.

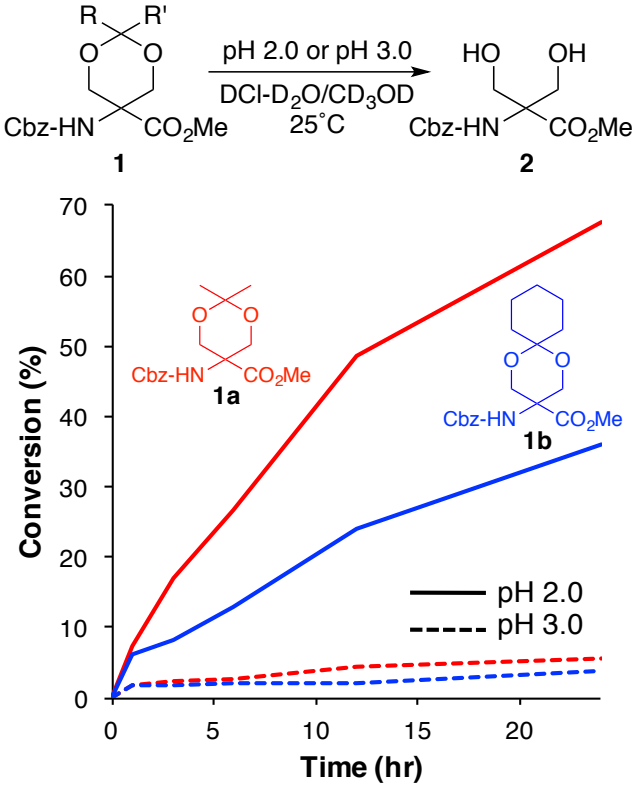


Figure S1. Conversion of acetal **1** into diol **2** under the acidic conditions of pH 2.0 (solid line) or pH 3.0 (dash line) DCl-D_2O/CD_3OD (50/50) at 25˚C. The concentration of acetal **1** was 10 mM.

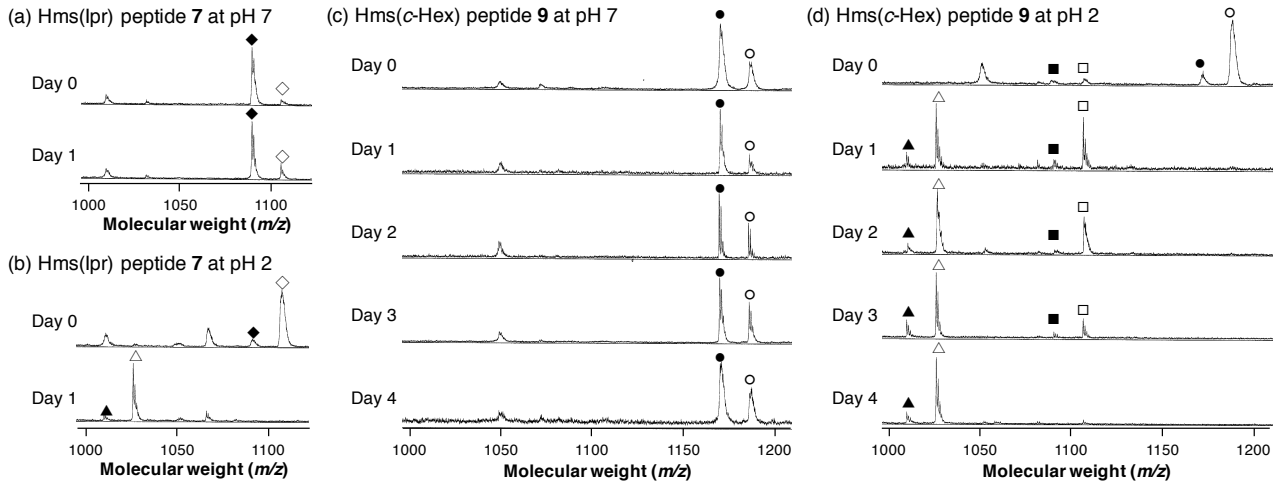


Figure S2. Time-dependent MALDI-TOF-MS spectra of the Hms(Ipr) octapeptide **7** (a, b) and Hms(*c*-Hex) octapeptide **9** (c, d) in TFE/H_2O (50/50) at pH 7 (a, c) and pH 2 containing HCl (b, d). Diamonds: the Hms(Ipr) octapeptide **7**; triangles: the Hms octapeptide **11**; circles: the Hms(*c*-Hex) octapeptide **9**; squares: an octapeptide containing one Hms and one Hms(*c*-Hex) (closed: Na^+ salt; open: K^+ salt). Peptide concentration: 50 μM.

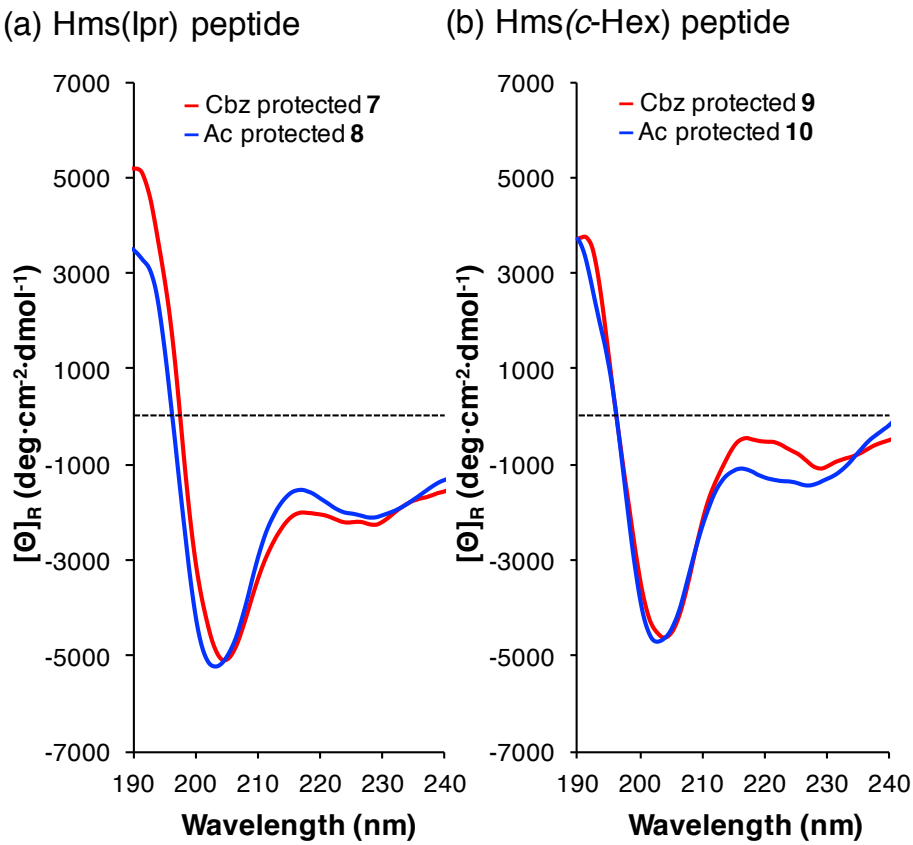


Figure S3. CD spectra of a) Hms(Ipr) octapeptides **7** and **8**, and b) Hms(*c*-Hex) octapeptides **9** and **10**. The peptide concentration was 0.1 mM in TFE.

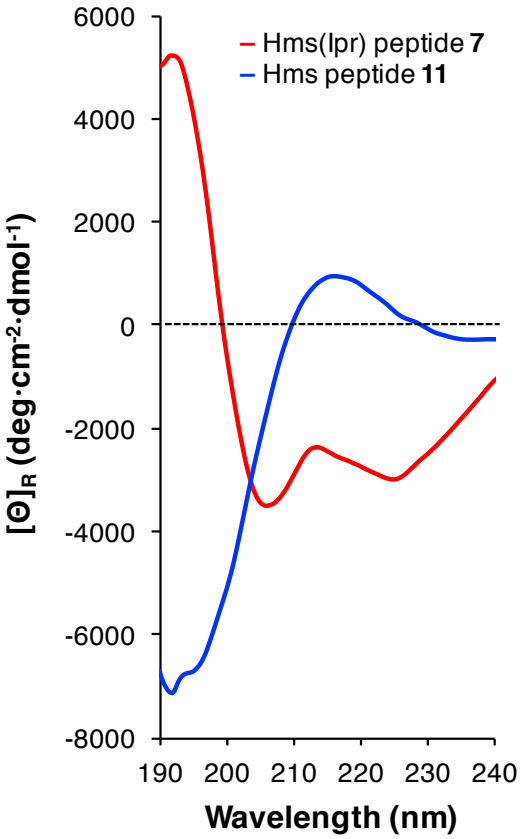


Figure S4. CD spectra of Hms(Ipr) octapeptides **7** and Hms octapeptides **11**. The peptide concentration was 0.1 mM in MeOH/H_2O (50/50).

Table S1. Crystal and diffraction parameters of the Hms(Ipr) octapeptide **7**.

empirical formula	$2(C_{59}H_{98}N_8O_{15})$, $3(C_2H_6O)$
Mr	2457.12
crystal diameters [mm]	0.25 × 0.06 × 0.02
crystal system	triclinic
lattice parameters:	
a, *b*, *c* [Å]	11.908, 17.703, 17.953
α, β, γ [°]	84.06, 70.79, 86.23
V [Å^3]	3552.7
space group	*P1*
Z value	1
D calc [g/cm^3]	1.148
μ (Mo$K\alpha$) [cm^{-1}]	0.083
no. of observations	12744 ($I > 2\sigma(I)$)
no. of variables	1559
R_1, R_w	0.0998, 0.3067
Solvent	EtOH/$CHCl_3$

Table S2. Selected torsion angles ω, ϕ, ψ, and χ [˚] for the Hms(Ipr) octapeptide **7** as determined by an X-ray crystallographic analysis.

