Stabilized α-helix-catalyzed enantioselective epoxidation of α,β-unsaturated ketones

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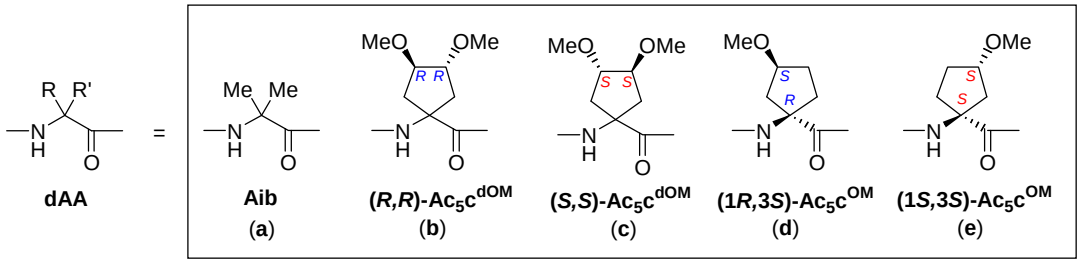
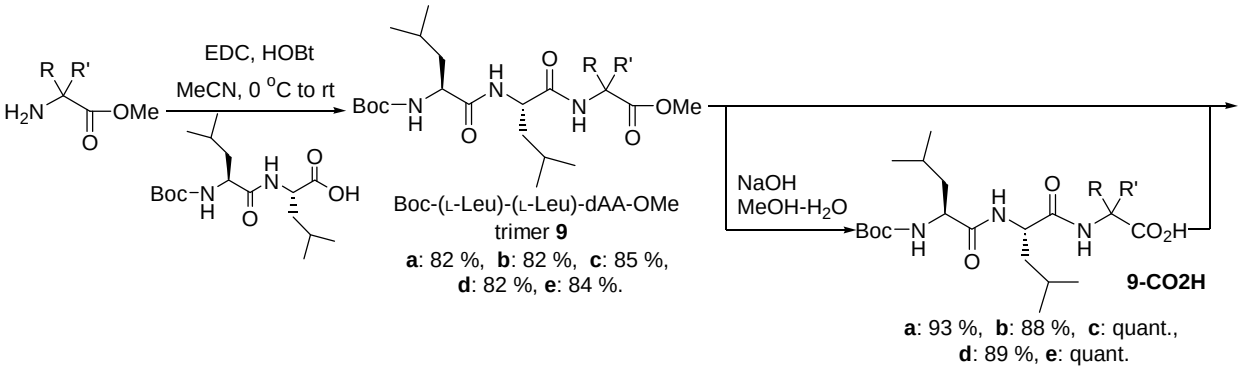
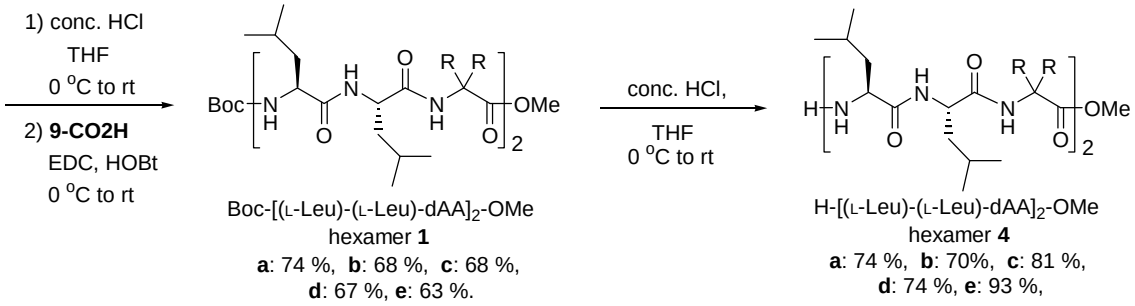
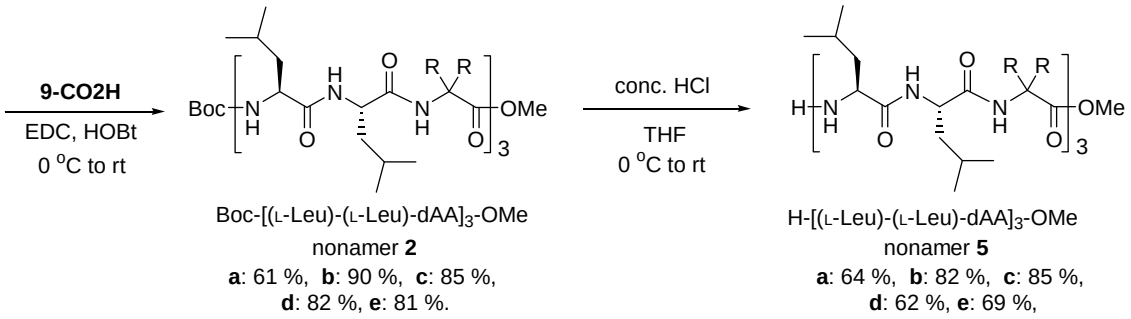
Supporting Information

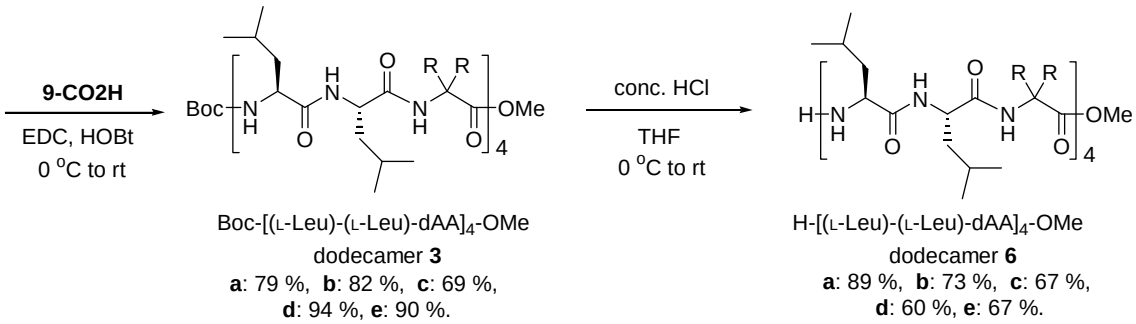
Synthesis of oligopeptides: Boc or H-[L-Leu-L-Leu-dAA]$_m$-OMe.











Experimental Section

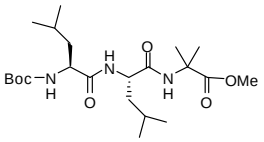
General. Optical rotations $[\alpha]_D$ were measured with a *Jasco DIP-316* polarimeter using a 0.5 or 1.0 dm cell. Circular dichroism spectra (CD) were measured with a *Jasco J-720W* spectropolarimeter using 1.0 mm path length cell. Infrared spectra (IR) were recorded on a *Jasco FT/IR-420* spectrometer for conventional measurement (KBr), and the solution ($CDCl_3$) method using 0.1 mm path length of NaCl cell. ^{1}H NMR spectra were determined at 400 or 500 MHz (*Varian Unity*). FAB-MS spectra were taken on a *Jeol JMS-SX 102* spectrometer. Chromatographic enantiomeric excess (ee) determinations were performed on *Jasco* HPLC instrument (Chiralcel OD column, Chiralpack AD column). Amino acids (*R*,*R*)-Ac_5c^{dOM} (**b**) and (*S*,*S*)-Ac_5c^{dOM} (**c**) were prepared from L- or D-dimethyl tartrate,[S1] and amino acids (1*R*,3*S*)-Ac_5c^{OM} (**d**) and (1*S*,3*S*)-Ac_5c^{OM} (**e**) were prepared from L-(—)-malic acid.[S2]

General procedure for peptide-catalyzed asymmetric epoxidation of chalcone. THF (1 mL) was added to the mixture of peptide catalyst (0.25 equiv) and chalcone (1.0 equiv) in a screw vial equipped with a magnetic stirring bar. Urea-hydrogenperoxide (1.1 equiv) and DBU (5.6 equiv) were added at 0 ºC, and the mixture was gradually warmed to room temperature. After being stirred for 24 h, the reaction mixture was diluted with EtOAc, and washed with saturated aqueous $Na_2S_2O_3$. Then, organic layer was evaporated to give an oily residue, which was purified by flash column chromatography on silica gel.

General procedure for the preparation of α,β-unsaturated enones (7a－e, g, h).[S3] 1N aqueous NaOH or KOH solution (2.6 mL) was added to the stirred solution of ketone derivative (1.1 equiv), aldehyde (1.0 equiv) in MeOH (8 mL) at ^oC. After being stirred at room temperature for 24 h, the solution was neutralized with 2N aqueous HCl, extracted with EtOAc, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash column chromatography on silica gel (EtOAc/hexane) to give enones in 20－76 % yields.

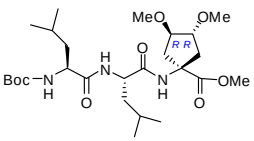
Enone (7f).[S4] *trans*-1-Phenylbut-2-en-1-ol (3.37 mmol) was prepared from PhMgBr and *trans*-crotonaldehyde. Oxidation of the alcohol with MnO_2 (10 equiv) gave the ketone (53 %) as an orange oil. The spectroscopic data of **7f** were identical with those of reported compound.[S4]

Boc-L-Leu-L-Leu-Aib-OMe (Aib-trimer; 9a).[S5]



1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC; 671 mg, 3.50 mmol), and 1-hydroxybenzotriazole hydrate (HOBt; 567 mg, 4.20 mmol) were added to a stirred solution of carboxylic acid **Boc-L-Leu-L-Leu-OH** (1.20 g, 3.50 mmol) in CH_2Cl_2 (18 mL) at 0 °C, and the solution was stirred for 30 min. Then, a solution of amine **H-Aib-OMe** (410 mg, 3.50 mmol) in CH_2Cl_2 (8 mL) was added. After being stirred at room temperature for 48 h, the solution was diluted with EtOAc, washed with 3% aqueous HCl, 5% aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. Removal of the solvent afforded a white solid, which was purified by column chromatography on silica gel. The fraction eluted with 50% EtOAc in hexane afforded trimer **9a** (907 mg, 82%) as colorless crystals: mp 149—151 °C; $[\alpha]^{28}_D$ = - 68.4 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3434 (br), 2960, 1734, 1683, 1506, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.73 (br s, 1H), 6.41 (br d, *J* = 8.4 Hz, 1H), 4.81 (br s, 1H), 4.39 (m, 1H), 4.06 (m, 1H), 3.71 (s, 3H), 1.48—1.73 (m, 12H), 1.45 (s, 9H), 0.79—0.96 (m, 12H); HR-ESI(+)MS calcd for $C_{22}H_{41}N_3O_6Na$ (M^++Na) 466.2888, found 466.2904.

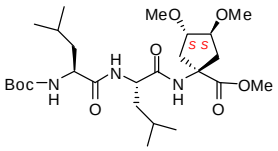
Boc-L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dOM}}-OMe {(*R*,*R*)-trimer; 9b}.[S5]



(*R*,*R*)-Trimer **9b** was prepared from **H-(*R*,*R*)-Ac$_5$c^{dOM}-OMe** and **Boc-L-Leu-L-Leu-OH** in a manner similar to that described for the preparation of **9a**: 82% yield; colorless crystals; mp 105—107 °C; $[\alpha]^{23}_D$ = - 88.3 (*c* 1.02, $CHCl_3$); IR ($CDCl_3$) 3431, 2960, 1742, 1698, 1683, 1507, 1456, 1369, 1237, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.88 (br s, 1H), 6.47 (br d, *J* = 8.0 Hz, 1H), 4.80 (br s, 1H), 4.38 (m, 1H), 4.07 (m, 1H), 3.77—3.86 (m, 2H), 3.69 (s, 3H), 3.34 (s, 3H), 3.33 (s, 3H), 2.47 (dd, *J* = 8.4, 15.2 Hz, 1H), 2.40 (dd, *J* = 6.4, 14.4 Hz, 1H), 2.33 (dd, *J* = 6.8, 14.4 Hz, 1H), 2.00 (dd, *J* = 3.2, 13.6 Hz, 1H), 1.48—1.71 (m, 6H), 1.44 (s, 9H), 0.90—0.96 (m, 12H); HR-ESI(+)MS calcd for $C_{26}H_{47}N_3O_8Na$ (M^++Na) 552.3255,

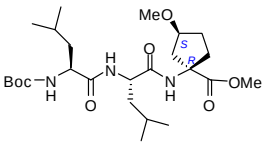
found 552.3240.

Boc-L-Leu-L-Leu-{(*S*,*S*)-Ac$_5$c^{dOM}}-OMe {(*S*,*S*)-trimer; 9c}.[S5]



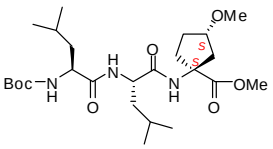
(*S*,*S*)-Trimer **9c** was prepared from **H-(*S*,*S*)-Ac$_5$c^{dOM}-OMe** and **Boc-L-Leu-L-Leu-OH** in a manner similar to that described for the preparation of **9a**: 85% yield; colorless crystals; mp 72—74 °C; $[\alpha]^{25}_{D}$ = - 31.2 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3432, 2983, 1743, 1683, 1506, 1455, 1436, 1369, 1162, 1105 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (br s, 1H), 6.40 (br d, *J* = 8.0 Hz, 1H), 4.80 (br s, 1H), 4.38 (m, 1H), 4.07 (m, 1H), 3.88 (m, 1H), 3.81 (m, 1H), 3.70 (s, 3H), 3.36 (s, 3H), 3.34 (s, 3H), 2.50 (dd, *J* = 6.4, 14.8 Hz, 1H), 2.43 (dd, *J* = 7.2, 14.2 Hz, 1H), 2.27 (dd, *J* = 6.8, 14.2 Hz, 1H), 1.99 (dd, *J* = 3.2, 13.6 Hz, 1H), 1.46—1.71 (m, 6H), 1.45 (s, 9H), 0.90—0.96 (m, 12H); HR-ESI(+)MS calcd for $C_{26}H_{47}N_3O_8Na$ (M^++Na) 552.3255, found 552.3229.

Boc-L-Leu-L-Leu-{(1*R*,3*S*)-Ac$_5$c^{OM}}-OMe {(1*R*,3*S*)-trimer; 9d}.



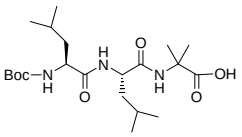
(1*R*,3*S*)-Trimer **9d** was prepared from **H-(1*R*,3*S*)-Ac$_5$c^{OM}-OMe** and **Boc-L-Leu-L-Leu-OH** in a manner similar to that described for the preparation of **9a**: 82% yield; colorless crystals; mp 109—111 °C; $[\alpha]^{27}_{D}$ = - 81.8 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3421, 2960, 1698, 1683, 1540, 1522, 1507, 1497, 1165, 1067 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (br s, 1H), 6.51 (br d, *J* = 6.6 Hz, 1H), 4.90 (br s, 1H), 4.40 (m, 1H), 4.08 (m, 1H), 3.93 (m, 1H), 3.68 (s, 3H), 3.26 (s, 3H), 2.25—2.35 (m, 2H), 1.45—2.14 (m, 10H), 1.44 (s, 9H), 0.90—0.95 (m, 12H); FAB(+)MS *m/z* 523 (M^++Na); HR-ESI(+)MS calcd for $C_{25}H_{45}N_3O_7Na$ (M^++Na] 522.3150, found 522.3124.

Boc-L-Leu-L-Leu-{(1*S*,3*S*)-Ac$_5$c^{OM}}-OMe {(1*S*,3*S*)-trimer; 9e}.