	Molecule A	Molecule B
ψ0	–173.3	179.8
ω0	–167.5	–170.1
ϕ1	–60.6	–60.1
ψ1	–46.2	–43.9
ω1	–177.7	179.8
ϕ2	–54.3	–55.3
ψ2	–51.8	–51.6
ω2	–178.7	–178.1
ϕ3	–56.2	–52.7
ψ3	–47.9	–50.6
ω3	–177.2	–179.1
ϕ4	–62.0	–61.1
ψ4	–40.8	–44.9
ω4	177.6	–178.9
ϕ5	–64.8	–57.4
ψ5	–37.4	–46.7
ω5	177.7	–178.3
ϕ6	–62.0	–62.2
ψ6	–36.3	–28.1
ω6	–179.3	–179.9
ϕ7	–81.8	–91.9
ψ7	–38.1	–19.0
ω7	–172.5	–169.6
ϕ8	–104.3	–116.2
ψ8	–96.3	–106.3
ω8	173.7	177.5
χ1	170.2	–179.2
χ2	–175.7	–175.6
χ3	66.0	64.2
χ3’	–67.9	–64.9
χ4	–65.7	–67.9

χ5	–70.9	178.3
χ6	61.7	67.8
χ6’	–60.8	–69.3
χ7	–59.8	–60.9
χ8	–63.2	–65.6

Table S3. Intra- and intermolecular H-bond parameters for the Hms(Ipr) octapeptide **7**.

Peptide[a)]	Donor D–H	Acceptor A	Distance [Å] D···A	Angle [°] D–H···A	Symmetry operation
A	N_{4a}–H	O_{0a}	3.09	167	x, y, z
	N_{5a}–H	O_{1a}	2.96	166	x, y, z
	N_{6a}–H	O_{2a}	3.03	161	x, y, z
	N_{7a}–H	O_{3a}	3.17	150	x, y, z
	N_{8a}–H	O_{4a}	2.87	151	x, y, z
B	N_{4b}–H	O_{0b}	3.06	169	x, y, z
	N_{5b}–H	O_{1b}	2.83	167	x, y, z
	N_{6b}–H	O_{2b}	3.02	168	x, y, z
	N_{7b}–H	O_{3b}	3.24	139	x, y, z
	N_{7b}–H	O_{4b}	3.07	132	x, y, z
	N_{8b}–H	O_{4b}	2.94	124	x, y, z
	EtO–H (*i*)	$O_{EtO–H\ (iii)'}$	2.75	148	x, –1+y, –1+z
	N_{1a}–H	$O_{6b'}$	2.90	141	x, 1+y, 1+z
	EtO–H (*ii*)	$O_{7b'}$	2.81	159	x, y, 1+z
	N_{1b}–H	O_{6a}	2.81	161	x, y, z
	N_{2b}–H	O_{7a}	2.92	151	x, y, z
	EtO–H (*iii*)	O_{6b}	2.77	132	x, y, z

[a)] The number of amino acid residues began at the N-terminus of the peptide chain.

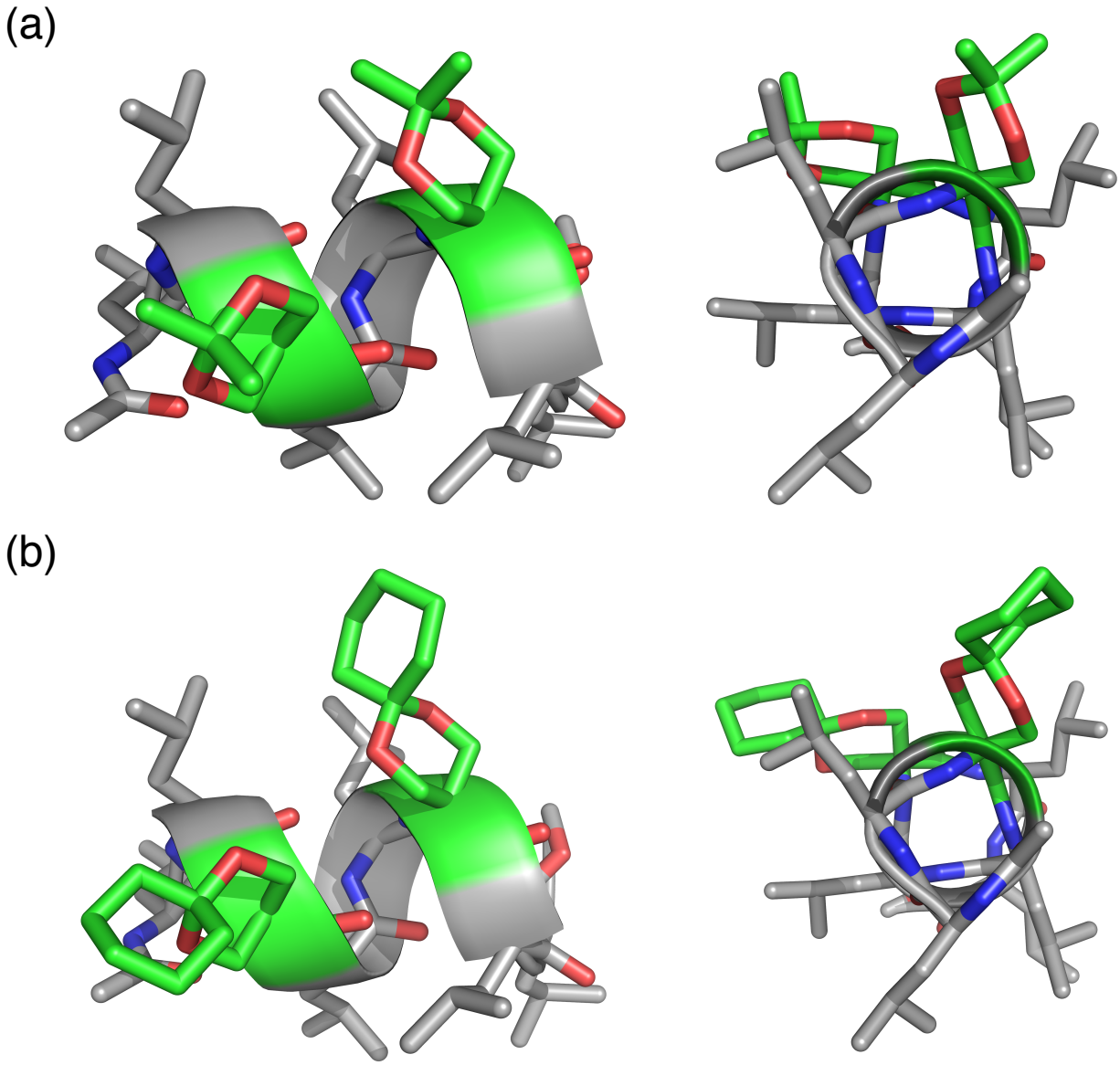
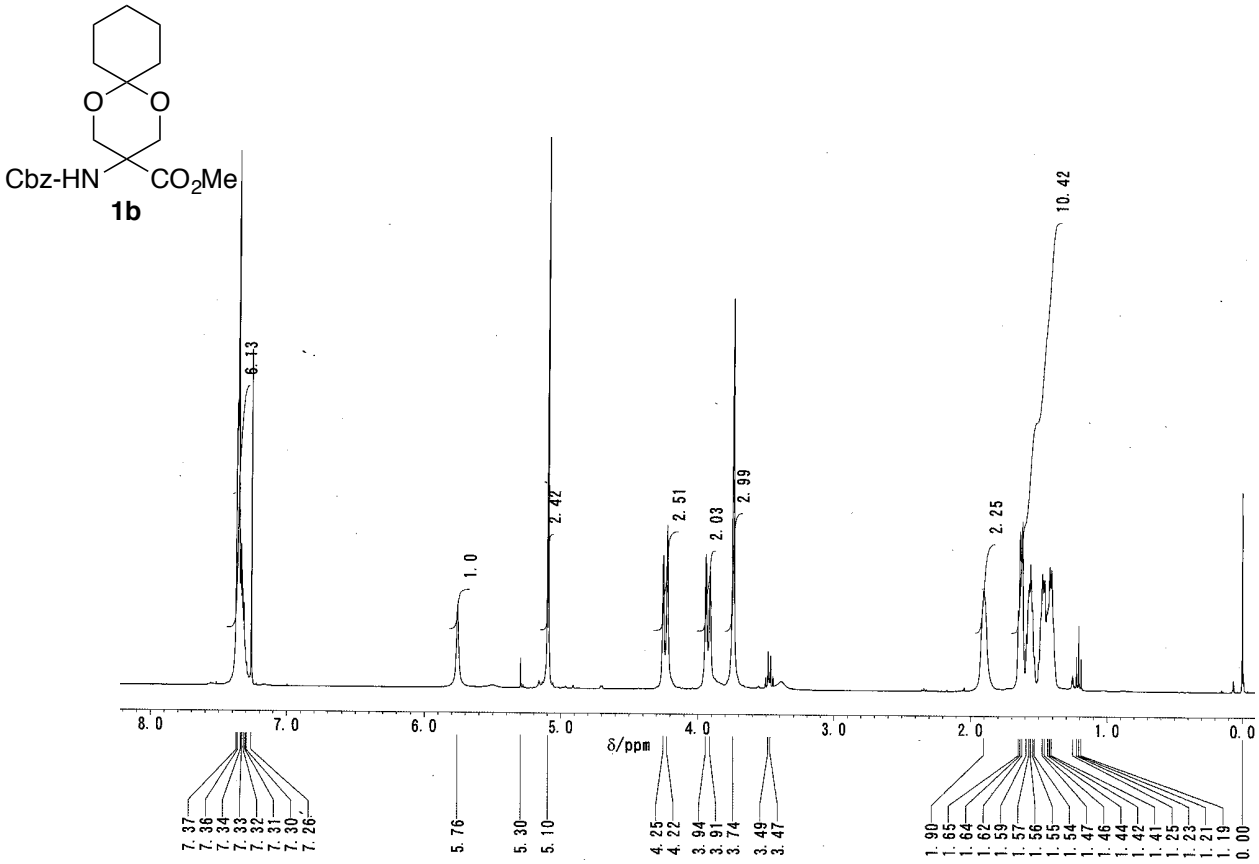


Figure S5. The calculated minimum energies for α-helical structures of a) Hms(Ipr) octapeptide **8** and b) Hms(*c*-Hex) octapeptide **10**. Hms(Ipr) and Hms(*c*-Hex) residues are highlighted in green.