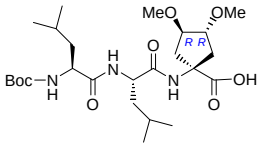


(1*S*,3*S*)-Trimer **9e** was prepared from **H-(1*S*,3*S*)-Ac$_5$c^{OM}-OMe** and **Boc-L-Leu-L-Leu-OH** in a manner similar to that described for the preparation of **9a**: 84% yield; colorless crystals; mp 137—139 °C; $[\alpha]^{27}_{D}$ = - 76.6 (*c* 1.00, $CHCl_3$);

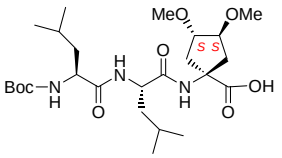
IR ($CDCl_3$) 3433, 3363, 2961, 2935, 2872, 1736, 1684, 1498, 1369, 1163, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (br s, 1H), 6.48 (br d, *J* = 6.9 Hz, 1H), 4.92 (br s, 1H), 4.38 (m, 1H), 3.97—4.08 (m, 2H), 3.70 (s, 3H), 3.29 (s, 3H), 2.24—2.38 (m, 3H), 1.46—2.06 (m, 9H), 1.45 (s, 9H), 0.89—0.96 (m, 12H); FAB(+)MS *m/z* 523 (M^++Na); HR-ESI(+)MS calcd for $C_{25}H_{45}N_3O_7Na$ (M^++Na) 522.3150, found 522.3131.

Boc-L-Leu-L-Leu-Aib-OH {Aib-trimer acid; 9a-CO2H}.[5S] 

1N aqueous NaOH (9 mL) was added to a stirred solution of **9a** (2.00 g, 4.509 mmol) in MeOH (40 mL) at 0°C. After being stirred at room temperature for 12 h, the solution was acidified with 1N aqueous HCl, and then, MeOH was evaporated. The aqueous phase was extracted with EtOAc, and dried over Na_2SO_4. Removal of the solvent afforded a white solid, which was purified by column chromatography on silica gel. The fraction eluted with 10% MeOH in $CHCl_3$ gave Aib-trimer acid **9a-CO2H** (1.80 g, 93%) as colorless crystals: mp 92—95 °C; $[\alpha]^{26}_D$ = - 58.4 (*c* 1.01, $CHCl_3$); IR (KBr) 3309 (br), 3072, 2958, 2872, 1691, 1654, 1527, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 (br s, 1H), 6.96 (br d, *J* = 8.0 Hz, 1H), 4.99 (br s, 1H), 4.52 (m, 1H), 4.12 (m, 1H), 1.48—1.70 (m, 12H), 1.44 (s, 9H), 0.90—0.95 (m, 12H); HR-ESI(+)MS calcd for $C_{21}H_{39}N_3O_6Na$ (M^++Na) 452.2731, found 452.2750.

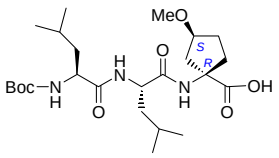
Boc-L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dOM}}-OH {(*R*,*R*)-trimer acid; 9b-CO2H}.[5S] 

(*R*,*R*)-Trimer acid **9b-CO2H** was prepared from **9b** in a manner similar to that described for the preparation of **9a-CO2H**: 88% yield; colorless crystals; mp 81—83°C; $[\alpha]^{28}_D$ = - 75.0 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3316, 3072, 2958, 2935, 2872, 1693, 1652, 1526, 1367 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (br s, 1H), 6.91 (br s, 1H), 5.00 (br s, 1H), 4.40 (m, 1H), 4.12 (m, 1H), 3.81—3.86 (m, 2H), 3.36 (s, 3H), 3.35 (s, 3H), 2.50—2.56 (m, 2H), 2.36 (dd, *J* = 6.0, 14.8 Hz, 1H), 2.06 (m, 1H), 1.50—1.66 (m, 6H), 1.44 (s, 9H), 0.89—0.95 (m, 12H); HR-ESI(+)MS calcd for $C_{25}H_{45}N_3O_8Na$ (M^++Na) 538.3099, found 538.3110.

Boc-L-Leu-L-Leu-{(*S*,*S*)-Ac$_5$c^{dOM}}-OH {(*S*,*S*)-trimer acid; 9c-CO2H}.[5S] 

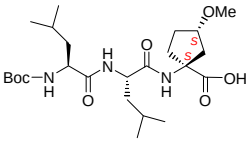
(*S*,*S*)-Trimer acid **9c-CO2H** was prepared from **9c** in a manner similar to that described for the preparation of **9a-CO2H**: quantitative; colorless crystals; mp 76—77 °C; $[\alpha]^{25}_{D}$ = - 30.0 (*c* 1.01, $CHCl_3$); IR (KBr) 3317 (br), 3071, 2958, 2935, 1693, 1651, 1526, 1367, 1170, 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (br s, 1H), 6.93 (br s, 1H), 5.00 (br s, 1H), 4.42 (m, 1H), 4.10 (m, 1H), 3.89 (m, 1H), 3.83 (m, 1H), 3.36 (s, 3H), 3.35 (s, 3H), 2.60 (dd, *J* = 6.4, 14.4 Hz, 1H), 2.44 (dd, *J* = 7.2, 14.0 Hz, 1H), 2.28 (dd, *J* = 6.0, 14.0 Hz, 1H), 2.07 (dd, *J* = 3.2, 14.4 Hz, 1H), 1.45—1.66 (m, 6H), 1.44 (s, 9H), 0.90—0.95 (m, 12H); HR-ESI(+)MS calcd for $C_{25}H_{45}N_3O_8Na$ (M^++Na) 538.3099, found 538.3101.

Boc-L-Leu-L-Leu-{(1*R*,3*S*)-Ac_5c^{OM}}-OH {(1*R*,3*S*)-trimer acid; 9d-CO2H}. (1*R*,3*S*)-Trimer acid **9d-CO2H** was prepared from **9d** in a manner similar to that described for the preparation of **9a-CO2H**: 89% yield;

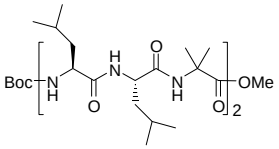


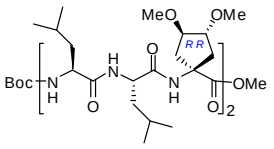
colorless crystals; mp 85—88 °C; $[\alpha]^{26}_{D}$ = - 61.9 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3308, 2958, 2872, 1695, 1651, 1526, 1367, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (br s, 1H), 6.83 (br d, *J* = 8.8 Hz, 1H), 4.95 (br s, 1H), 4.40 (m, 1H), 4.11 (m, 1H), 3.95 (m, 1H), 3.27 (s, 3H), 2.44 (dd, *J* = 6.0, 14.4 Hz, 1H), 2.20—2.31 (m, 2H), 2.00—2.10 (m, 3H), 1.87 (m, 1H), 1.50—1.70 (m, 5H), 1.44 (s, 9H), 0.90—0.95 (m, 12H); FAB(+)MS *m/z* 509 (M^++Na); HR-ESI(+)MS calcd for $C_{24}H_{43}N_3O_7Na$ (M^++Na): 508.2993, found 508.3005.

Boc-L-Leu-L-Leu-{(1*S*,3*S*)-Ac_5c^{OM}}-OH {(1*S*,3*S*)-trimer acid; 9e-CO2H}. (1*S*,3*S*)-Trimer acid **9e-CO2H** was prepared from **9e** in a manner similar to that described for the preparation of **9a-CO2H**: quantitative; colorless

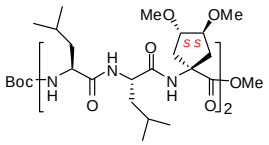


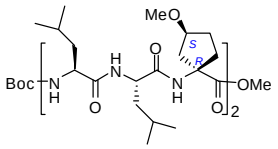
crystals; mp 91—94 °C; $[\alpha]^{20}_{D}$ = - 52.2 (*c* 1.02, $CHCl_3$); IR ($CDCl_3$) 3317, 3072, 2959, 2935, 2872, 1692, 1649, 1527, 1367, 1170, 1105 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (br s, 1H), 6.52 (br d, *J* = 6.8 Hz, 1H), 4.83 (br s, 1H), 4.41 (m, 1H), 4.14 (m. 1H), 4.06 (m, 1H), 3.40 (s, 3H), 2.63 (dd, *J* = 4.4, 14.8 Hz, 1H), 2.08—2.36 (m, 5H), 1.48—1.73 (m, 6H), 1.44 (s, 9H), 0.91—0.96 (m, 12H); FAB(+)MS *m/z* 509 (M^++Na); HR-ESI(+)MS calcd for $C_{24}H_{43}N_3O_7Na$ (M^++Na) 508.2993, found 508.2990.

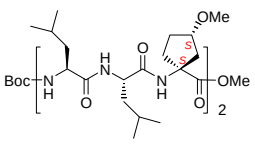
Boc-[L-Leu-L-Leu-Aib]$_2$-OMe {Aib-hexamer; 1a}.  Concentrated HCl (3.6 mL) was added to a solution of **9a** (1.14 g, 2.57 mmol) in THF (10 mL) at 0 ^{o}C, and the whole was stirred at room temperature for 12 h. Then, the solution was neutralized with 5% aqueous $NaHCO_3$, extracted with EtOAc, and dried over $MgSO_4$. Removal of the solvent afforded a crude amine **9a-NH2** (686 mg, 78%), which was used without further purification. A mixture of EDC (421 mg, 2.20 mmol), HOBt (297 mg, 2.20 mmol), and carboxylic acid **9a-CO2H** (944 mg, 2.20 mmol) in CH_2Cl_2 (13 mL) was stirred at 0 ^{o}C for 30 min, then, a solution of amine **9a-NH2** (686 mg, 2.00 mmol) in CH_2Cl_2 (8 mL) was added. After being stirred at room temperature for 48 h, the solution was diluted with EtOAc, washed with 3% aqueous HCl, 5% aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (66% EtOAc in hexane) to give Aib-hexamer **1a** (1.43 g, 95%) as colorless crystals: mp 196—198 °C; $[\alpha]^{27}_{D}$ = - 22.8 (*c* 1.01, $CHCl_3$); IR ($CDCl_3$) 3430 (br), 3332, 3019, 2965, 1733, 1699, 1669, 1524, 1428, 1046 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (br d, *J* = 6.8 Hz, 1H), 7.38 (br s, 1H), 6.20 (br d, *J* = 4.2 Hz, 1H), 7.11 (br s, 1H), 6.48 (br s, 1H), 4.95 (br s, 1H), 4.39 (m, 1H), 4.18 (m, 1H), 3.91—3.97 (m, 2H), 3.68 (s, 3H), 1.42—1.82 (m, 24H), 1.50 (s, 9H), 0.86—1.00 (m, 24H); FAB(+)MS *m/z* 778 (M^++Na); HR-ESI(+)MS calcd for $C_{38}H_{70}N_6O_9Na$ (M^++Na) 777.5096, found 777.5132.

Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dOM}}]$_2$-OMe {(*R*,*R*)-hexamer; 1b}.  (*R*,*R*)-Hexamer **1b** was prepared from **9b-NH2** and **9b-CO2H** in a manner similar to that described for the preparation of **1a**: 68% yield; colorless crystals; mp 167—169 °C; $[\alpha]^{24}_{D}$ = - 22.8 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3431, 3335, 2960, 1733, 1698, 1669, 1524, 1508, 1488, 1158, 1120 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (br s, 1H), 7.31—7.32 (m, 2H), 7.26 (br s, 1H), 6.47 (br s, 1H), 4.96 (br s, 1H), 4.36 (m, 1H), 4.22 (m, 1H), 3.87—3.95 (m, 4H), 3.77—3.83 (m, 2H), 3.69 (s, 3H), 3.33—3.36 (m, 9H), 3.26 (s, 3H), 3.01 (dd, *J* = 5.6, 11.6 Hz, 1H), 2.88 (dd, *J* = 6.0, 11,6 Hz, 1H), 2.64 (dd, *J* = 6.0, 11.6 Hz, 1H), 2.53 (dd, *J* = 6.0, 11.6 Hz, 1H), 2.21 (dd, *J* = 6.0, 11.6 Hz, 1H), 2.07 (dd, *J* = 3.2, 13.2 Hz, 1H), 1.91—1.99 (m, 2H),

1.64—1.83 (m, 12H), 1.52 (s, 9H), 0.85—1.00 (m, 24H); FAB(+)MS *m/z* 950 (M^++Na); HR-ESI(+)MS calcd for $C_{46}H_{82}N_6O_{13}Na$ (M^++Na) 949.5832, found 949.5817.

Boc-[L-Leu-L-Leu-{(*S*,*S*)-Ac$_5$c^{dOM}}]$_2$-OMe {(*S*,*S*)-hexamer; 1c}. 
(*S*,*S*)-Hexamer **1c** was prepared from **9c-NH2** and **9c-CO2H** in a manner similar to that described for the preparation of **1a**: 68% yield; colorless crystals; mp 150—152 °C; $[\alpha]^{28}_D$ = + 4.1 (*c* 1.04, $CHCl_3$); IR ($CDCl_3$) 3333, 2959, 2901, 2826, 1741, 1670, 1522, 1508, 1159, 1051 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23—7.35 (m, 4H), 6.70 (br s, 1H), 4.87 (br s, 1H), 4.35 (q, *J* = 7.6, 1H), 4.21 (m, 1H), 4.00 (m, 1H), 3.90—4.00 (m, 2H), 3.67—3.84 (m, 6H), 3.31—3.36 (m, 12H), 2.92 (dd, *J* = 7.6, 14.0 Hz, 1H), 2.65 (dd, *J* = 8.0, 14.0 Hz, 1H), 2.58 (dd, *J* = 6.8, 13.6 Hz, 1H), 2.42 (dd, *J* = 6.4, 13.6 Hz, 1H), 2.30 (dd, *J* = 6.8, 14.0 Hz, 1H), 2.13 (dd, *J* = 7.2, 14.0 Hz, 1H), 1.98 (dd, *J* = 6.8, 14.0 Hz, 1H), 1.91 (m, 1H), 1.60—1.80 (m, 12H), 1.49 (s, 9H), 0.85—1.00 (m, 24H); FAB(+)MS *m/z* 950 (M^++Na); HR-ESI(+)MS calcd for $C_{46}H_{82}N_6O_{13}Na$ (M^++Na) 949.5832, found 949.5806.

Boc-[L-Leu-L-Leu-{(1*R*,3*S*)-Ac$_5$c^{OM}}]$_2$-OMe {(1*R*,3*S*)-hexamer; 1d}. 
(1*R*,3*S*)-Hexamer **1d** was prepared from **9d-NH2** and **9d-CO2H** in a manner similar to that described for the preparation of **1a**: 67% yield; colorless crystals; mp 184—186 °C; $[\alpha]^{27}_D$ = - 1.5 (*c* 1.01, $CHCl_3$); IR ($CDCl_3$) 3431, 3335, 2960, 1732, 1716, 1698, 1669, 1540, 1522, 1456, 1159 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (br s, 1H), 7.34 (br s, 2H), 7.30 (br d, *J* = 6.0 Hz, 1H), 6.47 (br d, *J* = 3.9 Hz, 1H), 4.92 (br s, 1H), 4.39 (q, *J* = 8.2 Hz, 1H), 4.20 (q, *J* = 6.4 Hz, 1H), 3.89—3.96 (m, 4H), 3.68 (s, 3H), 3.26 (s, 3H), 3.18 (s, 3H), 2.84—2.89 (m, 2H), 1.63—2.33 (m, 22H), 1.50 (s, 9H), 0.86—1.00 (m, 24H); FAB(+)MS *m/z* 890 (M^++Na); HR-ESI(+)MS calcd for $C_{44}H_{78}N_6O_{11}Na$ (M^++Na) 889.5612, found 889.5653.

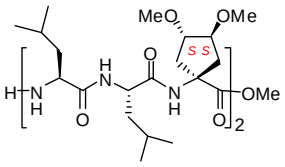
Boc-[L-Leu-L-Leu-{(1*S*,3*S*)-Ac$_5$c^{OM}}]$_2$-OMe {(1*S*,3*S*)-hexamer; 1e}. 
(1*S*,3*S*)-Hexamer **1e** was prepared from **9e-NH2** and **9e-CO2H** in a manner similar to that described for the preparation of **1a**: 63% yield; colorless

crystals; mp 208—210 °C; $[\alpha]^{27}_D$ = - 10.2 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3431 (br), 3332, 2961, 1698, 1667, 1526, 1468, 1369, 1256 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (br s, 1H), 7.32 (br d, *J* = 5.5 Hz, 1H), 7.18 (br s, 1H), 6.55 (br s, 1H), 5.00 (d, *J* = 8.5 Hz, 1H), 4.33 (q, *J* = 8.0 Hz, 1H), 4.19 (m, 1H), 4.41—3.97 (m, 3H), 3.90 (m, 1H), 3.68 (s, 3H), 3.28 (s, 3H), 3.27(s, 3H), 2.77 (m, 1H), 2.54 (dd, *J* = 6.6 Hz, 14.4 Hz, 1H), 2.45 (dd, *J* = 6.6 Hz, 14.4 Hz, 1H), 2.38 (dd, *J* = 5.3 Hz, 14.4 Hz, 1H), 2.25 (m, 1H), 2.11—2.17 (m, 2H), 1.99 (dd, *J* = 8.0 Hz, 14.2 Hz, 1H), 1.63—1.96 (m, 16H), 1.51 (s, 9H), 0.86—1.00 (m, 24H); FAB(+)MS *m/z* 890 (M^++Na); HR-ESI(+)MS calcd for $C_{44}H_{78}N_6O_{11}Na$ (M^++Na) 889.5612, found 889.5621.

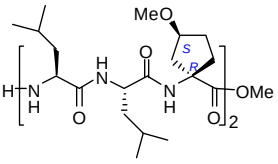
H-[L-Leu-L-Leu-Aib]$_2$-OMe {Aib-hexamer amine; 4a}. Concentrated HCl (2 mL) was added to a solution of **9a** (632 mg, 0.838 mmol) in THF (7 mL) at 0 °C and the solution was stirred at room temperature for 24 h. Then, the solution was neutralized with 5% aqueous $NaHCO_3$, extracted with EtOAc, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (10% MeOH in $CHCl_3$) to give Aib-hexamer amine **4a** (407 mg, 74%) as colorless crystals: mp 169—171 °C; $[\alpha]^{24}_D$ = - 43.8 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3327 (br), 2960, 2872, 1733, 1669, 1540, 1522, 1508, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.42 (br d, *J* = 8.2 Hz, 1H), 7.18 (br d, *J* = 6.4 Hz, 1H), 7.06 (br s, 1H), 6.55 (br s, 1H), 4.37 (m, 1H), 4.19 (m, 1H), 3.96 (m, 1H), 3.69 (s, 3H), 3.40 (dd, *J* = 3.6, 10.4 Hz, 1H), 1.56—1.82 (m, 12H), 1.52—1.53 (m, 6H), 1.48 (s, 3H), 1.42 (s, 3H), 0.86—1.01 (m, 24H); FAB(+)MS *m/z* 677 (M^++Na); HR-ESI(+)MS calcd for $C_{33}H_{62}N_6O_7Na$ (M^++Na) 677.4572, found 677.4602.

H-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dOM}}]$_2$-OMe {(*R*,*R*)-hexamer amine; 4b}. (*R*,*R*)-Hexamer amine **4b** was prepared from **1b** in a manner similar to that described for the preparation of **4a**: 70% yield; colorless crystals; mp 156—158 °C; $[\alpha]^{24}_D$ = - 61.2 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3334 (br), 2960, 2935, 2873, 1734, 1668, 1523, 1467, 1105 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (br s, 1H), 7.24—7.22 (m, 2H), 7.19 (br d, *J* = 8.4 Hz, 1H), 6.80 (br s, 1H), 4.36 (m, 1H), 4.19 (m, 1H), 4.04 (m, 1H), 3.79—3.90 (m,

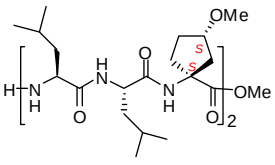
5H), 3.70 (s, 3H), 3.41 (dd, *J* = 3.6, 9.6 Hz, 1H), 3.35 (s, 6H), 3.33 (s, 3H), 3.31 (s, 3H), 2.68—2.78 (m, 2H), 2.58 (m, 1H), 2.27 (m, 1H), 2.16—2.22 (m, 2H), 2.04 (m, 1H), 1.96 (m, 1H), 1.60—1.81 (m, 12H), 0.87—0.99 (m, 24H); FAB(+)MS *m/z* 850 (M^++Na); HR-ESI(+)MS calcd for $C_{41}H_{74}N_6O_{11}Na$ (M^++Na) 849.5308, found 849.5275.



H-[L-Leu-L-Leu-{(*S*,*S*)-Ac$_5$c^{dOM}}]$_2$-OMe {(*S*,*S*)-hexamer amine; 4c}. (*S*,*S*)-Hexamer amine **4c** was prepared from **1c** in a manner similar to that described for the preparation of **4a**: 81% yield; colorless foam; $[\alpha]^{25}_D$ = + 3.6 (*c* 0.58, $CHCl_3$); IR (neat) 3311 (br), 2956, 2871, 1741, 1651, 1537, 1468, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (br s, 1H), 7.35 (br d, *J* = 8.0 Hz, 1H), 7.26—7.30 (m, 2H), 6.94 (br s, 1H), 4.36 (m, 1H), 4.21 (m, 1H), 3.86—3.98 (m, 2H), 3.72—3.84 (m, 6H), 3.67 (s, 3H), 3.39 (s, 3H), 3.35 (s, 3H), 3.34 (s, 3H), 3.31 (s, 3H), 2.88 (m, 1H), 2.50—2.60 (m, 2H), 2.27 (m, 1H), 2.12 (m, 1H), 1.98 (m, 1H), 1.54—1.82 (m, 14H), 0.85—1.00 (m, 24H); FAB(+)MS *m/z* 850 (M^++Na); HR-ESI(+)MS calcd for $C_{41}H_{74}N_6O_{11}Na$ (M^++Na) 849.5308, found 849.5274.



H-[L-Leu-L-Leu-{(1*R*,3*S*)-Ac$_5$c^{OM}}]$_2$-OMe {(1*R*,3*S*)-hexamer amine; 4d}. (1*R*,3*S*)-Hexamer amine **4d** was prepared from **1d** in a manner similar to that described for the preparation of **4a**: 74% yield; colorless crystals; mp 158—160 °C; $[\alpha]^{24}_D$ = - 22.9 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3334 (br), 2960, 2872, 1732, 1669, 1521, 1508, 1456, 1216, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (br d, *J* = 4.0 Hz, 1H), 7.30—7.32 (m, 2H), 7.23 (br s, 1H), 6.59 (br s, 1H), 4.39 (m, 1H), 4.19 (m, 1H), 3.92—3.99 (m, 3H), 3.68 (s, 3H), 3.39 (dd, *J* = 3.2, 13.2 Hz, 1H), 3.26 (s, 3H), 3.23 (s, 3H), 2.77 (dd, *J* = 6.4, 13.6 Hz, 1H), 2.69 (dd, *J* = 5.6, 14.8 Hz, 1H), 1.54—2.28 (m, 22H), 0.86—1.01 (m, 24H); FAB(+))MS *m/z* 768 (M^++H); HR-ESI(+)MS calcd for $C_{39}H_{70}N_6O_9Na$ (M^++Na) 789.5096, found 789.5117.



H-[L-Leu-L-Leu-{(1*S*,3*S*)-Ac$_5$c^{OM}}]$_2$-OMe {(1*S*,3*S*)-hexamer amine; 4e}. (1*S*,3*S*)-Hexamer amine **4e** was prepared from **1e** in a manner similar to that described for the preparation of **4a**: 93% yield; colorless crystals; mp

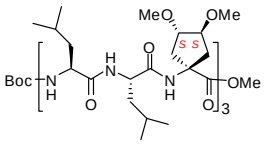
168—170 °C; $[\alpha]^{25}_D$ = - 70.4 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3337 (br), 2960, 2872, 1733, 1668, 1521, 1508, 1217, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (br d, *J* = 6.0 Hz, 1H), 7.44 (br d, *J* = 6.0 Hz, 1H), 7.20 (br s, 1H), 7.14 (br d, *J* = 8.0 Hz, 1H), 7.01 (br s, 1H), 4.31 (m, 1H), 4.14—4.19 (m, 2H), 3.71—4.02 (m, 2H), 3.70 (s, 3H), 3.40 (dd, *J* = 4.0, 10.0 Hz, 1H), 3.30 (s, 3H), 3.28 (s, 3H), 2.35—2.50 (m, 3H), 2.04—2.21 (m, 4H), 1.58—1.91 (m, 16H), 0.88—0.97 (m, 24H); FAB(+)MS *m/z* 768 (M^++H); HR-ESI(+)MS calcd for $C_{39}H_{70}N_6O_9Na$ (M^++Na) 789.5096, found 789.5113.

Boc-[L-Leu-L-Leu-Aib]$_3$-OMe {Aib-nonamer; 2a}. A solution of EDC (121 mg, 0.630 mmol), HOBt (85 mg, 0.630 mmol), carboxylic acid **9a-CO2H** (270 mg, 0.630 mmol), and amine **4a** (344 mg, 0.525 mmol) in CH_2Cl_2 (14 mL) was stirred at room temperature for 48 h. Then, the solution was diluted with EtOAc, washed with 3% aqueous HCl, 5% aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (65% EtOAc in hexane) to give Aib-nonamer **2a** (343 mg, 61%) as colorless crystals: mp 215—217 °C; $[\alpha]^{28}_D$ = - 22.5 (*c* 1.03, $CHCl_3$); IR ($CDCl_3$) 3429, 3315, 3019, 2961, 2872, 1710, 1699, 1659, 1530, 1215 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (br d, *J* = 4.0 Hz, 1H), 7.55 (br d, *J* = 6.0 Hz, 1H), 7.50 (br s, 1H), 7.41 (br s, 1H), 7.36 (br d, *J* = 4.0 Hz, 1H), 7.27 (br d, *J* = 4.8 Hz, 1H), 7.21 (br s, 1H), 6.58 (br s, 1H), 5.09 (br s, 1H), 4.39 (m, 1H), 4.17 (m, 1H), 3.91—4.03 (m, 4H), 3.68 (s, 3H), 1.47—1.91 (m, 45H), 0.86—1.01 (m, 36H); HR-ESI(+)MS calcd for $C_{54}H_{99}N_9O_{12}Na$ (M^++Na) 1088.7305, found 1088.7307.

Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dOM}}]$_3$-OMe {(*R*,*R*)-nonamer; 2b}. (*R*,*R*)-Nonamer **2b** was prepared from **4b** and **9b-CO2H** in a manner similar to that described for the preparation of **2a**: 90% yield; colorless crystals; mp 178—180 °C; $[\alpha]^{24}_D$ = - 13.3 (*c* 0.80, $CHCl_3$); IR ($CDCl_3$) 3430, 3316, 2826, 1698, 1655, 1532, 1158, 1121 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (br d, *J* = 4.4 Hz, 1H), 7.63 (br s, 1H), 7.51 (br d, *J* = 4.0 Hz, 1H), 7.49 (br s, 1H), 7.44 (br s, 1H), 7.35 (br d, *J* = 4.8 Hz, 1H), 7.33 (br d, *J* = 6.4 Hz, 1H), 6.52 (br d, *J* = 2.4 Hz, 1H), 5.05 (br s, 1H), 4.35 (m, 1H), 4.20 (m, 1H), 3.89—4.04 (m, 7H),

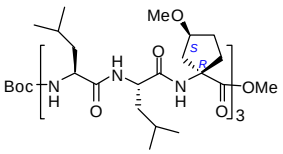
3.76—3.83 (m, 3H), 3.69 (s, 3H), 3.31—3.39 (m, 15H), 3.25 (s, 3H), 3.18 (dd, *J* = 4.0, 12.0 Hz, 1H), 3.00 (dd, *J* = 5.2, 12.0 Hz, 1H), 2.91 (dd, *J* = 6.0, 11.2 Hz, 1H), 2.84 (dd, *J* = 5.2, 11.2 Hz, 1H), 2.66 (dd, *J* = 5.6, 11.6 Hz, 1H), 2.60 (dd, *J* = 6.0, 12.4 Hz, 1H), 2.15—2.23 (m, 2H), 1.45—2.00 (m, 22H), 1.52 (s, 9H), 0.85—1.00 (m, 36H); HR-ESI(+)MS calcd for $C_{66}H_{117}N_9O_{18}Na$ (M^++Na) 1346.8409, found 1346.8453.

Boc-[L-Leu-L-Leu-{(*S*,*S*)-Ac$_5$c^{dOM}}]$_3$-OMe {(*S*,*S*)-nonamer; 2c}.

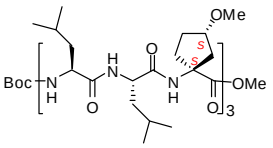


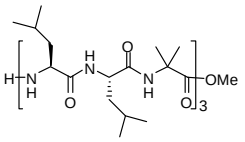
(*S*,*S*)-Nonamer **2c** was prepared from **4c** and **9c-CO2H** in a manner similar to that described for the preparation of **2a**: 85% yield; colorless crystals; mp 102—104 °C; $[\alpha]^{26}_D$ = + 22.8 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3325, 2959, 2901, 2826, 1661, 1525, 1508, 1159, 1106 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (br d, *J* = 5.2 Hz, 1H), 7.34—7.45 (m, 6H), 6.83 (br s, 1H), 5.02 (br s, 1H), 4.32 (m, 1H), 4.18 (m, 1H), 3.93—4.10 (m, 4H), 3.68—3.85 (m, 9H), 3.32—3.38 (m, 18H), 3.00 (dd, *J* = 4.0, 12.0 Hz, 1H), 2.65—2.80 (m, 3H), 1.47—2.40 (m, 26H), 1.50 (s, 9H), 0.85—1.02 (m, 36H); HR-ESI(+)MS calcd for $C_{66}H_{117}N_9O_{18}Na$ (M^++Na) 1346.8409, found 1346.8427.

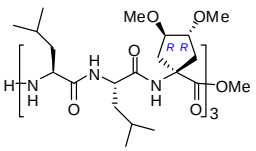
Boc-[L-Leu-L-Leu-{(1*R*,3*S*)-Ac$_5$c^{OM}}]$_3$-OMe {(1*R*,3*S*)-nonamer; 2d}.



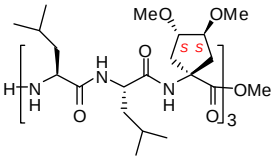
(1*R*,3*S*)-Nonamer **2d** was prepared from **4d** and **9d-CO2H** in a manner similar to that described for the preparation of **2a**: 82% yield; colorless crystals; mp 228—230 °C; $[\alpha]^{27}_D$ = + 5.0 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3430, 3316, 2960, 2872, 1698, 1654, 1531, 1508, 1257, 1159 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (br d, *J* = 4.7 Hz, 1H), 7.57 (br s, 1H), 7.53 (br s, 1H), 7.50 (br d, *J* = 5.6 Hz, 1H), 7.46 (br s, 1H), 7.42 (br d, *J* = 8.2 Hz, 1H), 7.36 (br d, *J* = 5.8 Hz, 1H), 6.52 (br d, *J* = 3.4 Hz, 1H), 5.00 (br s, 1H), 4.37 (m, 1H), 3.90—4.27 (m, 8H), 3.68 (s, 3H), 3.26 (s, 3H), 3.24 (s, 3H), 3.20 (s, 3H), 3.02 (dd, *J* = 6.7, 14.6 Hz, 1H), 2.89 (dd, *J* = 6.7, 13.9 Hz, 1H), 2.86 (dd, *J* = 6.2, 14.6 Hz, 1H), 2.15—2.47 (m, 4H), 1.56—2.06 (m, 29H), 1.51 (s, 9H), 0.85—1.01 (m, 36H); FAB(+)MS *m/z* 1257 (M^++Na); HR-ESI(+)MS calcd for $C_{63}H_{111}N_9O_{15}Na$ (M^++Na) 1256.8092, found 1256.8142.

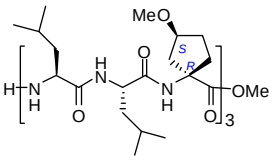
Boc-[L-Leu-L-Leu-{(1*S*,3*S*)-Ac$_5$c^{OM}}]$_3$-OMe {(1*S*,3*S*)-nonamer; 2e}. 
(1*S*,3*S*)-Nonamer **2e** was prepared from **4e** and **9e-CO2H** in a manner similar to that described for the preparation of **2a**: 81% yield; colorless crystals; mp 234—236 °C; $[\alpha]^{27}_D$ = + 5.6 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3429 (br), 3317, 2961, 2937, 2872, 1658, 1258, 1159 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (br s, 1H), 7.59 (br d, *J* = 5.1 Hz, 1H), 7.56 (br s, 1H), 7.45 (br d, *J* = 5.1 Hz, 1H), 7.39 (br d, *J* = 7.7 Hz, 1H), 7.31 (br d, *J* = 6.2 Hz, 1H), 7.28 (br s, 1H), 6.58 (br s, 1H), 5.17 (br s, 1H), 3.90—4.33 (m, 9H), 3.68 (s, 3H), 3.29 (s, 3H), 3.28 (s, 3H), 3.27 (s, 3H), 2.74—2.89 (m, 3H), 2.51—2.59 (m, 2H), 2.37 (dd, *J* = 5.1 Hz, 14.1 Hz, 1H), 2.12—2.28 (m, 3H), 1.54—1.98 (m, 27H), 1.53 (s, 9H), 0.85—1.01 (m, 36H); FAB(+)MS *m/z* 1257 (M^++Na); HR-ESI(+)MS calcd for $C_{63}H_{111}N_9O_{15}Na$ (M^++Na) 1256.8092, found 1256.8141.