Cbz-HN
CO2Me
1b
6.13
1.0
2.42
2.51
2.03
2.99
2.25
10.42
δ/ppm
7.37
7.36
7.34
7.33
7.32
7.31
7.30
7.26
5.76
5.30
5.10
4.25
4.22
3.94
3.91
3.74
3.49
3.47
1.90
1.65
1.64
1.62
1.59
1.57
1.56
1.55
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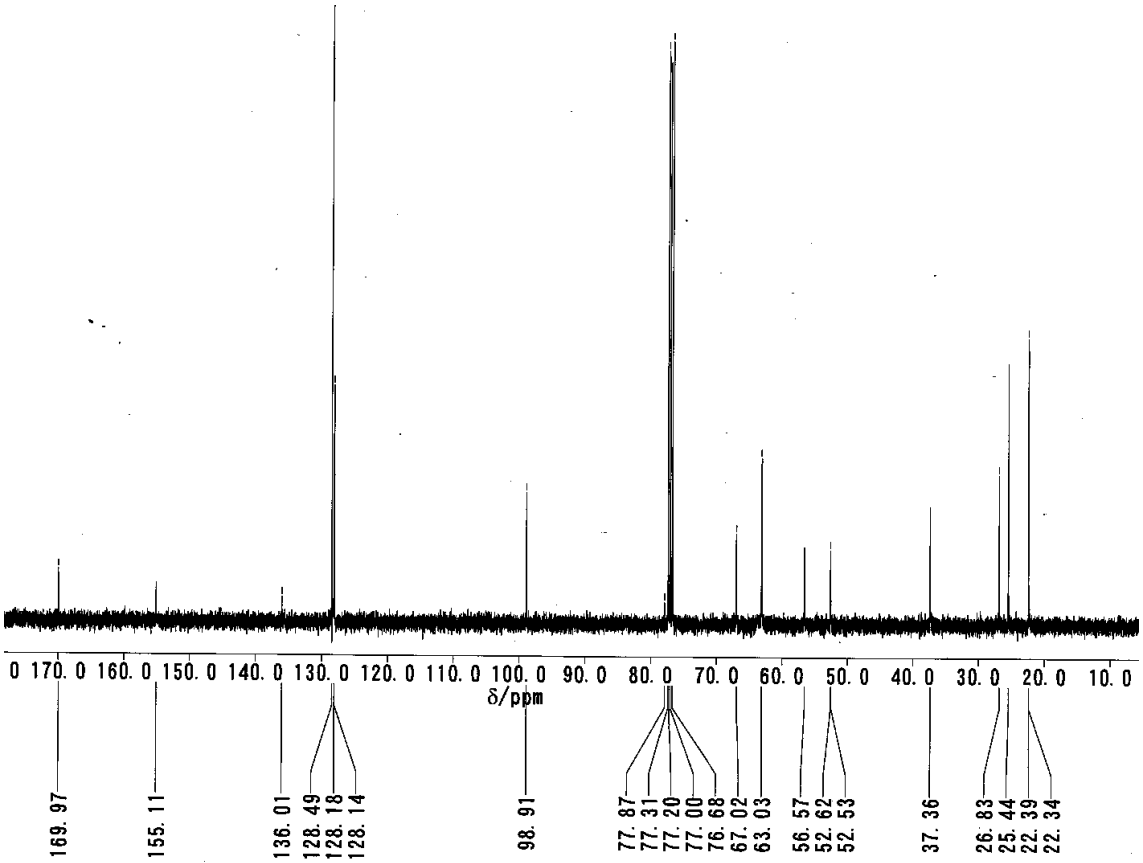
1.41
1.25
1.23
1.21
1.19
0.00


δ/ppm
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155.11
136.01
128.49
128.18
128.14
98.91
77.87
77.31
77.20
77.00
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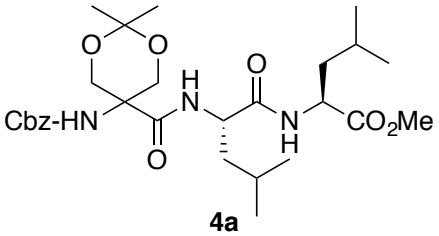
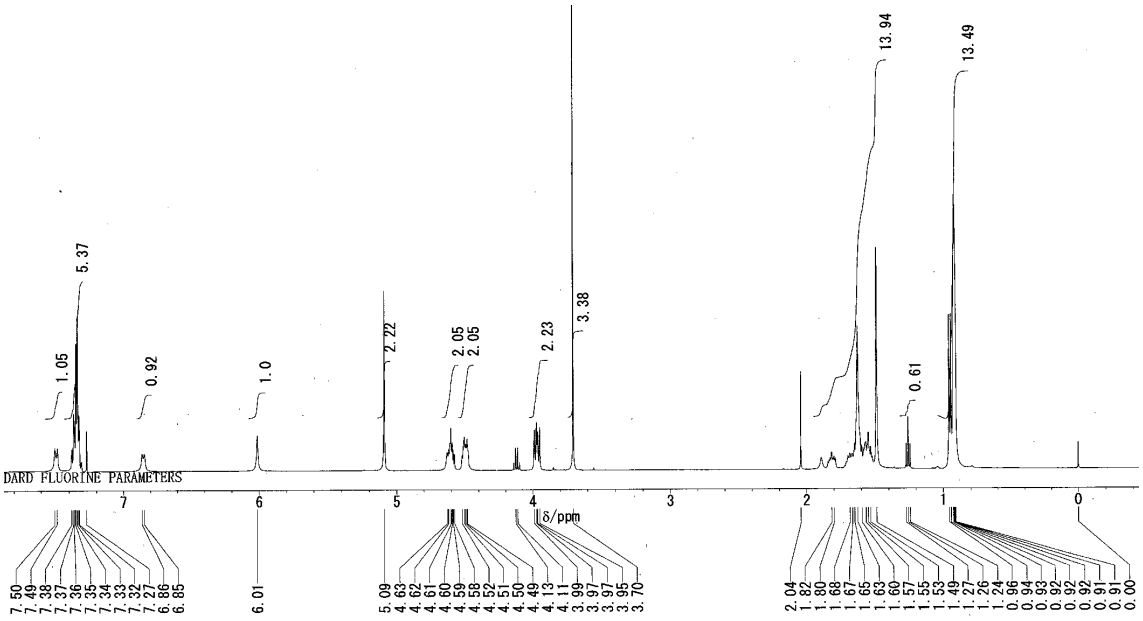
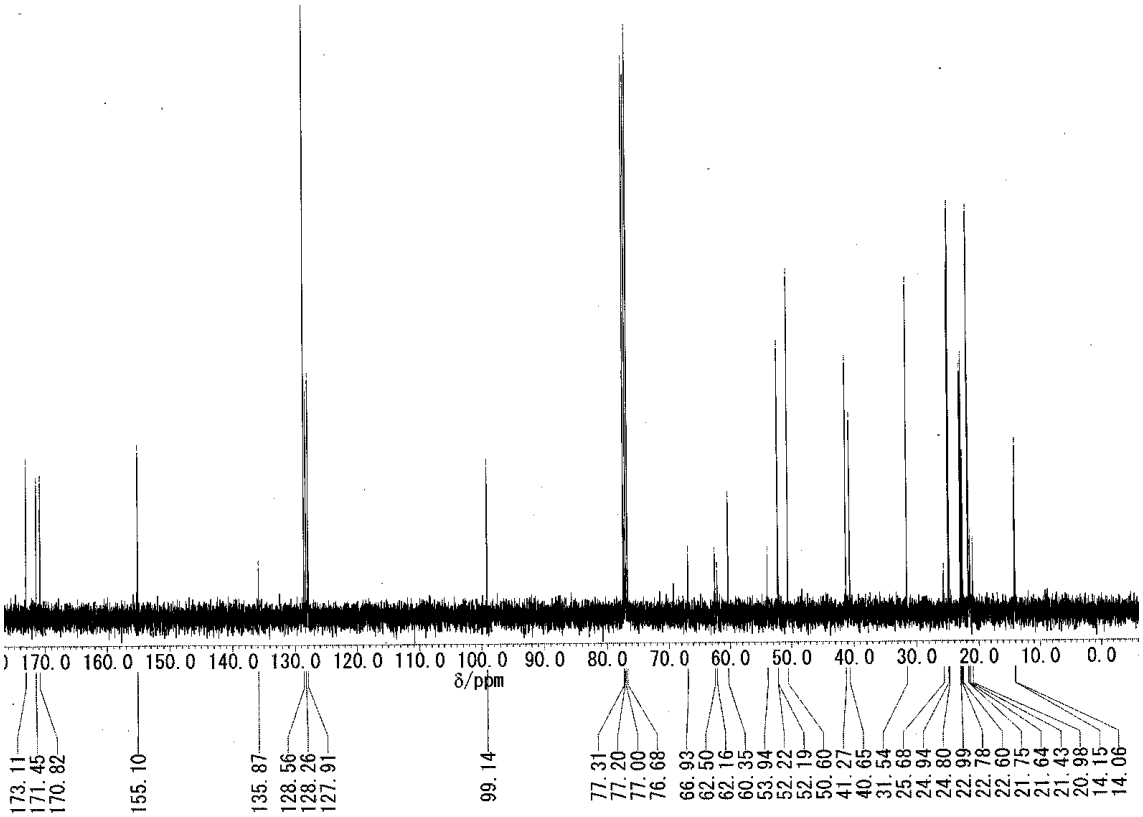
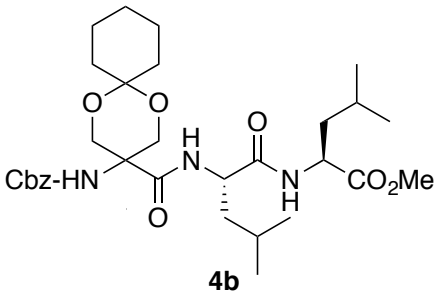
52.53
37.36
26.83
25.44
22.39
22.34