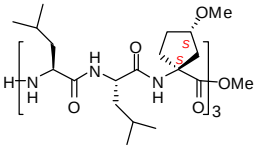
H-[L-Leu-L-Leu-Aib]$_3$-OMe {Aib-nonamer amine; 5a}. 
Aib-nonamer amine **5a** was prepared from **2a** in a manner similar to that described for the preparation of **4a**: 81% yield; colorless crystals; mp 245—247 °C; $[\alpha]^{24}_D$ = - 26.9 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3313 (br), 2960, 2871, 1733, 1656, 1531, 1468, 1157 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (br d, *J* = 6.0 Hz, 1H), 7.55 (br d, *J* = 6.0 Hz, 1H), 7.48 (br d, *J* = 6.0 Hz, 1H), 7.38 (br s, 1H), 7.21—7.26 (m, 3H), 6.55 (br s, 1H), 4.36 (m, 1H), 4.15 (m, 1H), 4.02 (m, 1H), 3.92 (m, 2H), 3.68 (s, 3H), 3.41 (m, 1H), 1.40—1.81 (m, 36H), 0.85—1.03 (m, 36H); FAB(+)MS *m/z* 989 (M^++Na); HR-ESI(+)MS calcd for $C_{49}H_{92}N_9O_{10}$ (M^++H) 966.6962, found 966.6960.

H-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dOM}}]$_3$-OMe {(*R*,*R*)-nonamer amine; 5b}. 
(*R*,*R*)-Nonamer amine **5b** was prepared from **2b** in a manner similar to that described for the preparation of **4a**: 82% yield; colorless crystals; mp 232—235 °C; $[\alpha]^{24}_D$ = - 25.1 (*c* 1.00, $CHCl_3$); IR (KBr) 3316 (br), 2960, 2936, 2872, 1734, 1657, 1531, 1467, 1120 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (br d, *J* = 6.0 Hz, 1H), 7.69 (br d, *J* = 6.0 Hz, 1H), 7.62 (br s, 1H), 7.51 (br d, *J* = 6.4 Hz, 1H), 7.40 (br s, 1H), 7.31—7.35 (m, 2H), 6.67 (br s,

1H), 4.34 (m, 1H), 4.18 (m, 1H), 3.76—3.94 (m, 9H), 3.70 (s, 3H), 3.43 (m, 1H), 3.31—3.36 (m, 18H), 3.18 (m, 1H), 2.65—2.94 (m, 4H), 2.14—2.24 (m, 4H), 1.56—2.00 (m, 21H), 0.85—1.02 (m, 36H); FAB(+)MS *m/z* 1247 (M^++Na); HR-ESI(+)MS calcd for $C_{61}H_{109}N_9O_{16}Na$ (M^++Na) 1246.7884, found 1246.7931.

H-[L-Leu-L-Leu-{(*S*,*S*)-Ac$_5$c^{dOM}}]$_3$-OMe {(*S*,*S*)-nonamer amine; 5c}. 
(*S*,*S*)-Nonamer amine **5c** was prepared from **2c** in a manner similar to that described for the preparation of **4a**: 85% yield; colorless crystals; mp 64—66 °C; $[\alpha]^{26}_D$ = + 25.5 (*c* 1.01, $CHCl_3$); IR (KBr) 3319 (br), 2957, 2871, 1742, 1655, 1535, 1467, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (br s, 1H), 7.72 (br d, *J* = 4.8 Hz, 1H), 7.48 (br d, *J* = 4.4 Hz, 1H), 7.26—7.38 (m, 4H), 7.13 (br s, 1H), 4.33 (m, 1H), 4.20 (m, 1H), 4.05 (m, 1H), 3.72—3.94 (m, 9H), 3.68 (s, 3H), 3.32—3.41 (m, 18H), 2.98 (m, 1H), 2.64—2.72 (m, 2H), 2.50 (m, 1H), 2.35 (dd, *J* = 7.2, 14.0 Hz, 1H), 1.58—2.27 (m, 15H), 0.85—1.05 (m, 36H); FAB(+)MS *m/z* 1247 (M^++Na); HR-ESI(+)MS) calcd for $C_{61}H_{109}N_9O_{16}Na$ (M^++Na) 1246.7884, found 1246.7879.

H-[L-Leu-L-Leu-{(1*R*,3*S*)-Ac$_5$c^{OM}}]$_3$-OMe {(1*R*,3*S*)-nonamer amine; 5d}. 
(1*R*,3*S*)-Nonamer amine **5d** was prepared from **2d** in a manner similar to that described for the preparation of **4a**: 62% yield; colorless crystals; mp 240—242 °C; $[\alpha]^{24}_D$ = + 4.4 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3421, 3316 (br), 2960, 2872, 1732, 1655, 1530, 1508, 1102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (br d, *J* = 4.8 Hz, 1H), 7.57 (br d, *J* = 5.2 Hz, 1H), 7.52 (br s, 1H), 7.45 (br s, 1H), 7.41 (br d, *J* = 8.0 Hz, 1H), 7.35 (br d, *J* = 6.0 Hz, 1H), 7.26 (br s, 1H), 6.46 (br s, 1H), 4.37 (m, 1H), 4.18 (m, 1H), 3.92—4.04 (m, 7H), 3.68 (s, 3H), 3.40 (m, 1H), 3.24—3.26 (s, 9H), 3.01 (dd, *J* = 6.8, 14.8 Hz, 1H), 2.89 (dd, *J* = 6.8, 14.4 Hz, 1H), 2.79 (dd, *J* = 5.6, 14.4 Hz, 1H), 2.24—2.45 (m, 2H), 1.57—2.12 (m, 30H), 0.85—1.03 (m, 36H); FAB(+)MS *m/z* 1135 (M^++H); HR-ESI(+)MS calcd for $C_{58}H_{103}N_9O_{13}Na$ (M^++Na) 1156.7568, found 1156.7613.

H-[L-Leu-L-Leu-{(1*S*,3*S*)-Ac$_5$c^{OM}}]$_3$-OMe {(1*S*,3*S*)-nonamer amine; 5e}. 
(1*S*,3*S*)-Nonamer amine **5e** was prepared from **2e** in a manner similar to that

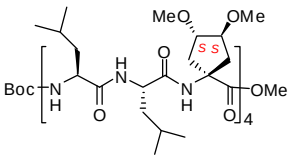
described for the preparation of **4a**: 69% yield; colorless crystals; mp 241—243 °C; $[\alpha]^{25}_D$ = - 6.1 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3316 (br), 2960, 2936, 1654, 1532, 1508, 1101 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.60 (br d, *J* = 4.0 Hz, 1H), 7.53 (br s, 1H), 7.52 (br d, *J* = 5.2 Hz, 1H), 7.40 (br d, *J* = 7.2 Hz, 1H), 7.30 (br d, *J* = 6.4 Hz, 1H), 7.21 (br s, 1H), 6.89 (br s, 1H), 4.30 (m, 1H), 4.18 (m, 1H), 3.91—4.06 (m, 6H), 3.68 (s, 3H), 3.44 (m, 1H), 3.27—3.28 (m, 9H), 2.75—2.83 (m, 3H), 2.54 (dd, *J* = 6.8, 14.8 Hz, 1H), 2.35 (dd, *J* = 4.8 Hz, 14.4 Hz, 1H), 2.28 (dd, *J* = 7.6 Hz, 11.2 Hz, 1H), 1.57—2.17 (m, 29H), 0.85—1.02 (m, 36H); FAB(+)MS *m/z* 1135 (M^++H); HR-ESI(+)MS calcd for $C_{58}H_{103}N_9O_{13}Na$ (M^++Na) 1156.7568, found 1156.7612.

Boc-[L-Leu-L-Leu-Aib]$_4$-OMe {Aib-dodecamer; 3a}. A solution of EDC (46 mg, 0.238 mmol), HOBt (32 mg, 0.238 mmol), and carboxylic acid **9a-CO2H** (102 mg, 0.238 mmol) in CH_2Cl_2 (4 mL) was stirred at 0 °C for 30 min. Then, a solution of amine **5a** (115 mg, 0.119 mmol) in CH_2Cl_2 (6 mL) was added. After being stirred at room temperature for 48 h, the solution was diluted with EtOAc, washed with 3% aqueous HCl, 5% aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (65% EtOAc in hexane) to give Aib-dodecamer **3a** (129 mg, 79%) as colorless crystals: mp 250—252 °C; $[\alpha]^{28}_D$ = - 23.1 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3310, 3019, 2962, 2871, 1698, 1654, 1428, 1215, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (br d, *J* = 5,0 Hz, 1H), 7.75 (br d, *J* = 5,0 Hz, 1H), 7.58 (br d, *J* = 8.2 Hz, 1H), 7.54 (br s, 1H), 7.48 (br s, 1H), 7.45 (br s, 1H), 7.26—7.38 (m, 4H), 6.62 (br s, 1H), 5.12 (br s, 1H), 3.90—4.38 (m, 6H), 3.68 (s, 3H), 1.63—2.00 (m, 24H), 1.57 (s, 9H), 1.48—1.54 (m, 24H), 0.86—1.02 (m, 48H); FAB(+)MS *m/z* 1400 (M^++Na); HR-ESI(+)MS calcd for $C_{70}H_{128}N_{12}O_{15}Na$ (M^++Na) 1399.9514, found 1399.9518.

Boc-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dOM}}]$_4$-OMe {(*R*,*R*)-dodecamer; 3b}. (*R*,*R*)-Dodacamer **3b** was prepared from **5b** and **9b-CO2H** in a manner similar to that described for the preparation of **3a**: 82% yield (mixture of Me and Et esters); colorless crystals; mp 244—246 °C; $[\alpha]^{24}_D$ = - 9.8 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$)

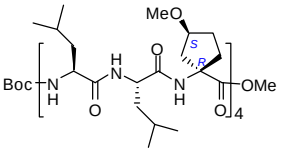
3312 (br), 3293, 2960, 2932, 2872, 1698, 1653, 1533, 1508, 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69—7.80 (m, 4H), 7.38—7.53 (m, 6H), 6.80 (br s, 1H), 5.00 (br s, 1H), 3.77—4.34 (m, 16H), 3.70 (s, 3H), 3.26—3.37 (m, 24H), 2.60—3.21 (m, 8H), 1.66—2.24 (m, 32H), 1.51 (s, 9H), 0.85—1.03 (m, 48H); FAB(+)MS *m/z* 1745 (M^++Na); HR-ESI(+)MS calcd for $C_{86}H_{152}N_{12}O_{23}Na$ (M^++Na) 1744.0986, found 1744.0979.

Boc-[L-Leu-L-Leu-{(*S*,*S*)-Ac_5c^{dOM}}]$_4$-OMe {(*S*,*S*)-dodecamer; 3c}.



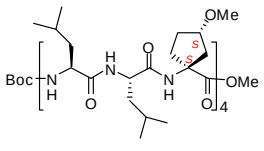
(*S*,*S*)-Dodacamer **3c** was prepared from **5c** and **9c-CO2H** in a manner similar to that described for the preparation of **3a**: 69% yield; colorless crystals; mp 122—124 °C; $[\alpha]^{26}_D$ = + 31.0 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3325, 2959, 2826, 1654, 1531, 1508, 1215, 1158, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (br s, 1H), 7.68 (d, *J* = 5,2 Hz, 1H), 7.57 (br s, 1H), 7.33—7.54 (m, 7H), 6.78 (br s, 1H), 5.30 (br s, 1H), 3.70—4.34 (m, 16H), 3.67 (s, 3H), 3.25—3.39 (m, 24H), 1.57—3.10 (m, 40H), 1.51 (s, 9H), 0.85—1.04 (m, 48H); FAB(+)MS *m/z* 1745 (M^++Na); HR-ESI(+)MS calcd for $C_{86}H_{152}N_{12}O_{23}Na$ (M^++Na) 1744.0986, found 1744.0926.

Boc-[L-Leu-L-Leu-{(1*R*,3*S*)-Ac_5c^{OM}}]$_4$-OMe {(1*R*,3*S*)-dodecamer; 3d}.



(1*R*,3*S*)-Dodacamer **3d** was prepared from **5d** and **9d-CO2H** in a manner similar to that described for the preparation of **3a**: 94% yield; colorless crystals; mp 271—273 °C; $[\alpha]^{27}_D$ = + 6.5 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3311, 2960, 2872, 2825, 1653, 1532, 1105 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (br d, *J* = 4.3 Hz, 1H), 7.74 (br d, *J* = 4.5 Hz, 1H), 7.66 (br s, 1H), 7.62 (br s, 1H), 7.53 (br s, 1H), 7.44—7.50 (m, 4H), 7.39 (br d, *J* = 5.6 Hz, 1H), 6.52 (br d, *J* = 3.9 Hz, 1H), 4.99 (br s, 1H), 4.37 (m, 1H), 4.18 (m, 1H), 3.88—4.06 (m, 10H), 3.68 (s, 3H), 3.26 (s, 3H), 3.25 (s, 3H), 3.24 (s, 3H), 3.20 (s, 3H), 2.80—3.08 (m, 4H), 1.54—2.50 (m, 44H), 1.52 (s, 9H), 0.86—1.02 (m, 48H); FAB(+)MS *m/z* 1625 (M^++Na); HR-ESI(+)MS calcd for $C_{82}H_{144}N_{12}O_{19}Na$ (M^++Na) 1624.0563, found 1624.0559.

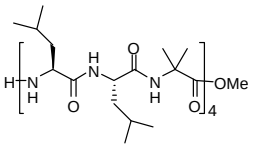
Boc-[L-Leu-L-Leu-{(1*S*,3*S*)-Ac_5c^{OM}}]$_4$-OMe {(1*S*,3*S*)-dodecamer; 3e}.



(1*S*,3*S*)-Dodacamer **3e** was prepared from **5e** and **9e-CO2H** in a manner

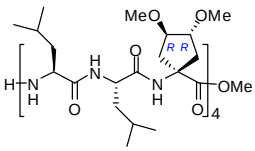
similar to that described for the preparation of **3a**: 90% yield; colorless crystals; mp 250—253 °C; $[\alpha]^{27}_D$ = + 9.6 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3428 (br), 3315, 2960, 2937, 2871, 1654, 1533,1368, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (br s, 1H), 7.62—7.71 (m, 4H), 7.53 (br d, *J* = 7.3 Hz, 1H), 7.47 (br s, 1H), 7.29—7.33 (m, 3H), 7.08 (br s, 1H), 5.76 (br s, 1H), 4.28 (m, 1H), 4.19 (m, 1H), 3.90—4.17 (m, 10H), 3.67 (s, 3H), 3.25—3.28 (m, 12H), 1.61—2.90 (m, 48H), 1.53 (s, 9H), 0.85—1.02 (m, 48H); FAB(+)MS *m/z* 1625 (M^++Na); HR-ESI(+)MS calcd for $C_{82}H_{144}N_{12}O_{19}Na$ (M^++Na) 1624.0563, found 1624.0547.

H-[L-Leu-L-Leu-Aib]$_4$-OMe {Aib-dodecamer amine; 6a}.



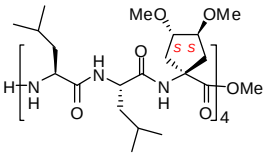
Aib-dodecamer amine **6a** was prepared from **3a** in a manner similar to that described for the preparation of **4a**: 89% yield; colorless crystals; mp 249—251 °C; $[\alpha]^{24}_D$ = - 30.5 (*c* 1.01, $CHCl_3$); IR ($CDCl_3$) 3309 (br), 2960, 2871, 1732, 1654, 1533, 1468, 1386, 1365, 1288 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (br s, 1H), 7.81—7.83 (m, 2H), 7.65 (br s, 1H), 7.50—7.52 (m, 3H), 7.30—7.32 (m, 3H), 7.03 (br s, 1H), 4.32 (m, 1H), 4.13 (m, 1H), 4.00—4.08 (m, 2H), 3.89—3.93 (m, 3H), 3.68 (s, 3H), 3.44 (m, 1H), 1.38—2.00 (m, 48H), 0.85—1.03 (m, 48H); FAB(+)MS *m/z* 1300 (M^++Na); HR-ESI(+)MS calcd for $C_{65}H_{120}N_{12}O_{13}Na$ (M^++Na) 1299.8990, found 1299.8949.

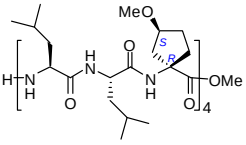
H-[L-Leu-L-Leu-{(*R*,*R*)-Ac$_5$c^{dOM}}]$_4$-OMe {(*R*,*R*)-dodecamer amine; 6b}.

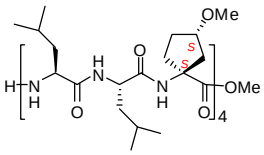


(*R*,*R*)-Dodecamer amine **6b** was prepared from **3b** in a manner similar to that described for the preparation of **4b**: 73% yield (mixture of Me and Et esters); colorless crystals; mp 249—251 °C; $[\alpha]^{24}_D$ = - 16.0 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3312 (br), 2959, 2936, 2872, 1654, 1535, 1508, 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (br, 1H), 7.98 (br s, 1H), 7.85—7.88 (m, 3H), 7.76 (br s, 1H), 7.63 (br s, 1H), 7.57 (br s, 1H), 7.42 (br d, *J* = 3.2 Hz, 1H), 7.34—7.37 (m, 2H) 4.30 (m, 1H), 4.16 (m, 1H), 3.91—4.06 (m, 10H), 3.73—3.82 (m, 3H), 3.71 (s, 3H), 3.51 (m, 1H), 3.28—3.36 (m, 24H), 3.18 (dd, *J* = 8.0, 14.4 Hz, 1H), 3.08 (dd, *J* = 8.0, 15.2 Hz, 1H), 3.00 (dd, *J* = 6.8, 14.8 Hz, 1H), 2.83—2.90 (m, 2H), 2.64 (m, 1H), 2.39 (m, 1H), 1.65—2.24 (m, 32H), 1.03—0.86 (m, 48H); FAB(+)MS *m/z* 1645 (M^++Na); HR-ESI(+)MS calcd for

$C_{81}H_{122}N_{12}O_{21}$ (M^++H) 1622.0642, found 1622.0564.

H-[L-Leu-L-Leu-{(*S*,*S*)-Ac$_5$c^{dOM}}]$_4$-OMe {(*S*,*S*)-dodecamer amine; 6c}. 
(*S*,*S*)-Dodecamer amine **6c** was prepared from **3c** in a manner similar to that described for the preparation of **4c**: 67% yield; colorless crystals; mp 120—122 °C; $[\alpha]^{26}_D$ = + 31.7 (*c* 1.00, $CHCl_3$); IR (KBr) 3316 (br), 2957, 2871, 2825, 1740, 1663, 1538, 1468, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (br s, 1H), 7.73—7.80 (m, 2H), 7.62 (br s, 1H), 7.30—7.53 (m, 4H), 7.28—7.29 (m, 2H), 7.27 (br d, *J* = 4.4 Hz, 1H), 4.33 (m, 2H), 3.69—4.19 (m, 38H), 3.67 (s, 3H), 3.32—3.42 (m, 24H), 3.03 (m, 2H), 2.65—2.77 (m, 6H), 2.53 (m, 1H), 1.62—2.41 (m, 31H), 0.85—1.06 (m, 48H); FAB(+)MS *m/z* 1645 (M^++Na); HR-ESI(+)MS calcd for $C_{81}H_{122}N_{12}O_{21}Na$ (M^++Na) 1644.0461, found 1644.0382.

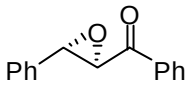
H-[L-Leu-L-Leu-{(1*R*,3*S*)-Ac$_5$c^{OM}}]$_4$-OMe {(1*R*,3*S*)-dodecamer amine; 6d}. 
(1*R*,3*S*)-Dodecamer amine **6d** was prepared from **3d** in a manner similar to that described for the preparation of **4d**: 60% yield; colorless crystals; mp 262—265 °C; $[\alpha]^{24}_D$ = + 6.2 (*c* 1.00, $CHCl_3$); IR ($CDCl_3$) 3311 (br), 2960, 2872, 2826, 1653, 1532, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (br s, 1H), 7.79 (br d, *J* = 3.2 Hz, 1H), 7.75 (br d, *J* = 3.2 Hz, 1H), 7.66 (br s, 1H), 7.58—7.59 (m, 2H), 7.52 (br s, 1H), 7.45—7.47 (m, 2H), 7.38 (br d, *J* = 4.8 Hz, 1H), 6.50 (br s, 1H), 4.36 (m, 1H), 4.11—4.16 (m, 2H), 3.94—4.02 (m, 5H), 3.68 (s, 3H), 3.41 (m, 1H), 3.24—3.26 (m, 12H), 2.78—3.05 (m, 4H), 1.57—2.50 (m, 44H), 0.87—1.04 (m, 48H); FAB(+)MS *m/z* 1525 (M^++Na); HR-ESI(+)MS calcd for $C_{77}H_{136}N_{12}O_{17}Na$ (M^++Na) 1524.0039, found 1524.0089.

H-[L-Leu-L-Leu-{(1*S*,3*S*)-Ac$_5$c^{OM}}]$_4$-OMe {(1*S*,3*S*)-dodecamer amine; 6e}. 
(1*S*,3*S*)-Dodecamer amine **6e** was prepared from **3e** in a manner similar to that described for the preparation of **4e**: 67% yield; colorless crystals; mp 243—245 °C; $[\alpha]^{25}_D$ = + 7.8 (*c* 1.03, $CHCl_3$); IR ($CDCl_3$) 3310 (br), 2959, 2935, 2871, 1653, 1540, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (br, 1H), 7.80—8.04 (m, 8H), 7.38 (br s, 1H), 7.10 (br

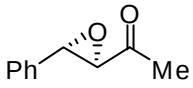
s, 1H), 3.91—4.27 (m, 11H), 3.69 (s, 3H), 3.49 (m, 1H), 3.24—3.28 (m, 12H), 1.79—2.82 (m, 48H), 0.90—1.02 (m, 48H); FAB(+)MS *m/z* 1525 (M^++Na); HR-ESI(+)MS calcd for $C_{77}H_{136}N_{12}O_{17}Na$ (M^++Na) 1524.0039, found 1524.0087.

Following epoxides are known compounds. The spectroscopic data of these compounds are in accordance with those of reported ones. The absolute configurations of epoxides were determined by the comparison of the specific rotations with literature values.

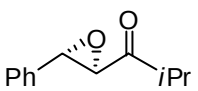
(2*R*,3*S*)-*trans*-Epoxy-3-phenyl-1-phenylpropan-1-one (8a). Colorless crystals; $[\alpha]^{23}_D$ = - 215.1 (*c* 1.00, $CHCl_3$) [Lit.,[6S] another (2*S*,3*R*)-enantiomer, $[\alpha]_D$ = + 182.2 (*c* 1.14, $CHCl_3$)]; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.00—8.02 (m, 2H), 7.36—7.62 (m, 8H), 4.29 (d, *J* = 1.6 Hz, 1H), 4.08 (d, *J* = 1.6 Hz, 1H). HPLC (DAICEL Chiralpak AD column, 4.6 mmϕ x 250 mm; 10% EtOH in hexane; flow rate, 1.0 mL/min): retention time (t_R) = 19.1 min (2*R*,3*S*-enantiomer, major), 26.4 min (2*S*,3*R*-enantiomer, minor).



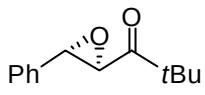
(3*R*,4*S*)-*trans*-Epoxy-4-phenylbutan-2-one (8b). Colorless oil; $[\alpha]^{26}_D$ = - 64.6 (*c* 1.05, $CHCl_3$) [Lit.,[7S] - 73.3 (*c* 1.00, $CHCl_3$)]; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.35—7.40 (m, 3H), 7.27—7.29 (m, 2H), 4.00 (d, *J* = 1.6 Hz, 1H), 3.49 (d, *J* = 1.6 Hz, 1H), 2.19 (s, 3H). HPLC (DAICEL Chiralpak AD column, 4.6 mmϕ x 250 mm; 10% EtOH in hexane; flow rate, 1.0 mL/min): t_R = 8.3 min (2*R*,3*S*-enantiomer, major), 18.9 min (2*S*,3*R*-enantiomer, minor).



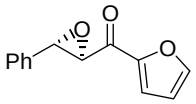
(4*R*,5*S*)-*trans*-Epoxy-2-methyl-5-phenylpentan-3-one (8c). Colorless crystals; $[\alpha]^{26}_D$ = - 149.8 (*c* 1.00, $CHCl_3$) [Lit.,[8S] - 208 (*c* 1.0, $CHCl_3$)]; ^{1}H NMR (400MHz, $CDCl_3$) δ7.28—7.40 (m, 5H), 3.92 (d, *J* = 2.0 Hz, 1H), 3.60 (d, *J* = 2.0 Hz, 1H), 1.17 (q, *J* = 5.2, 6H). HPLC (DAICEL Chiralpak AD column, 4.6 mmϕ x 250 mm; 5% EtOH in hexane; flow rate, 0.7 mL/min): t_R = 14.5 min (2*R*,3*S*-enantiomer, major), 25.4 min (2*S*,3*R*-enantiomer, minor).



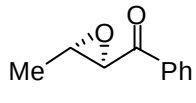
(1*S*,2*R*)-*trans*-1,2-Epoxy-4,4-dimethyl-1-phenylpentan-3-one (8d). Colorless crystals; $[\alpha]^{26}_{D}$ = - 158.1 (*c* 1.00, $CHCl_3$) [Lit.,[9S] - 194 (*c* 1, $CHCl_3$)]; ^1H NMR (400MHz, $CDCl_3$) δ7.30—7.39 (m, 5H), 3.86 (s, 2H), 1.24 (s, 9H). HPLC (DAICEL Chiralpak AD column, 4.6 mmϕ x 250 mm; 5% EtOH in hexane; flow rate, 0.7 mL/min): t_R = 15.0 min (2*S*,3*R*-enantiomer, minor), 20.8 min (2*R*,3*S*-enantiomer, major).



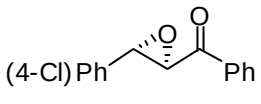
(2*R*,3*S*)-*trans*-Epoxy-3-phenyl-1-(2-furyl)propan-1-one (8e). Colorless crystals; $[\alpha]^{26}_{D}$ = - 190.0 (*c* 1.00, $CHCl_3$) [Lit.,[10S] - 200 (*c* 1.0, $CHCl_3$)]; ^1H NMR (400MHz, $CDCl_3$) δ 7.67 (m, 1H), 7.46 (d, *J* = 4.0 Hz, 1H), 6.59—6.60 (m, 5H), 4.2 (m, 2H). HPLC (DAICEL Chiralcel OD column, 4.6 mmϕ x 250 mm; 5% *i*PrOH in hexane; flow rate, 0.8 mL/min): t_R = 25.0 min (2*S*,3*R*-enantiomer, minor), 26.4 min (2*R*,3*S*-enantiomer, major).



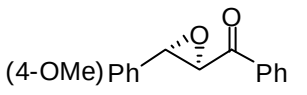
(2*R*,3*S*)-*trans*-Epoxy-3-methyl-1-phenylpropan-1-one (8f). Colorless crystals; $[\alpha]^{26}_{D}$ = - 5.5 (*c* 1.00, $CHCl_3$) [Lit.,[11S] - 10.0 (*c* 0.6, $CHCl_3$)]; ^1H NMR (400MHz, $CDCl_3$) δ8.01—8.26 (m, 2H), 7.61 (m, 1H), 7.48—7.52 (m, 1H), 3.97 (s, 1H), 3.23 (m, 1H), 1.52 (d, *J* = 4.4, 3H). HPLC (DAICEL Chiralcel OD column, 4.6 mmϕ x 250 mm; 5% *i*PrOH in hexane; flow rate, 0.8 mL/min): t_R = 9.1 min (2*S*,3*S*-enantiomer, minor), 9.8 min (2*R*,3*S*-enantiomer, major).



(2*R*,3*S*)-*trans*-Epoxy-3-(4-chlorophenyl)-1-phenylpropan-1-one (8g). Thin yellow crystals; $[\alpha]^{26}_{D}$ = - 214.4 (*c* 1.00, CH_2Cl_2) [Lit.,[10S] - 233 (*c* 1.0, CH_2Cl_2)]; ^1H NMR (400MHz, $CDCl_3$) δ7.99—8.01 (m, 2H), 7.61—7.65 (m, 2H), 7.48—7.52 (m, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 4.24 (d, *J* = 1.6 Hz, 1H), 4.06 (d, *J* = 1.6 Hz, 1H). HPLC (DAICEL Chiralcel OD column, 4.6 mmϕ x 250 mm; 2% *i*PrOH in hexane; flow rate, 0.6 mL/min): t_R = 39.9 min (2*S*,3*R*-enantiomer, minor), 43.2 min (2*R*,3*S*-enantiomer, major).



(2*R*,3*S*)-*trans*-Epoxy-3-(4-methoxyphenyl)-1-phenylpropan-1-one



(8h). Thin yellow crystals; $[\alpha]^{26}_{D}$ = - 191.5 (*c* 1.00, $CHCl_3$) [Lit.,[12S] another 2*S*,3*R*-enantiomer, + 131 (*c* 0.70, $CHCl_3$)]; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.2 Hz, 2H), 7.62 (m, 1H), 7.47—7.52 (m, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 6.94—6.92 (m, 2H), 4.28 (d, *J* = 1.6 Hz, 1H), 4.03 (d, *J* = 1.6 Hz, 1H), 3.83 (s, 3H). HPLC (DAICEL Chiralcel OD column, 4.6 mmϕ x 250 mm; 5% *i*PrOH in hexane; flow rate, 0.8 mL/min): t_R = 21.3 min (2*S*,3*R*-enantiomer, minor), 23.0 min (2*R*,3*S*-enantiomer, major).

References of Experimetal Section.

(S1) M. Tanaka, Y. Demizu, M. Doi, M. Kurihara, H. Suemune, *Angew. Chem. Int. Ed.*, **2004**, *43*, 5360—5363.

(S2) M. Nagano, M. Tanaka, M. Doi, Y. Demizu, M. Kurihara, H. Suemune, *Org. Lett.*, **2009**, *11*, 1135—1137.

(S3) M. Cabrera, M. Simoens, G. Falchi, M. L. Lavaggi, O. E. Piro, E. E. Castellano, A. Vidal, A. Azqueta, A. Monge, A. Lo´pez de Cera´in, G. Sagrera, G. Seoane, H. Cerecetto, M. Gonza´lez. *Bioorg. Med. Chem.* **2007**, *15*, 3356—3367.

(S4) F. D. Therkelsen, A. L. Hansen, E. B. Pedersen and C. Nielsen. *Org. Biomol. Chem.,* **2003**, *1*, 2908—2918.

(S5) Y. Demizu, M. Tanaka, M. Nagano, M. Kurihara, M. Doi and H. Suemune, *Chem. Pham. Bull.*, **2007**, *55*, 840—842.

(S6) M. Bougauchi, S. Watanabe, T. Arai, H. Sasaki, M. Shibasaki, *J. Am. Chem. Soc.*, **1997**, *119*, 2329—2330.

(S7) B. M. Adger, J. V. Barkley, S. Bergeron, M. W. Cappi, B. E. Flowerdew, M. P. Jackson, R. MacCague, T. C. Nugent, S. M. Roberts, *J. Chem. Soc., Perkin Trans. I*, **1997**, 3501—3507.

(S8) J. F. Bickley, S. M. Roberts, Y. Runhui, J. Skidmore, C. B. Smith, *Tetrahedron*, **2003**, *59*, 5731—5736.