Cbz-HN
O
O
H
N
O
N
H
CO2Me
O

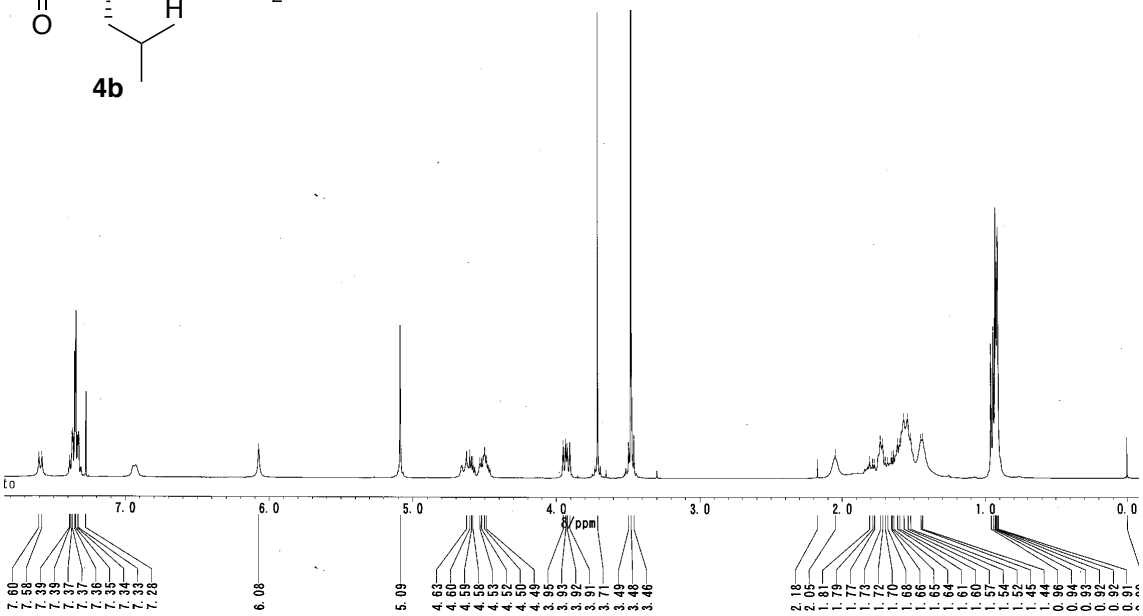
4a


13.94
13.49
5.37
3.38
2.22
2.05
2.05
2.23
1.05
0.92
1.0
0.61
DARD FLUORINE PARAMETERS
δ/ppm


δ/ppm


Cbz-HN
O
O
H
N
O
N
H
CO2Me
O

4b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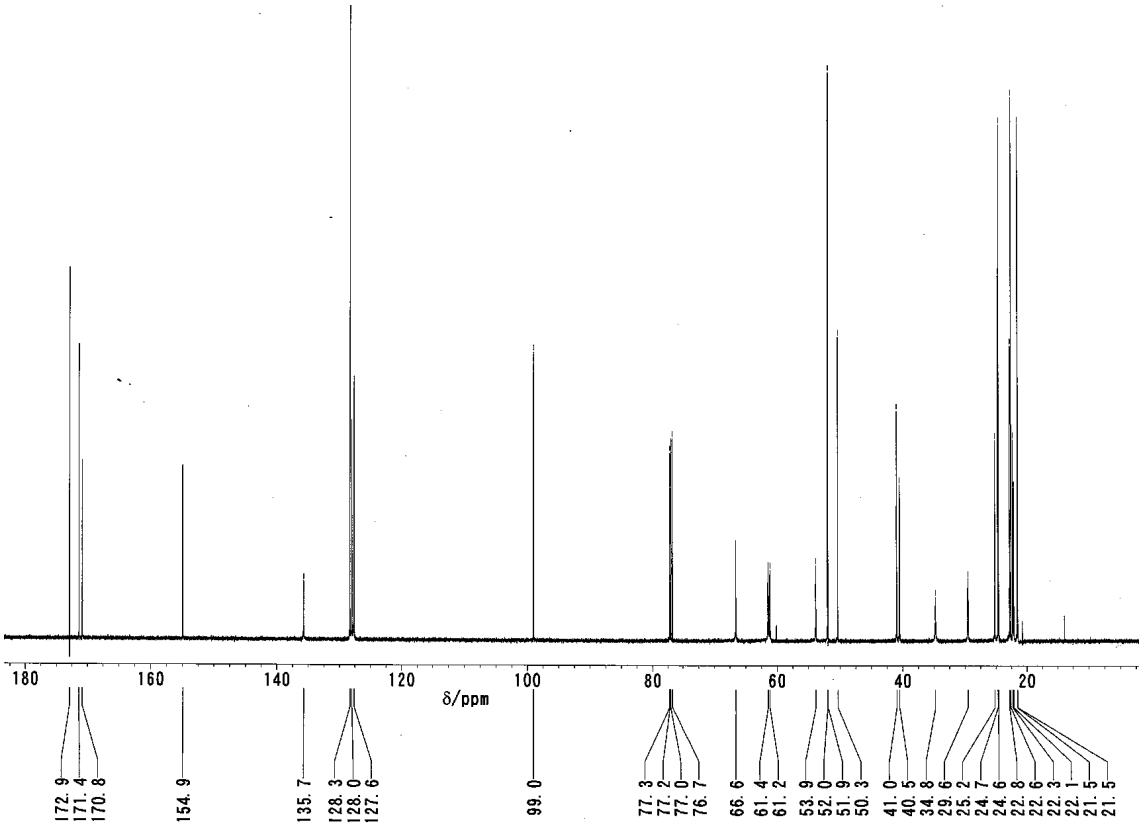
6.0
5.0
4.0
3.0
2.0
1.0
0.0
δ/ppm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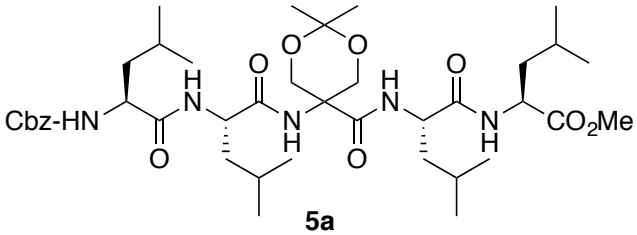
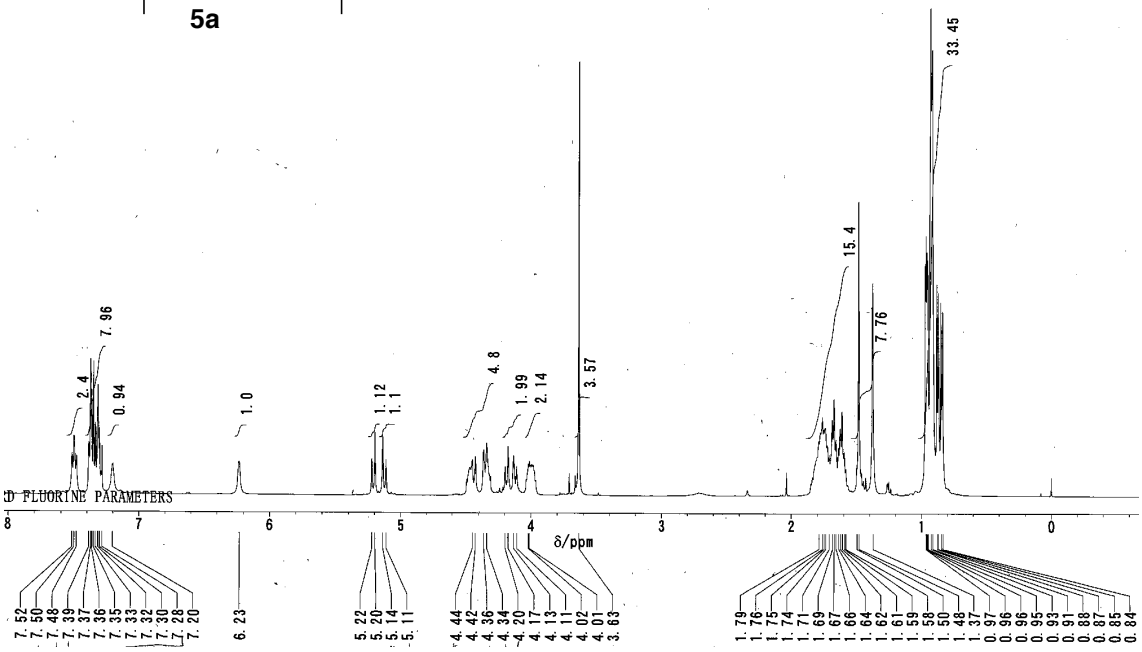
160
140
120
100
80
60
40
20
δ/ppm


Cbz-HN
O
H
N
O
N
H
O
O
O
H
N
O
N
H
CO2Me

5a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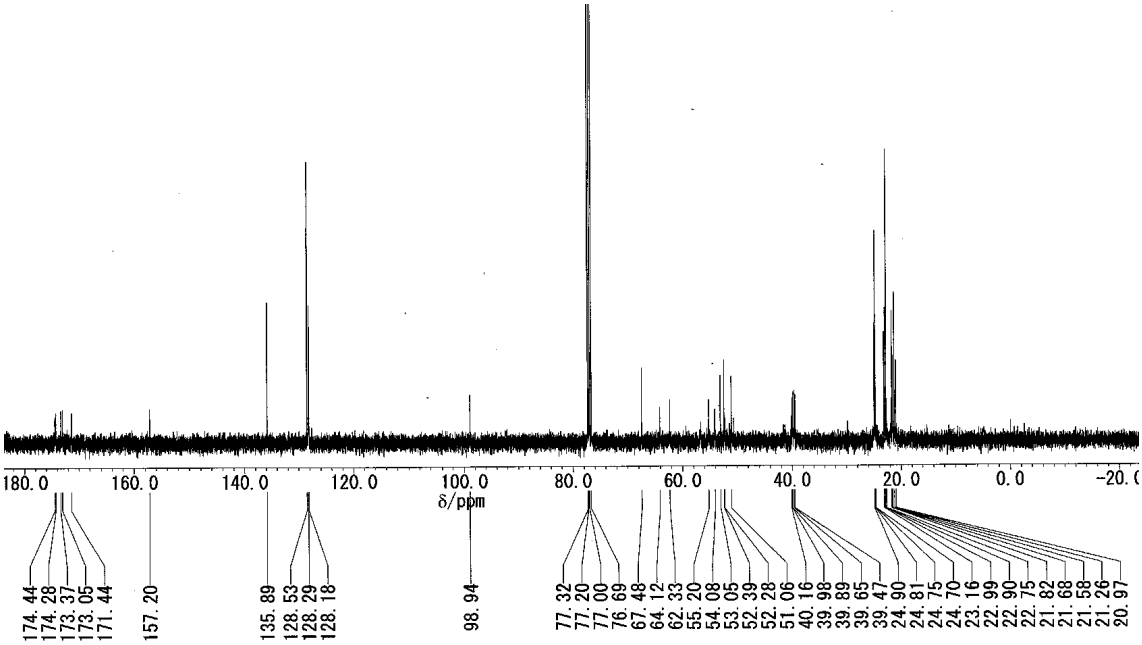
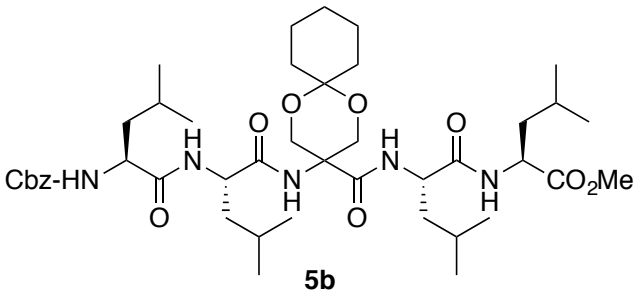
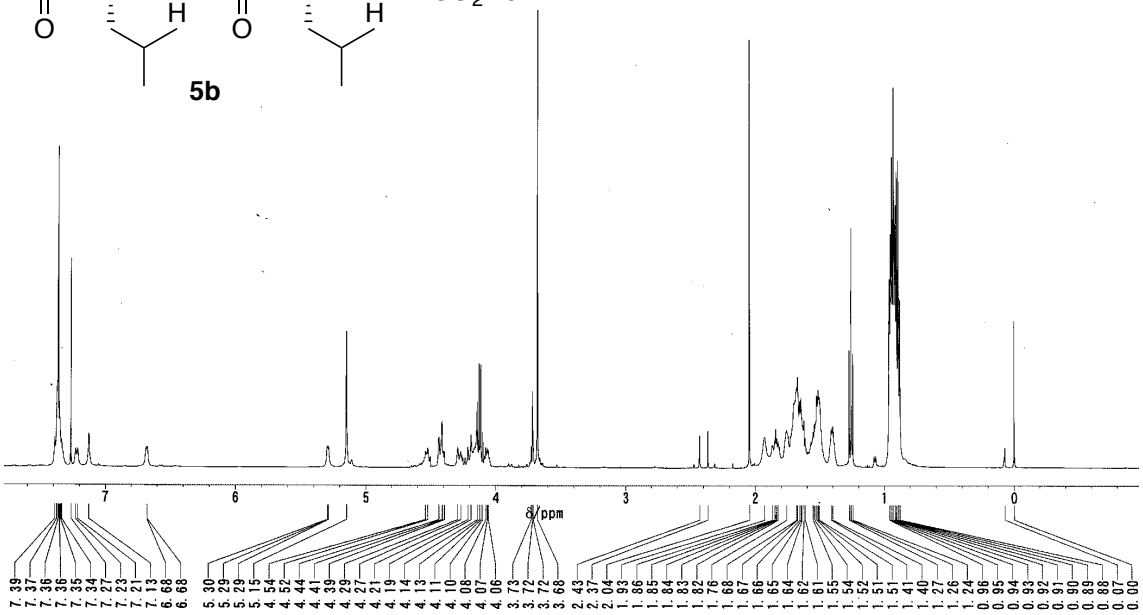
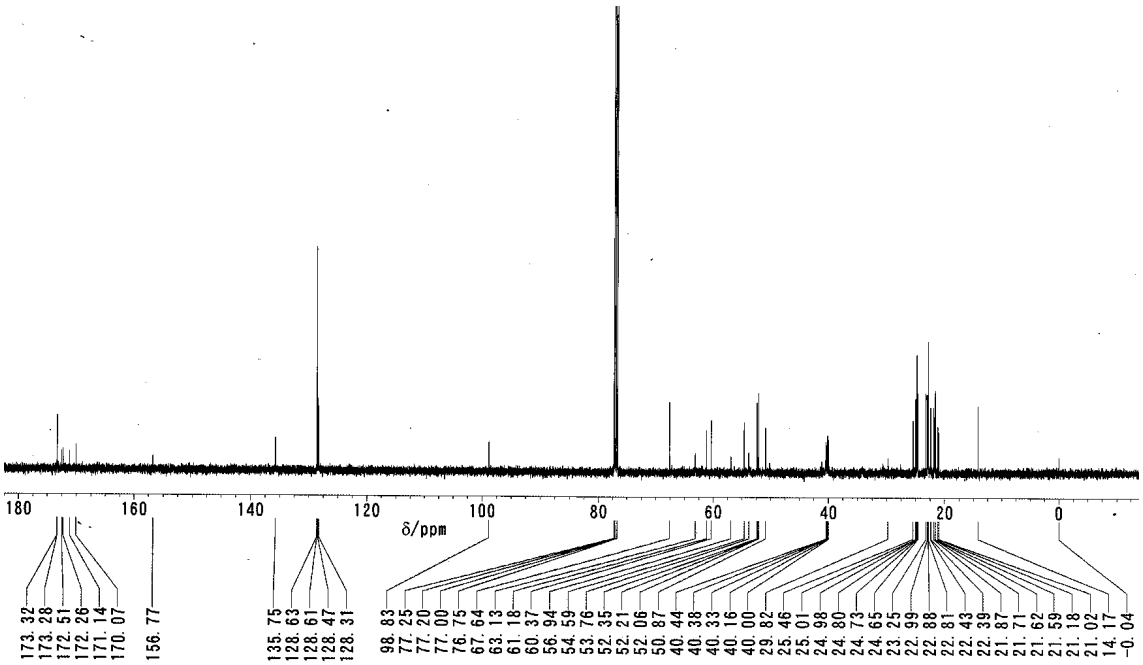
7.76
4.8
3.57
2.4
1.99
2.14
1.12
1.1
1.0
0.94
D FLUORINE PARAMETERS
δ/ppm

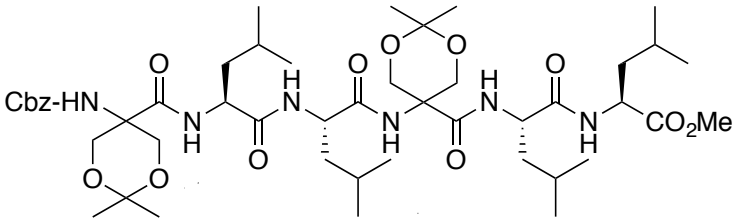

δ/ppm



5b







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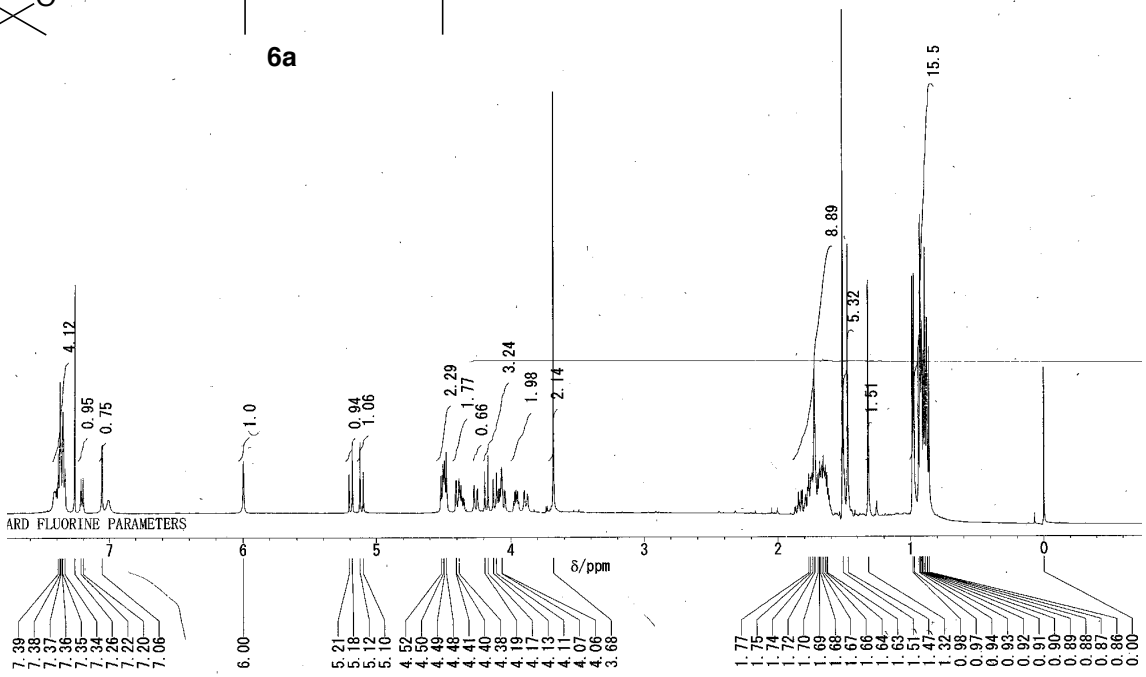