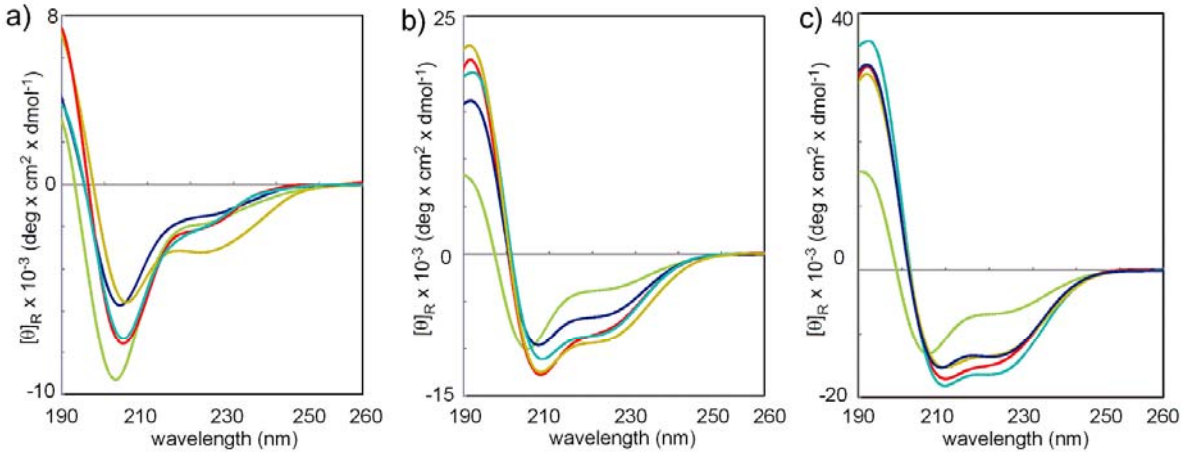
(S9) T. Nemoto, T. Ohshima, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.*, **2001**, *123*, 2725—2726.

(S10) B. M. Choudary, M. L. Kantam, K. V. S. Ranganath, K. Mahendar, B. Sreedhar, *J. Am. Chem. Soc.*, **2004**, *126*, 3396—3397.

(S11) A. Lattanzi, *Org. Lett*., **2005**, *7*, 2579—2582.

(S12) B. Lygo, P. G. Wainwright, *Tetrahedron*, **1999**, *55*, 6289—6300.

Fig. S1. CD spectra of Boc-[L-Leu-L-Leu-dAA]$_m$-OMe (m = 2,3,4).



CD spectra of Boc-{L-Leu-L-Leu-(1*S*,3*S*)-Ac$_5$c^{OM}}$_n$-OMe in TFE solution (100 μM). (a) **1a-1e**: hexamer (n = 2). (b) **2a-2e**: nonamer (n = 3). (c) **3a-3e**: dodecamer (n = 4). Aib: **a** (green); (*R*,*R*)-Ac$_5$c^{dOM}: **b** (sky blue); (*S*,*S*)-Ac$_5$c^{dOM}: **c** (yellow); (1*R*,3*S*)-Ac$_5$c^{OM}: **d** (dark blue); (1*S*,3*S*)-Ac$_5$c^{OM}: **e** (red).

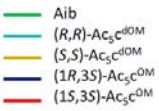
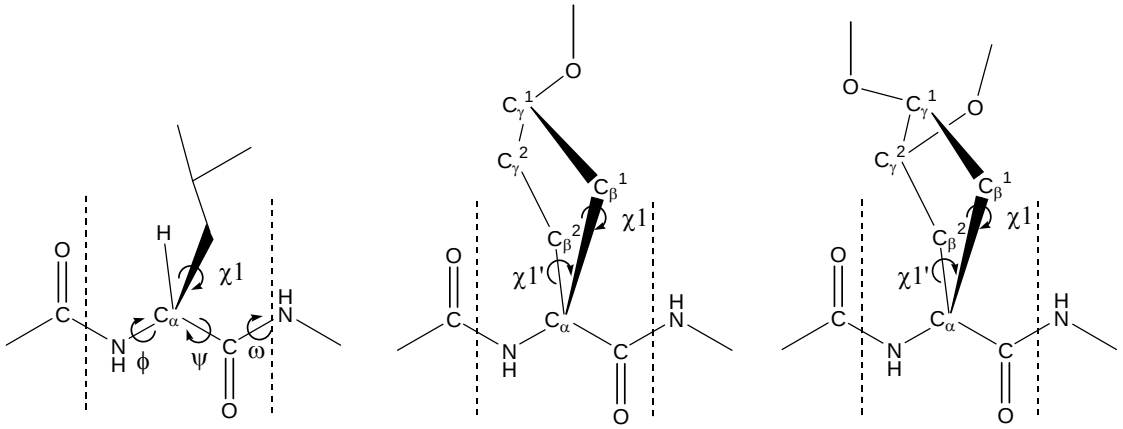


Table S2. Selected torsion angle (°) for Boc-[L-Leu-L-Leu-(1*S*,3*S*)-Ac_5c^{OM}]$_m$-OMe **1e** (m=2) and **2e** (m=3), and H-[L-Leu-L-Leu-(*S*,*S*)-Ac_5c^{dOM}]$_4$-OMe **6c** determined by the X-ray crystallographic analysis.



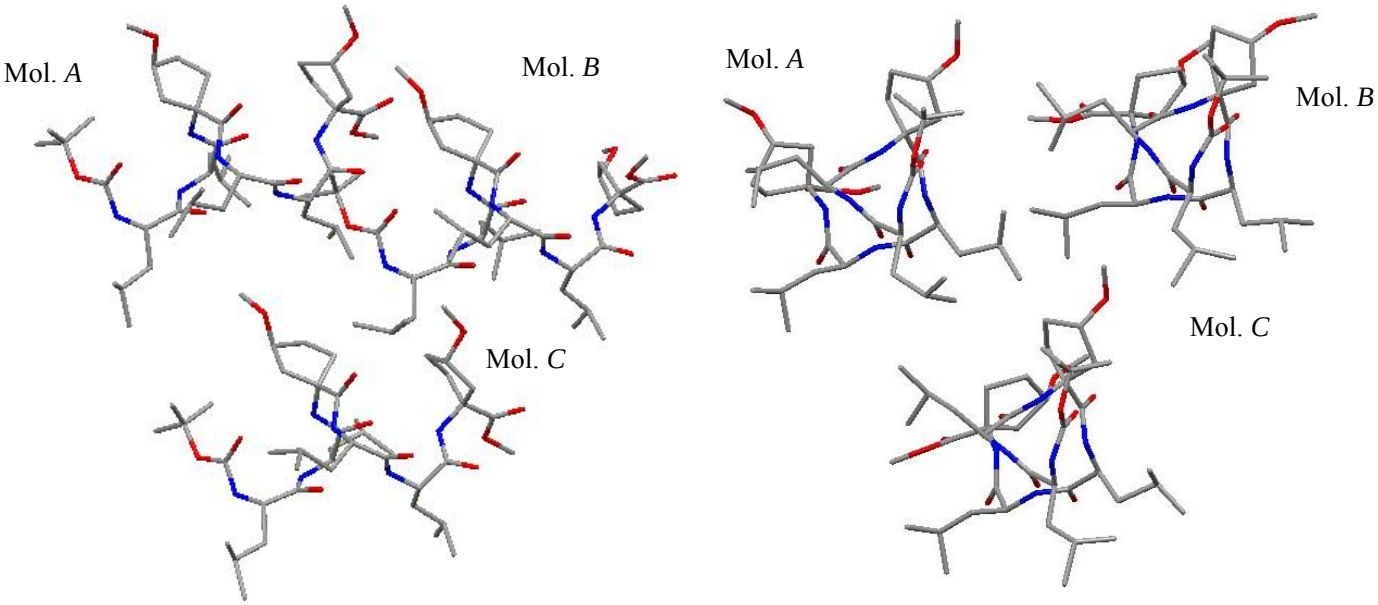
Torsion Angle	Boc-[L-Leu-L-Leu-(1*S*,3*S*)-Ac_5c^{OM}]$_2$-OMe **1e** Molecule *A*	Molecule *B*	Molecule *C*	Boc-[L-Leu-L-Leu-(1*S*,3*S*)-Ac_5c^{OM}]$_3$-OMe **2e** Molecule *A*	Molecule *B*	H-[L-Leu- L-Leu-(*S*,*S*)-Ac_5c^{dOM}]$_4$-OMe **6c**
ω0	171.8	176.0	178.4	168.3	–178.8	–
ϕ1	–67.8	–68.3	–68.5	–65.0	–80.1	–
ψ1	–16.3	–15.0	–14.6	–34.5	–43.2	–12.0
ω1	173.2	171.7	172.4	–177.9	–179.2	–173.5
ϕ2	–57.9	–55.3	–62.2	–59.3	–56.2	–50.3
ψ2	–30.0	–32.0	–24.5	–50.0	–41.5	–44.8
ω2	178.6	178.4	175.9	–177.8	–179.6	–176.4
ϕ3	–60.9	–61.7	–56.1	–54.3	–54.0	–57.7
ψ3	–33.0	–30.5	–38.4	–53.2	–47.4	–43.6
ω3	179.2	175.1	178.5	–173.5	–178.6	–179.4
ϕ4	–86.3	–86.6	–77.3	–65.0	–62.7	–70.0
ψ4	–36.8	–35.4	–39.8	–44.2	–45.6	–40.8

ω4	177.4	178.7	177.6	–177.9	–174.4	–179.1
ϕ5	–65.1	–62.2	–62.9	–66.7	–70.0	–60.5
ψ5	–42.3	–39.6	–40.8	–43.8	–34.7	–45.5
ω5	174.1	179.8	175.9	178.9	176.7	–179.2
ϕ6	–56.8	52.3	56.5	–55.1	–56.3	–58.1
ψ6	–37.7	39.5	38.0	–43.1	–44.4	–50.9
ω6	–165.5	177.3	175.0	–173.4	–179.6	–175.2
ϕ7	–	–	–	–72.9	–72.3	–64.2
ψ7	–	–	–	–45.3	–43.4	–45.4
ω7	–	–	–	–169.9	–173.4	–177.0
ϕ8	–	–	–	–85.3	–65.6	–61.6
ψ8	–	–	–	–29.8	–48.5	–41.2
ω8	–	–	–	–174.2	–179.2	–179.5
ϕ9	–	–	–	51.7	51.7	–55.3
ψ9	–	–	–	32.3	47.0	–41.9
ω9	–	–	–	172.4	175.5	–176.3
ϕ10	–	–	–	–	–	–78.2
ψ10	–	–	–	–	–	–26.6
ω10	–	–	–	–	–	176.8
ϕ11	–	–	–	–	–	–78.5
ψ11	–	–	–	–	–	–15.9
ω11	–	–	–	–	–	174.5
ϕ12	–	–	–	–	–	58.7
ψ12	–	–	–	–	–	36.2
ϕ12	–	–	–	–	–	179.7

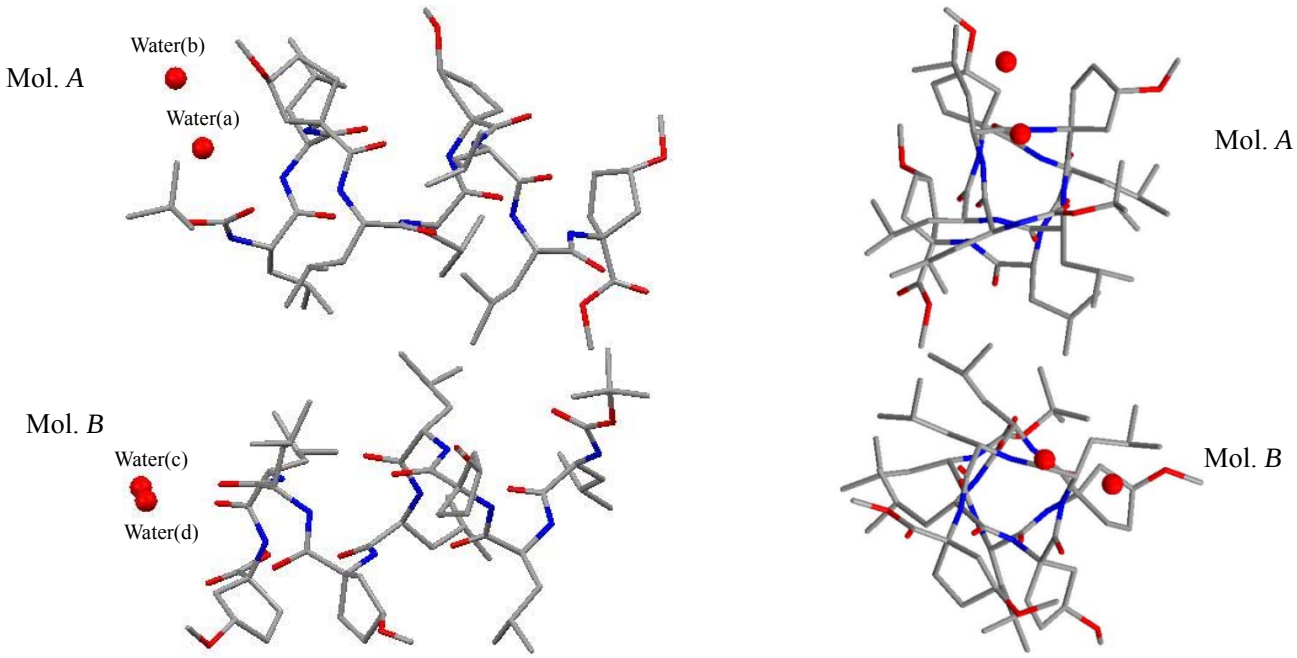
χ1	–85.8	–62.5	–61.1	–175.6	–178.5	–66.9
χ2	–111.2	–176.7	–80.6	–172.4	–177.2	–179.1
χ3	–86.3	–85.6	–97.7	–84.4	–93.7	–149.9
χ3’	75.9	73.1	71.4	80.4	76.8	126.4
χ4	–80.7	–71.1	–70.0	–70.0	–178.2	–61.1
χ5	–178.9	–176.8	–173.4	–160.5	–58.0	–66.6
χ6	–93.0	–84.5	–113.0	–81.0	–89.1	–148.5
χ6’	62.6	79.6	92.0	84.8	97.3	118.7
χ7	–	–	–	176.0	–72.1	179.0
χ8	–	–	–	–86.4	–179.9	–176.5
χ9	–	–	–	–84.0	–89.3	–143.0
χ9’	–	–	–	76.9	111.8	116.1
χ10	–	–	–	–	–	–65.0
χ11	–	–	–	–	–	–66.2
χ12	–	–	–	–	–	–124.8
χ12’	–	–	–	–	–	99.7

Fig. S2. Structures of Boc-protected Leu-heteropeptides **1e** and **2e**, and N-terminal free peptide **6c** determined by the X-ray crystallographic analysis.