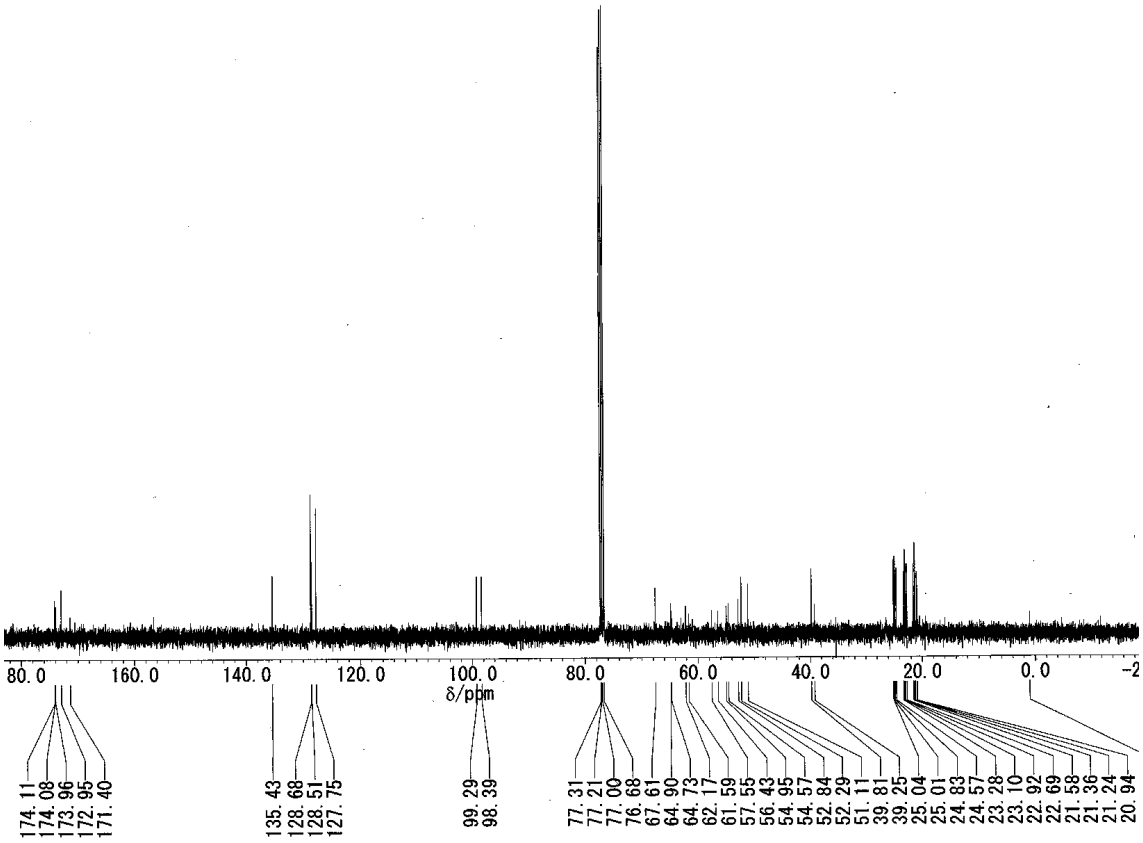

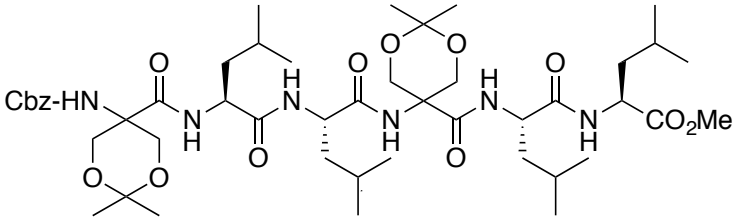

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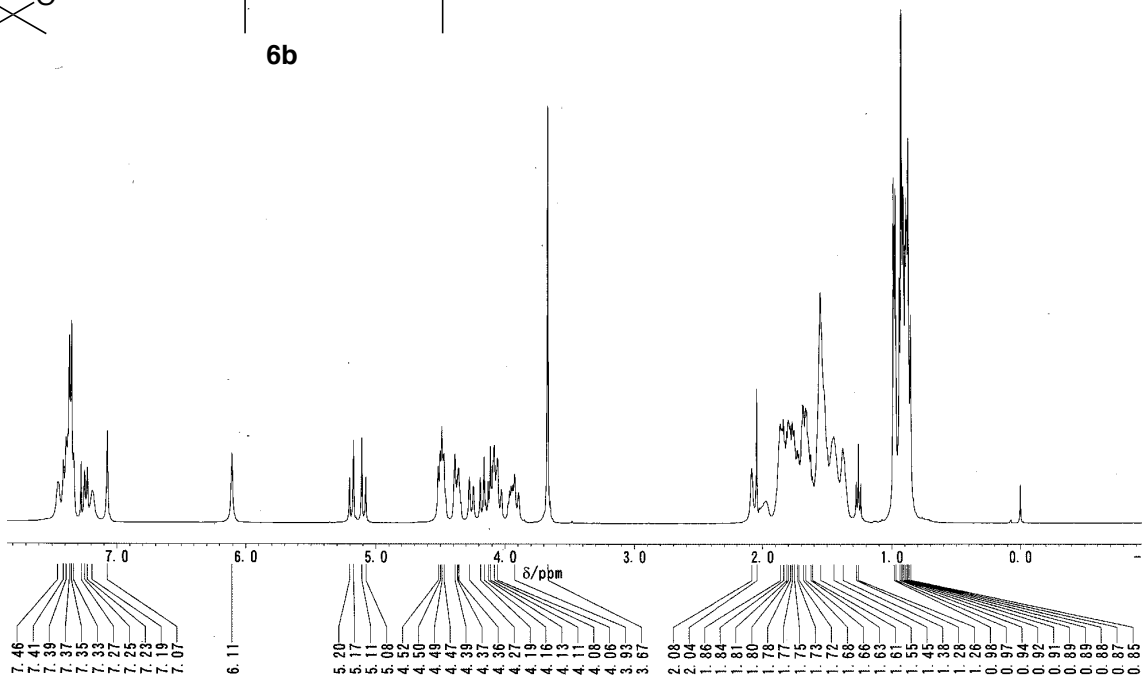