(a) Boc-[(Leu)$_2$-{(1*S*,3*S*)-Ac$_5$c^{OM}}]$_2$-OMe (**1e**); hexamer



(b) Boc-[(Leu)$_2$-{(1*S*,3*S*)-Ac$_5$c^{OM}}]$_3$-OMe (**2e**); nonamer



(c) H-[(Leu)$_2$-{(*S*,*S*)-Ac$_5$c^{dOM}}]$_4$-OMe (**6c**); dodecamer

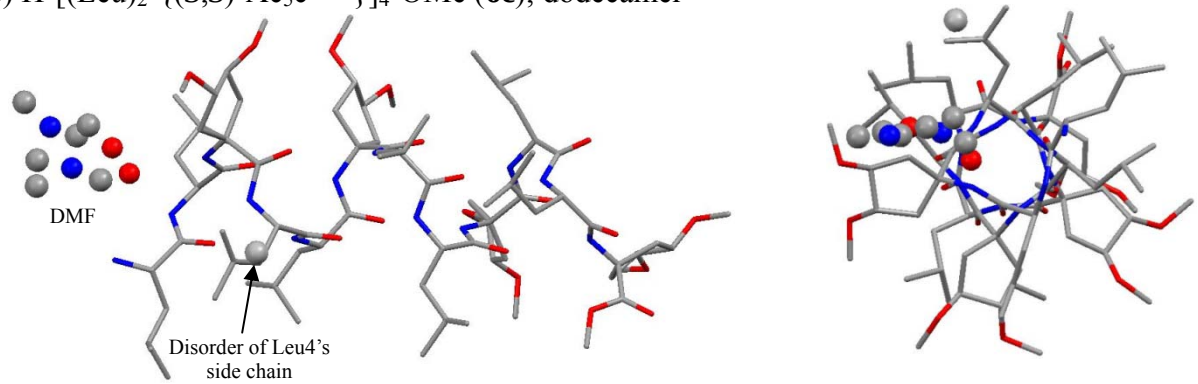


Table S2. Intra- and intermolecular H-bond parameters for Boc-[L-Leu-L-Leu-{(1*S*,3*S*)-Ac_5c^{OM}}]$_2$-OMe **1e.**

Peptide	Donor D—H	Acceptor A	Distance [Å] D···A	Angle [º] D—H···A	Symmetry Operations
Mol. *A* (*P*)	N3a-H	O0a	3.01	157.3	x,y,z
	N4a-H	O1a	2.98	137.6	x,y,z
	N5a-H	O1a	3.01	158.6	x,y,z
	N6a-H	O2a	3.02	163.8	x,y,z
Mol. *B* (*P*)	N3b-H	O0b	3.04	155.5	x,y,z
	N4b-H	O1b	2.95	135.2	x,y,z
	N5b-H	O1b	2.95	157.3	x,y,z
	N6b-H	O2b	3.02	164.7	x,y,z
Mol. *C* (*P*)	N3c-H	O0c	3.04	153.8	x,y,z
	N4c-H	O1c	2.98	131.7	x,y,z
	N5c-H	O1c	3.12	161.4	x,y,z
	N6c-H	O2c	2.92	162.7	x,y,z
	N1a-H	O5a’	2.99	165.3	-y.x-y,1/3+z
	N2a-H	O4a’	2.99	167.3	-y.x-y,1/3+z
	N2a’-H	O4a	2.99	167.3	-x+y.-x,-1/3+z
	N1a’-H	O5a	2.99	165.3	-x+y.-x,-1/3+z
	N1b-H	O5b’	2.86	157.1	1-y.x-y,1/3+z
	N2b-H	O4b’	2.92	162.9	1-y.x-y,1/3+z
	N2b’-H	O4b	2.92	162.9	1-x+y.1-x,-1/3+z
	N1b’-H	O5b	2.86	157.1	1-x+y.1-x,-1/3+z
	N1c-H	O5c’	2.90	153.6	1-y.1+x-y,1/3+z
	N2c-H	O4c’	3.02	165.4	1-y.1+x-y,1/3+z
	N2c’-H	O4c	3.02	165.4	-x+y.1-x,-1/3+z
	N1c’-H	O5c	2.90	153.6	-x+y.1-x,-1/3+z

Table S3. Intra- and intermolecular H-bond parameters for Boc-[L-Leu-L-Leu-{(1*S*,3*S*)-Ac_5c^{OM}}]$_3$-OMe **2e.**

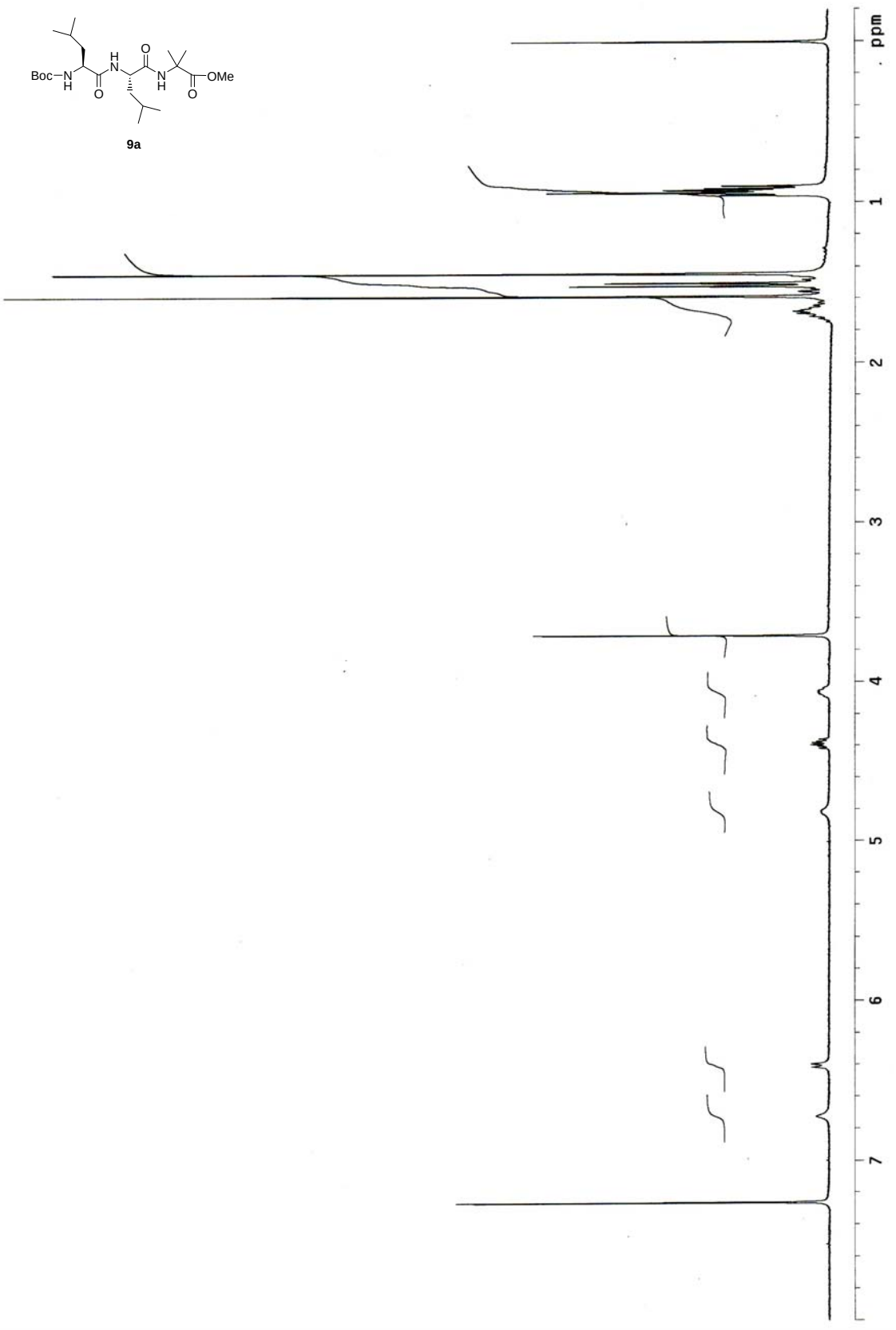
Peptide	Donor D—H	Acceptor A	Distance [Å] D···A	Angle [°] D—H···A	Symmetry Operations
Mol. *A* (*P*)	N4a-H	O0a	3.17	167.1	x,y,z
	N5a-H	O1a	2.80	167.8	x,y,z
	N6a-H	O2a	3.04	164.0	x,y,z
	N7a-H	O3a	3.07	149.4	x,y,z
	N8a-H	O4a	2.92	154.1	x,y,z
	N9a-H	O5a	2.98	159.4	x,y,z
Mol. *B* (*P*)	N4b-H	O1b	3.05	117.3	x,y,z
	N5b-H	O1b	3.09	161.0	x,y,z
	N6b-H	O2b	2.92	164.7	x,y,z
	N8b-H	O4b	2.99	156.6	x,y,z
	N9b-H	O5b	2.98	170.7	x,y,z
	N1a-H	O8a’	2.83	169.9	x,-1+y,z
	N1a’-H	O8a	2.83	169.9	x,-1+y,z
	Ow(a’)-H	O7a	2.83	160.5	x,1+y,z
	Ow(b’)-H	O6a	2.93	158.7	x,1+y,z
	Ow(b’’)-H	OM6a	2.92	153.1	2-x,1/2+y,1/2-z
	N1b’-H	O7b	2.90	140.1	x,-1+y,z
	N1b-H	O7b’	2.90	140.1	x,1+y,z
	N3b-H	Ow(d’)	2.95	154.9	x,1+y,z
	N3b’-H	Ow(d)	2.95	154.9	x,-1+y,z
	Ow(a)-H	O7a’	2.83	160.5	x,-1+y,z
	Ow(b)-H	O6a’	2.93	158.7	x,-1+y,z
	Ow(b)-H	OM6a’	2.92	153.1	2-x,-1/2+y,1/2-z

The distances of N7b ···O3b (3.41 Å) and N4b ··· O0b (3.88 Å) are too long for intramolecular H-bonds. The distance of N4a ··· O0a (3.17 Å) is a bit long for an intramolecular H-bond. W: water, OM: OMe group of cyclic amino acids.

Table S4. Intra- and intermolecular H-bond parameters for H-[L-Leu-L-Leu-{(*S*,*S*)-Ac_5c^{dOM}}]$_4$-OMe **6c.**

Peptide	Donor D—H	Acceptor A	Distance [Å] D···A	Angle [°] D—H···A	Symmetry Operations
(*P*)	N4-H	O1	2.92	119.6	x,y,z
	N5-H	O1	2.92	164.8	x,y,z
	N6-H	O2	2.90	170.1	x,y,z
	N7-H	O3	3.18	160.4	x,y,z
	N8-H	O4	2.86	166.5	x,y,z
	N9-H	O5	3.05	163.4	x,y,z
	N11-H	O7	2.90	145.2	x,y,z
	N12-H	O8	3.14	137.8	x,y,z
	N2'-H	O11	2.89	124.6	x,y,-1+z
	N2-H	O11'	2.89	124.6	x,y,1+z
	N2-H	O_{DMF}	3.06	91.0	x,y,z
	N3-H	O_{DMF}	2.81	172.9	x,y,z