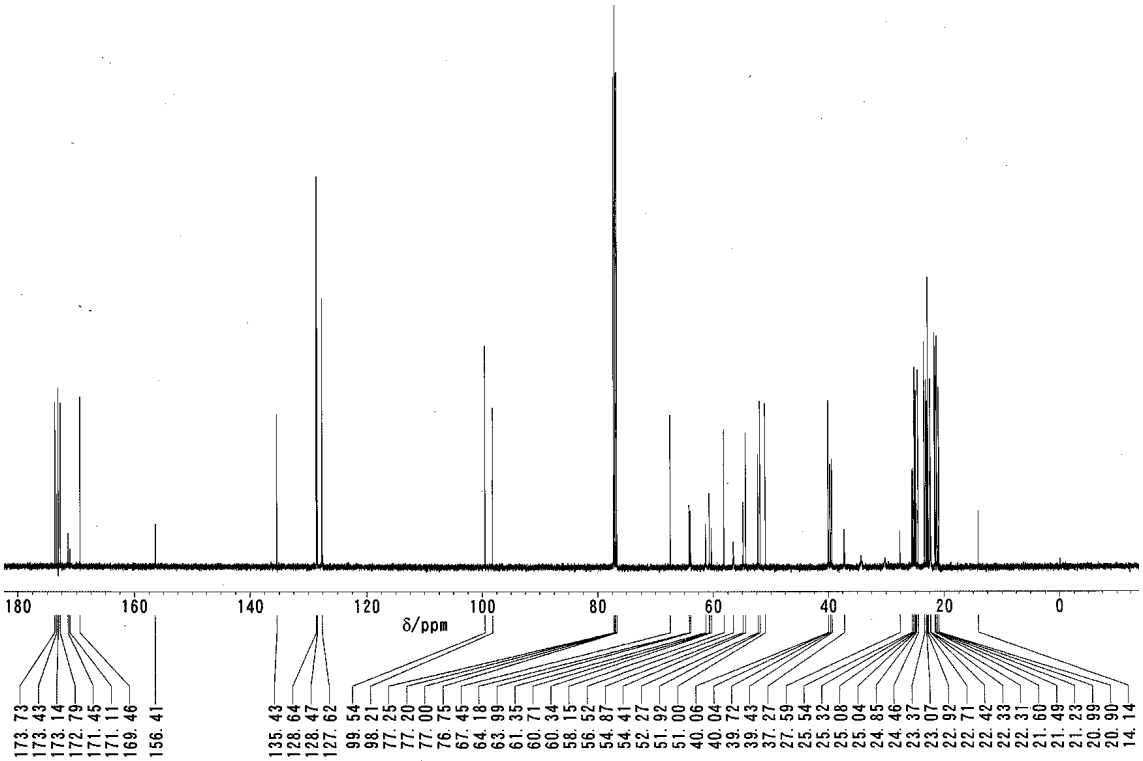

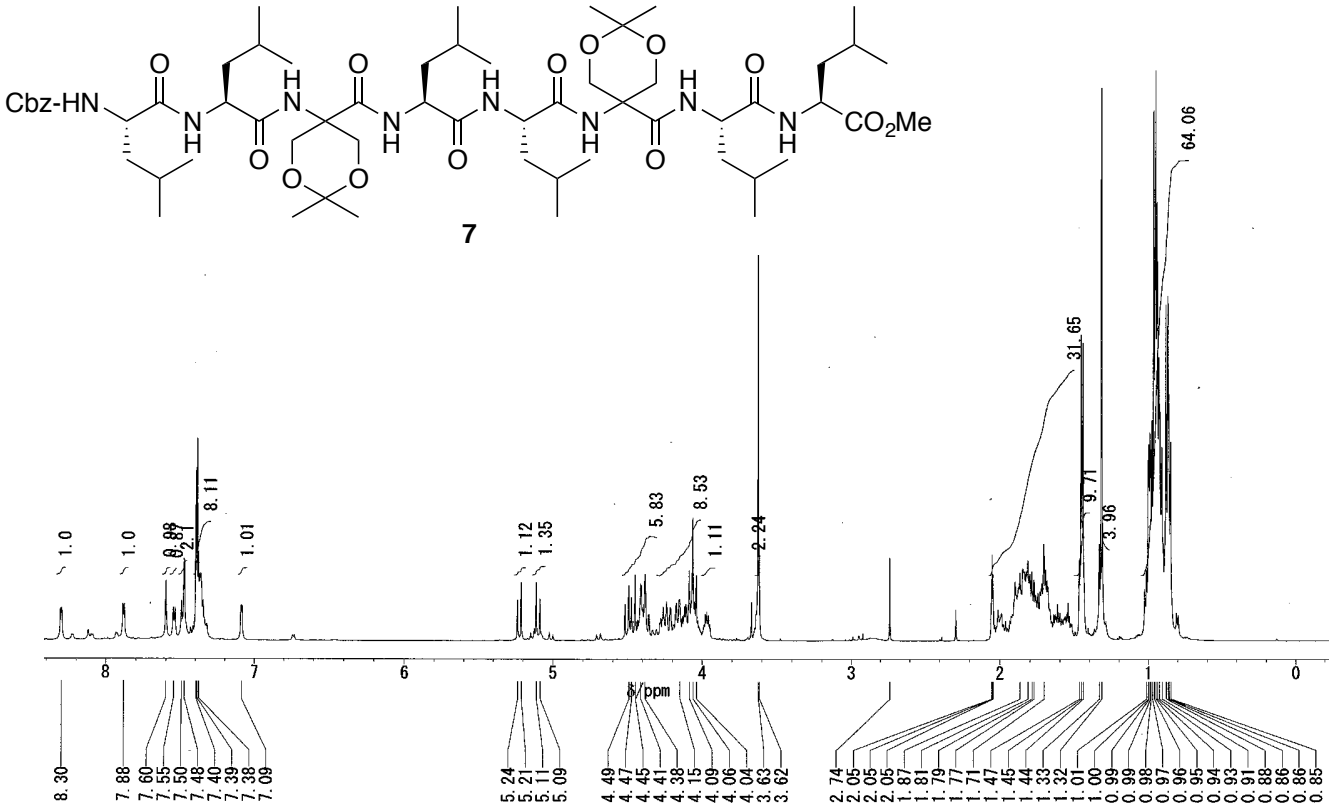
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CO2Me
7
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1.0
2.21
8.11
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8.53
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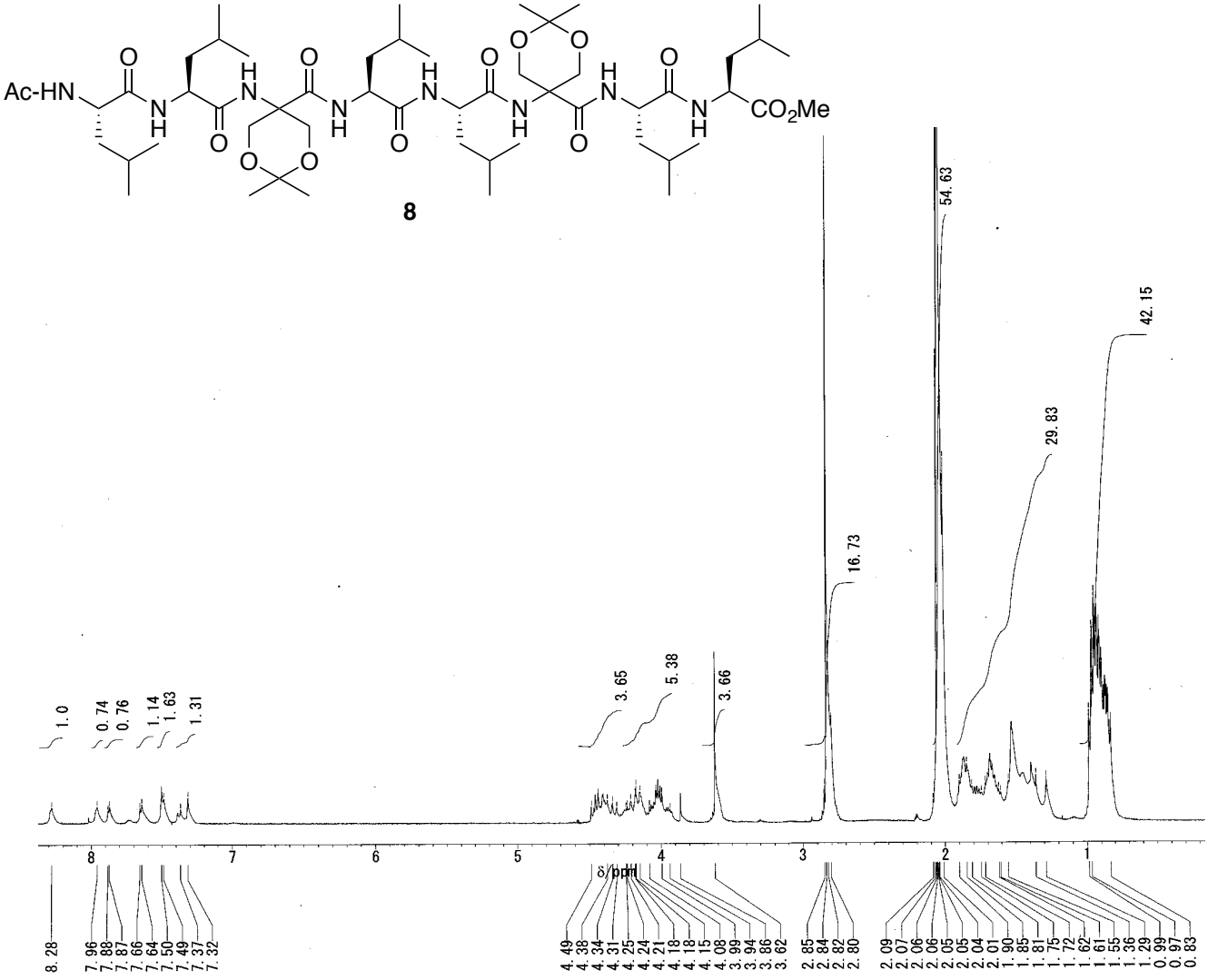
2.24
31.65
9.71
3.96
64.06
δ/ppm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CO2Me
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0.74
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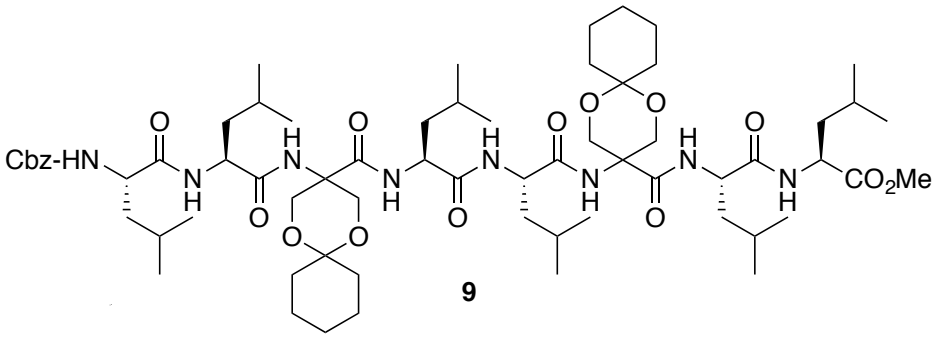
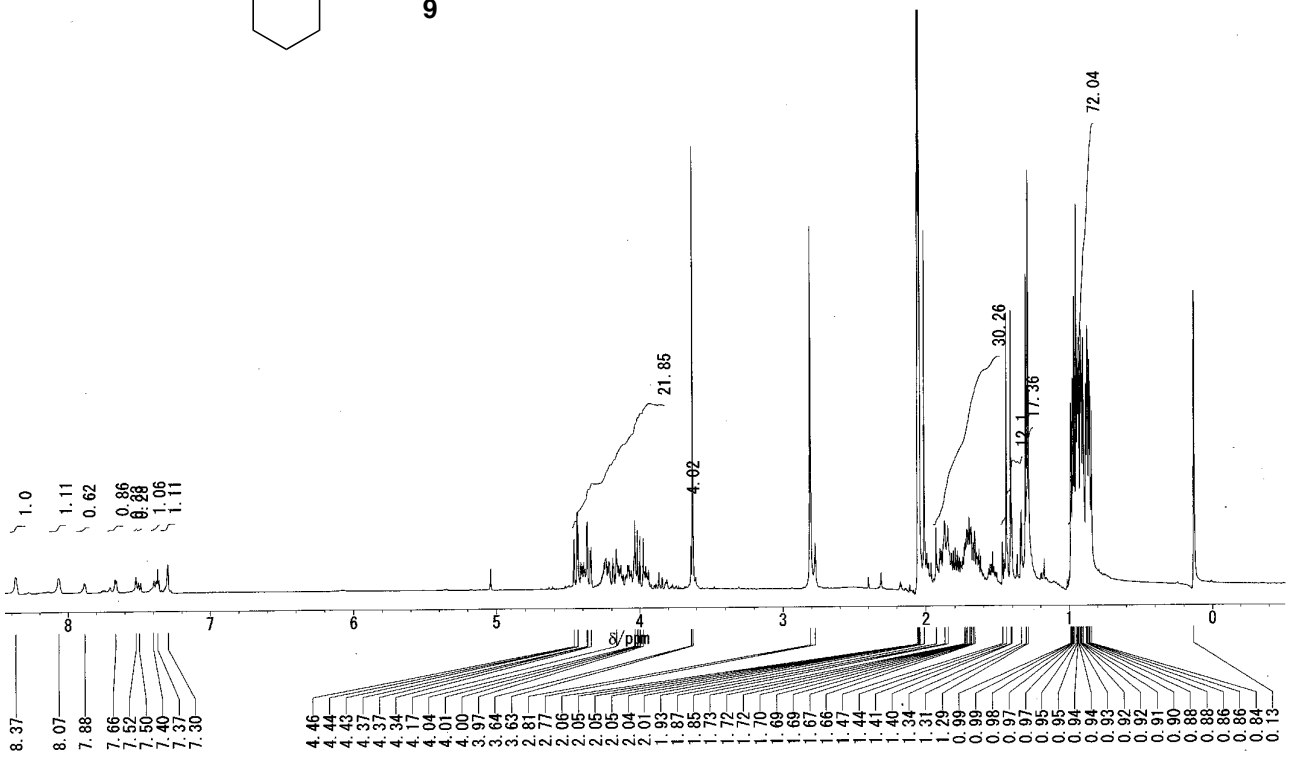
16.73
54.63
29.83
42.15
δ/ppm


Cbz-HN
CO2Me

9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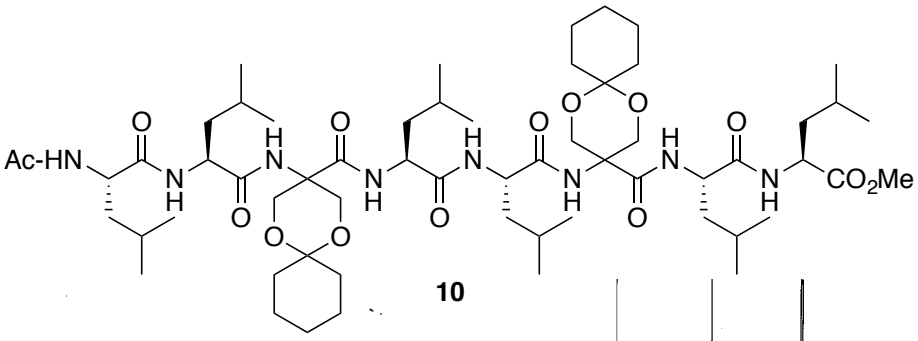
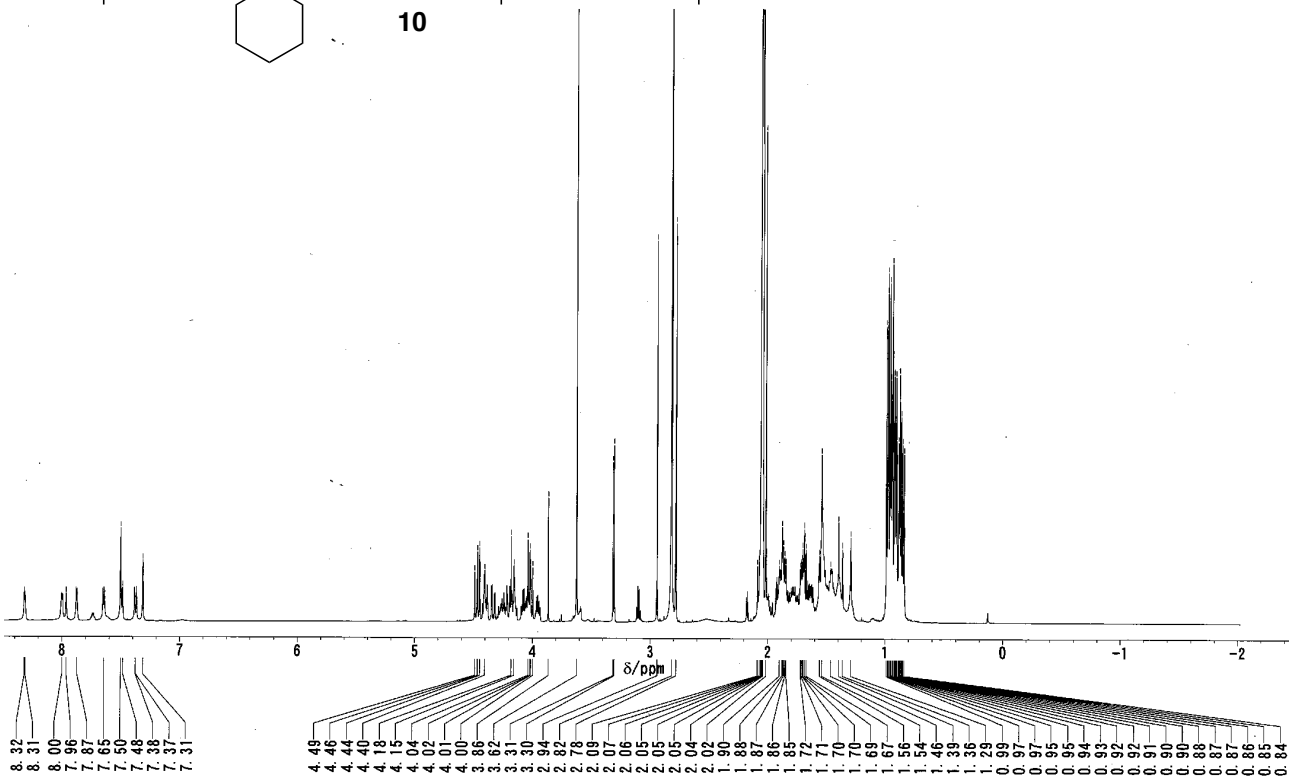
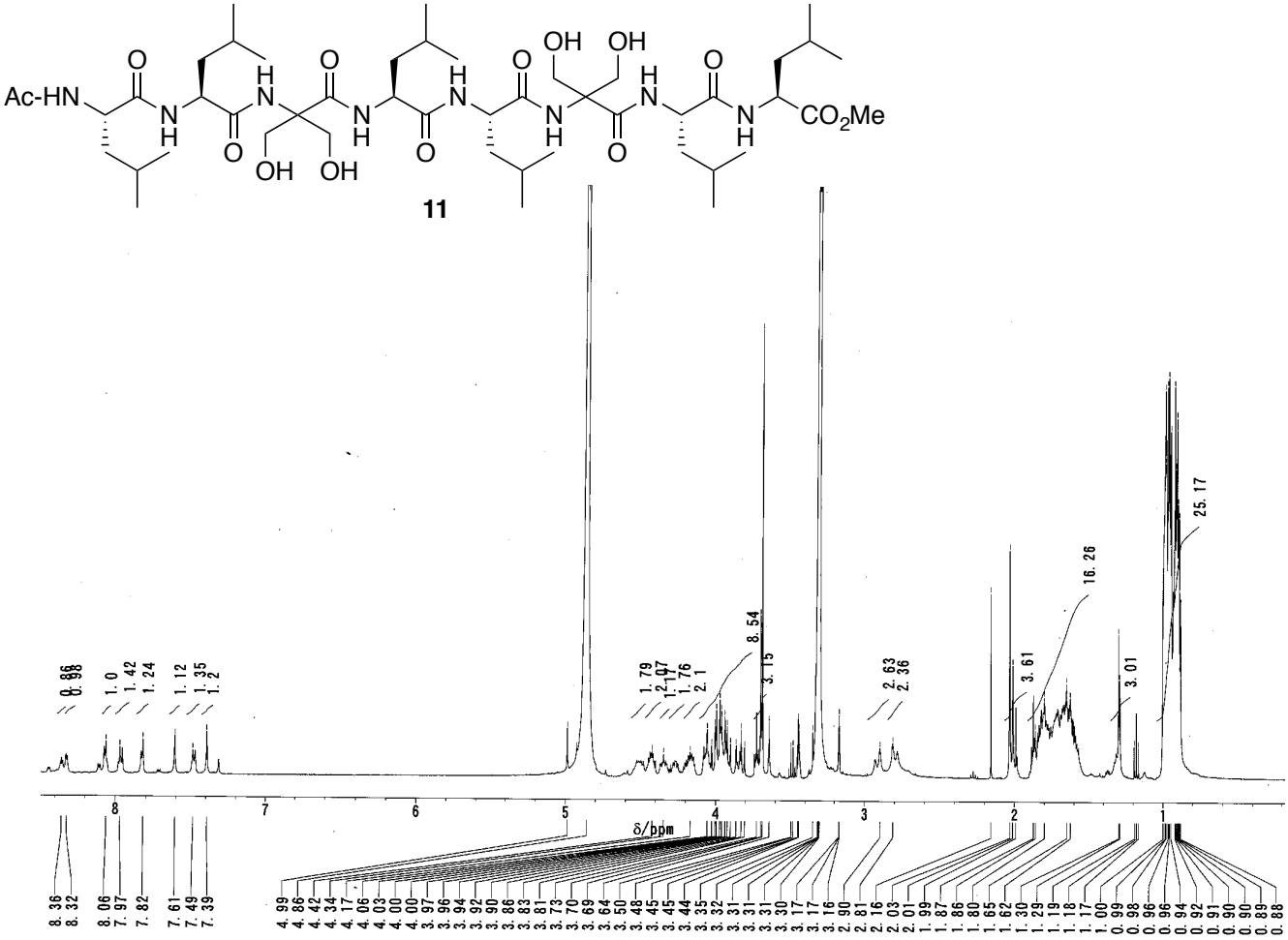
12.1
4.02
1.0
1.11
0.62
1.06
1.11
f1 (ppm)



10




Ac-HN
CO2Me
OH
OH
11
δ/ppm