The distance of N7 ··· O3 (3.18 Å) is a bit long for an intramolecular H-bond, and that of N10 ··· O6 (3.30 Å) is too long for an intramolecular H-bond. W: water, OM: OMe group of cyclic amino acids. The side chain of the Leu^4 residue was disordered, and one DMF molecule existed, but was disordered at two positions.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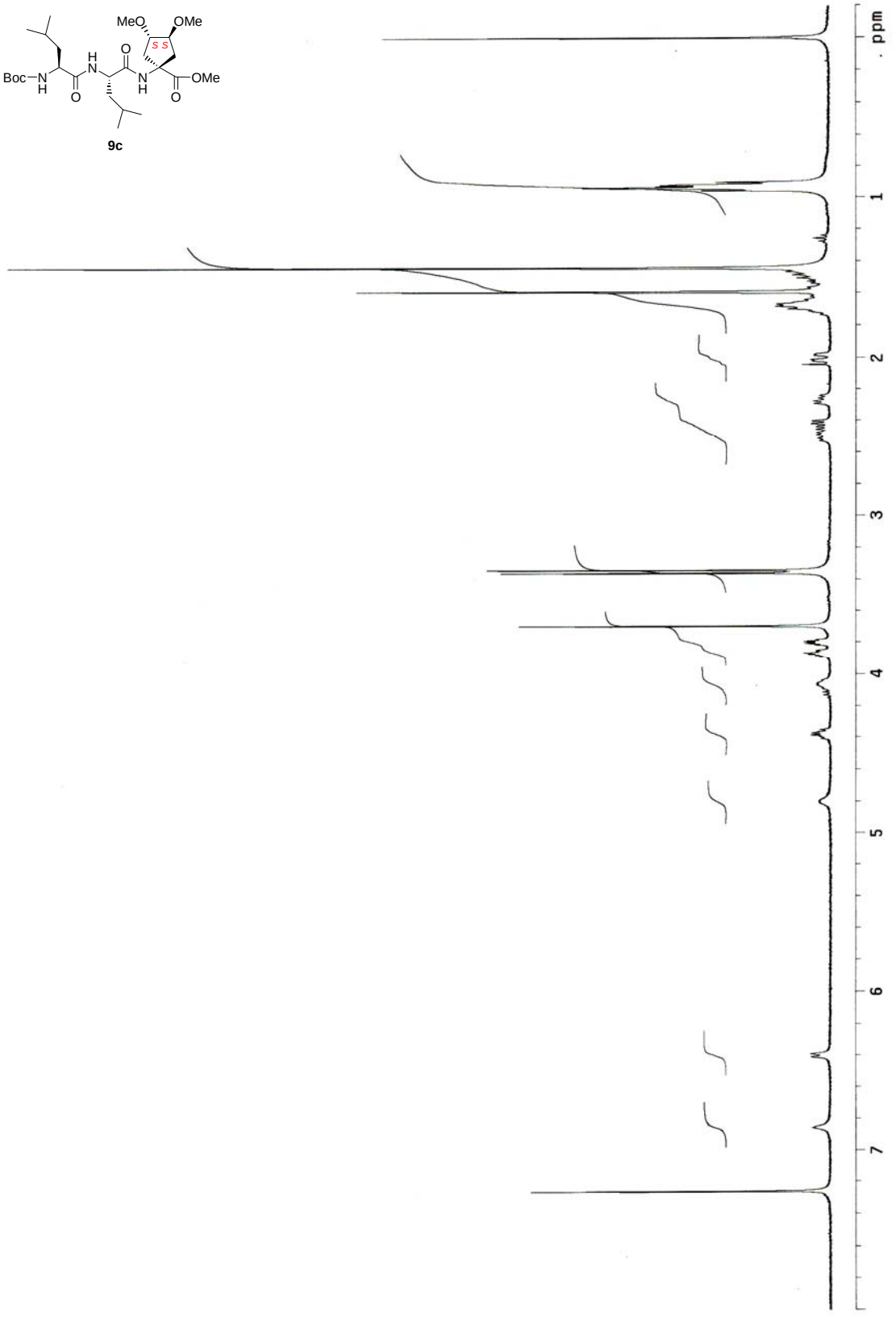
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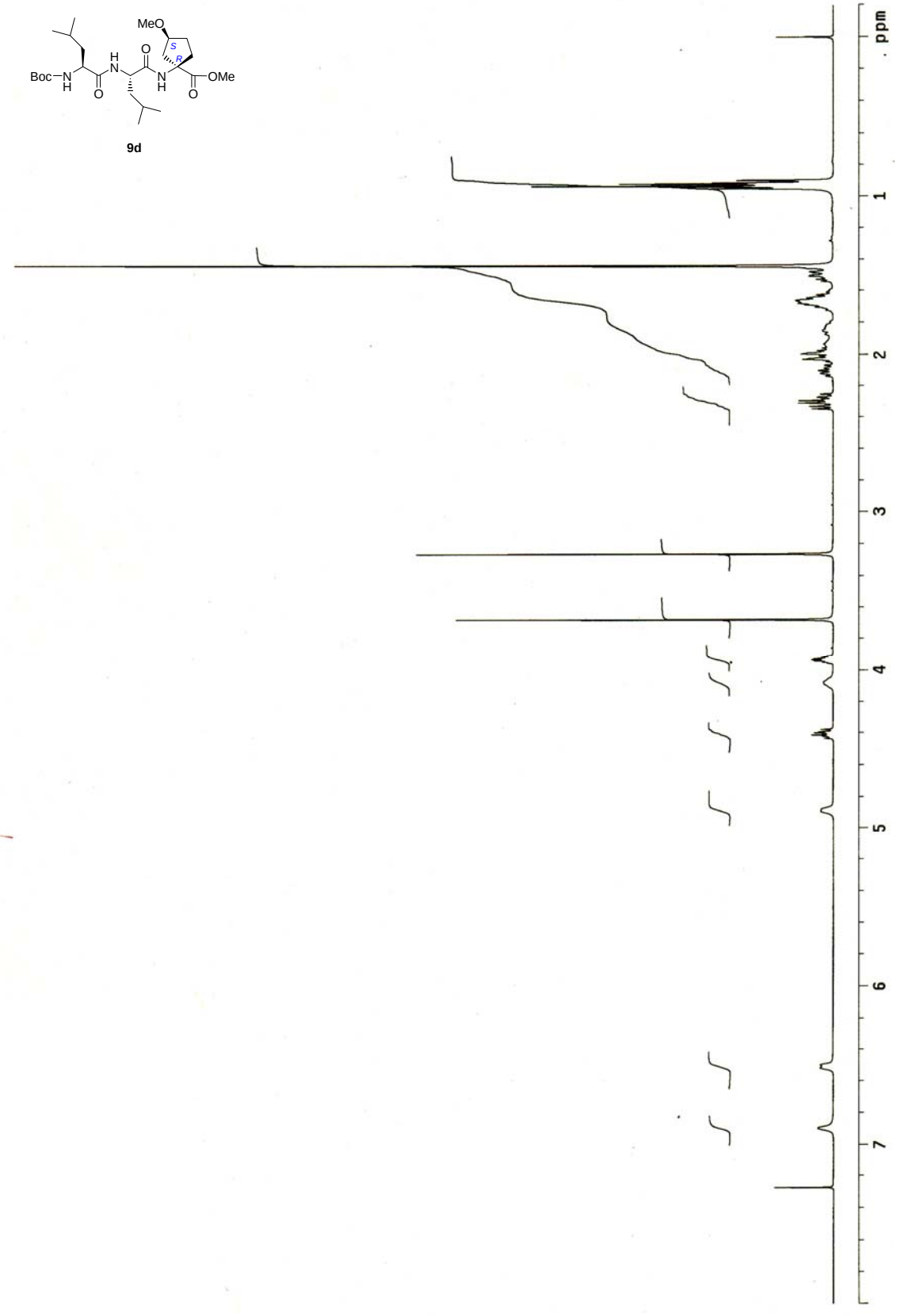
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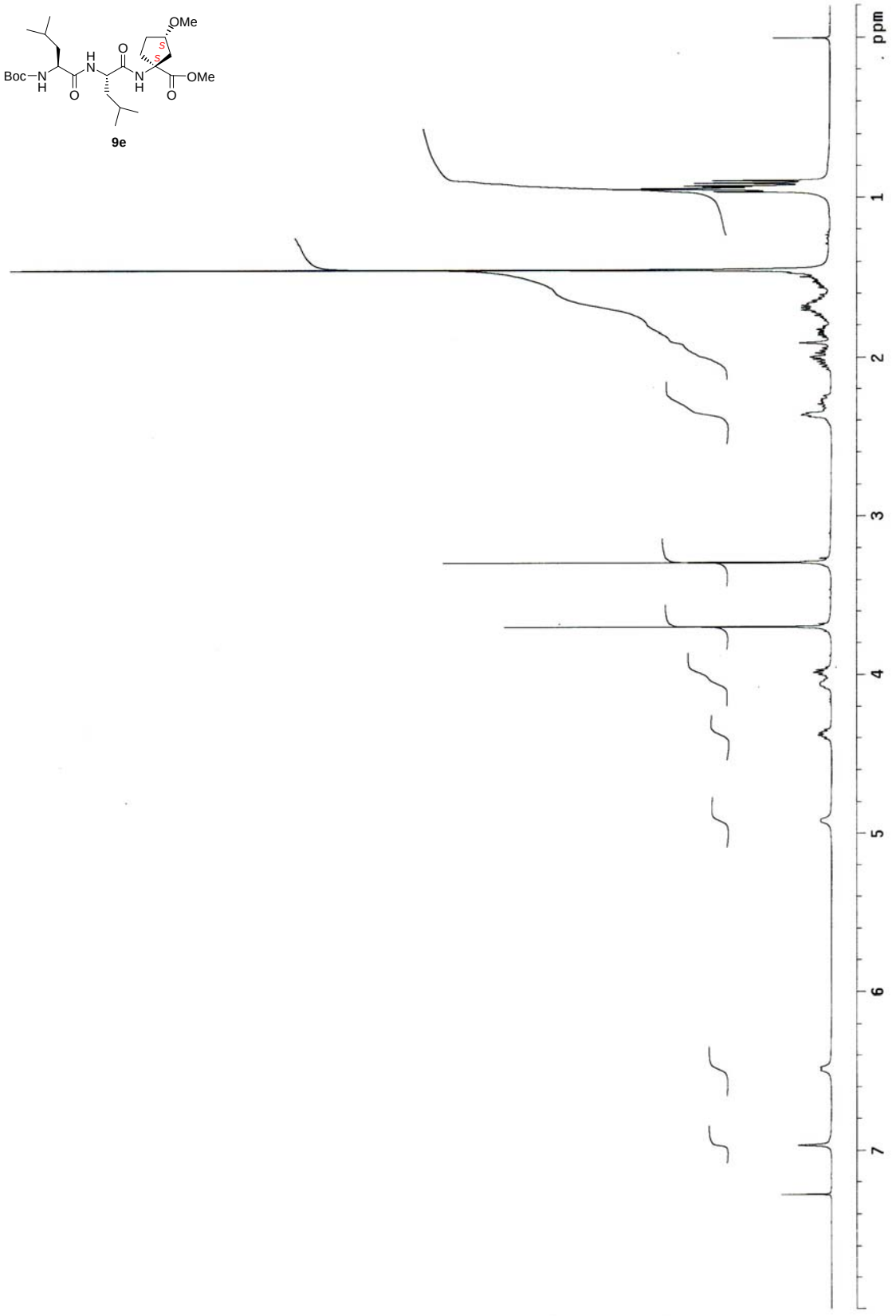
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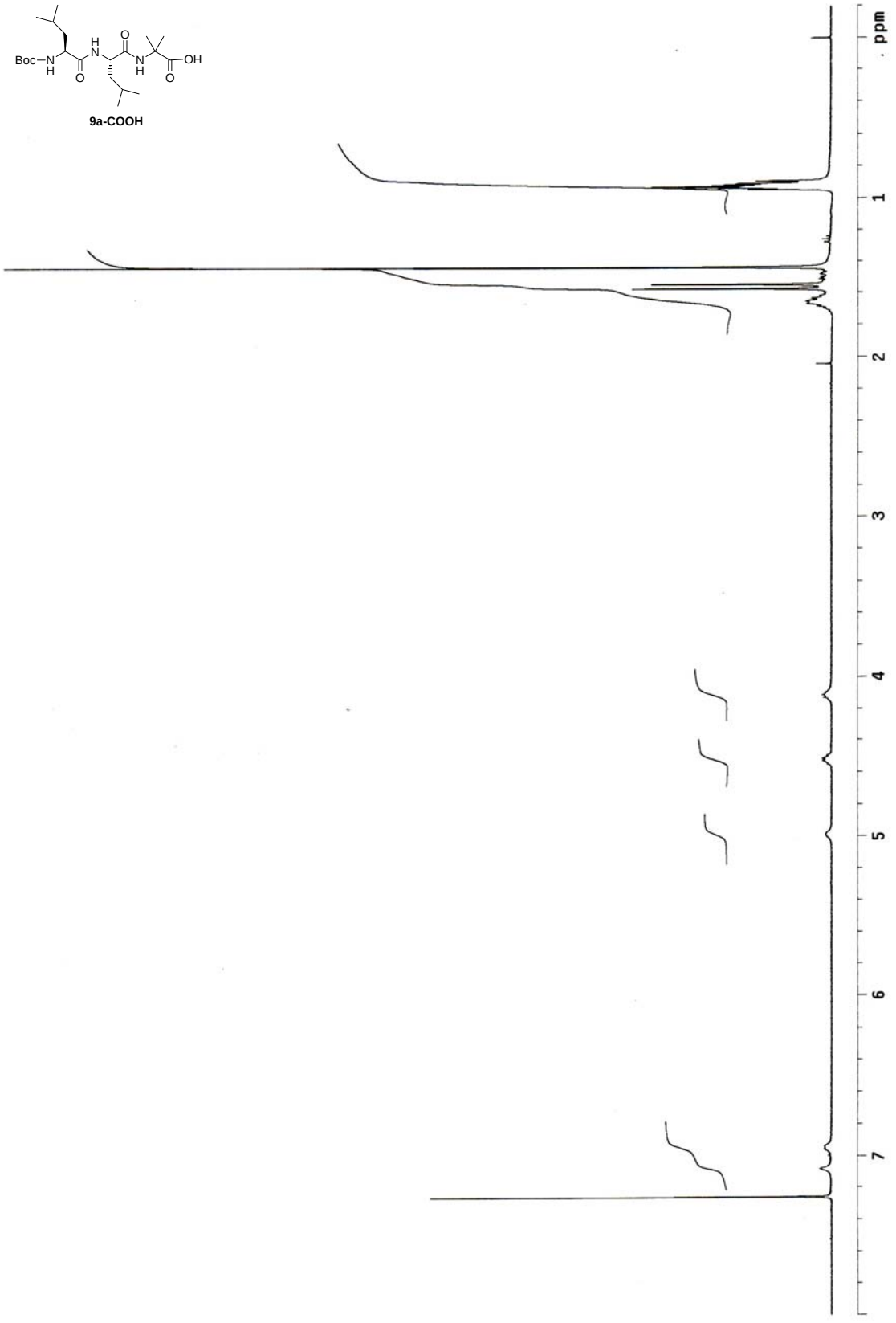
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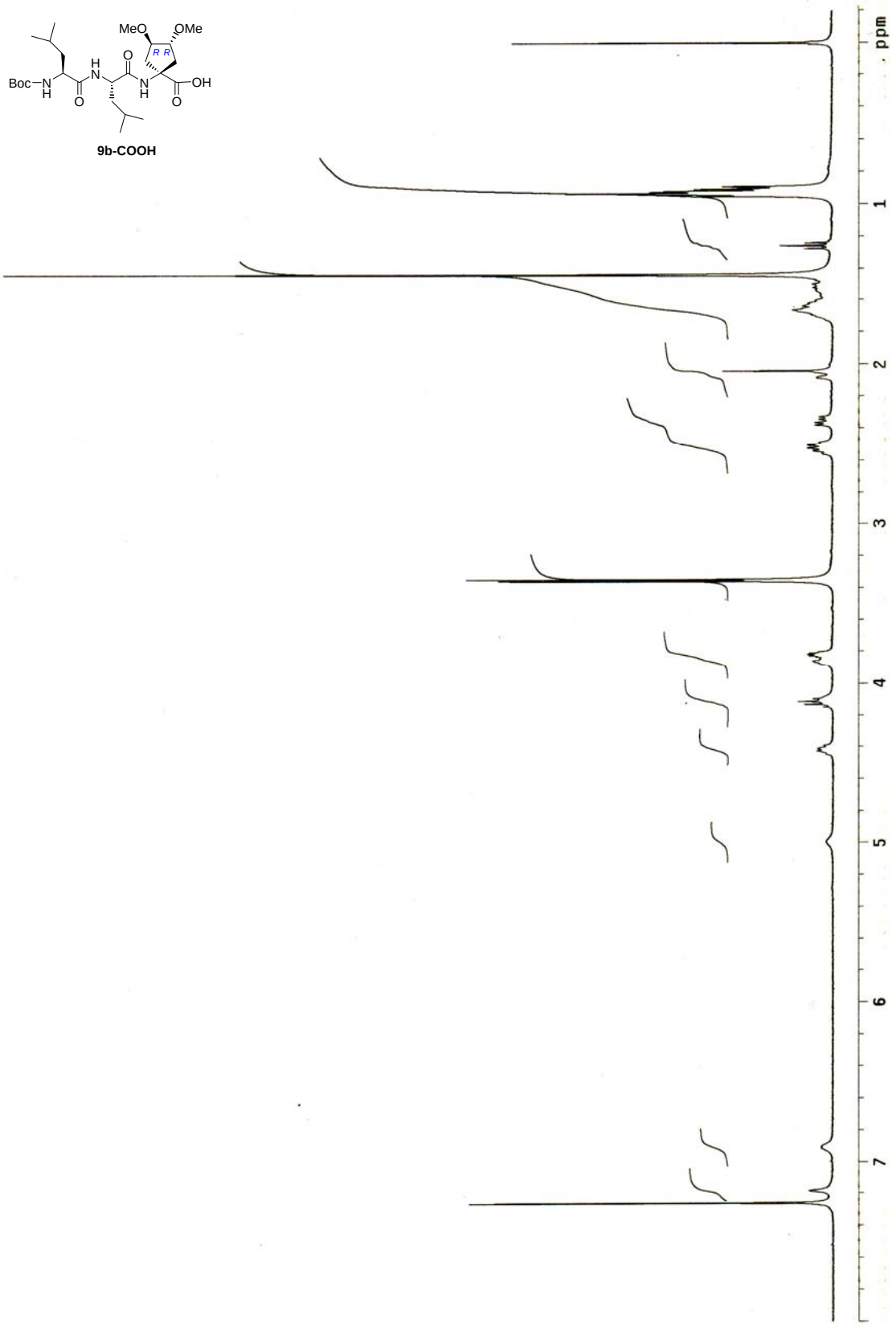
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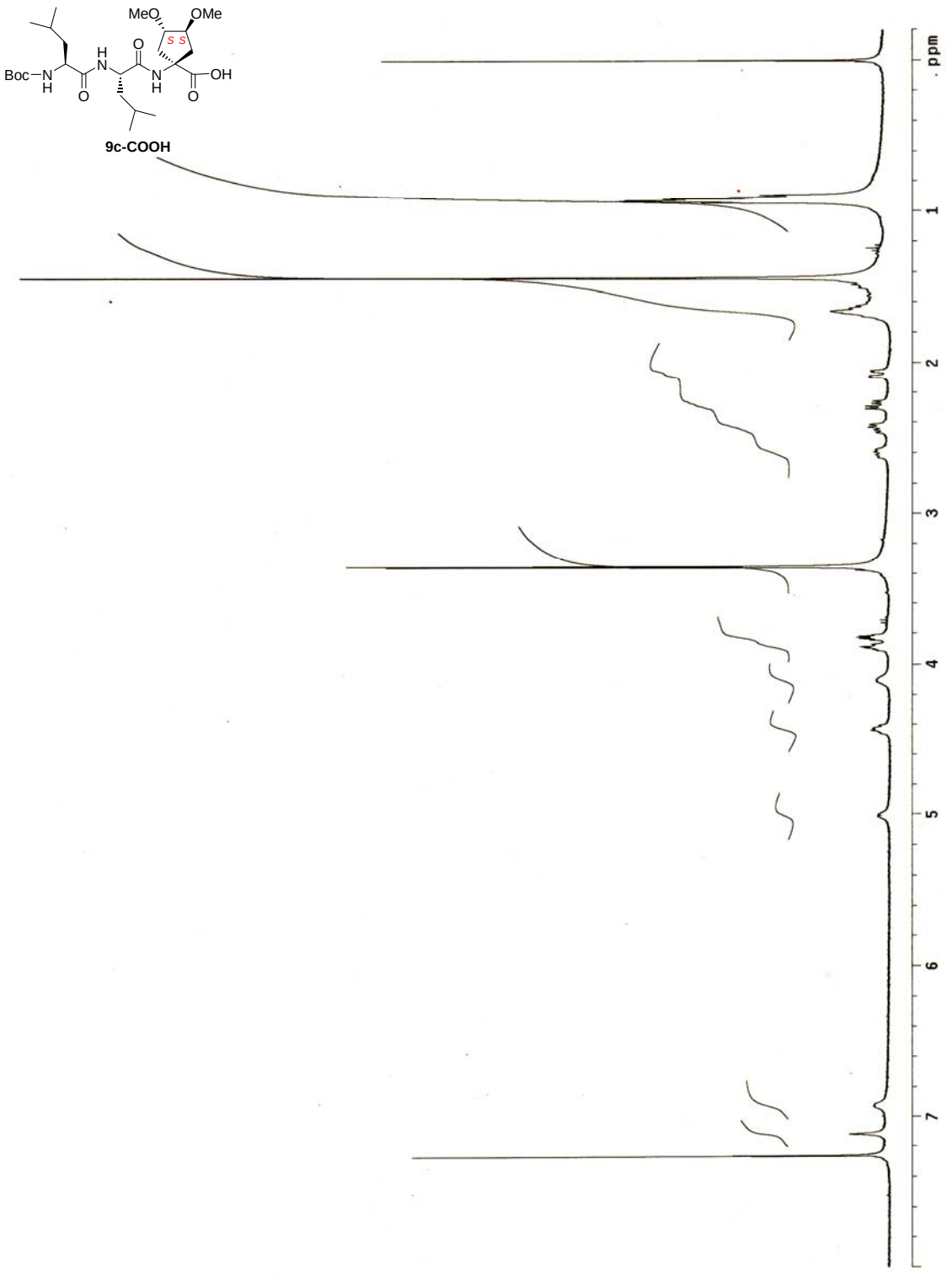
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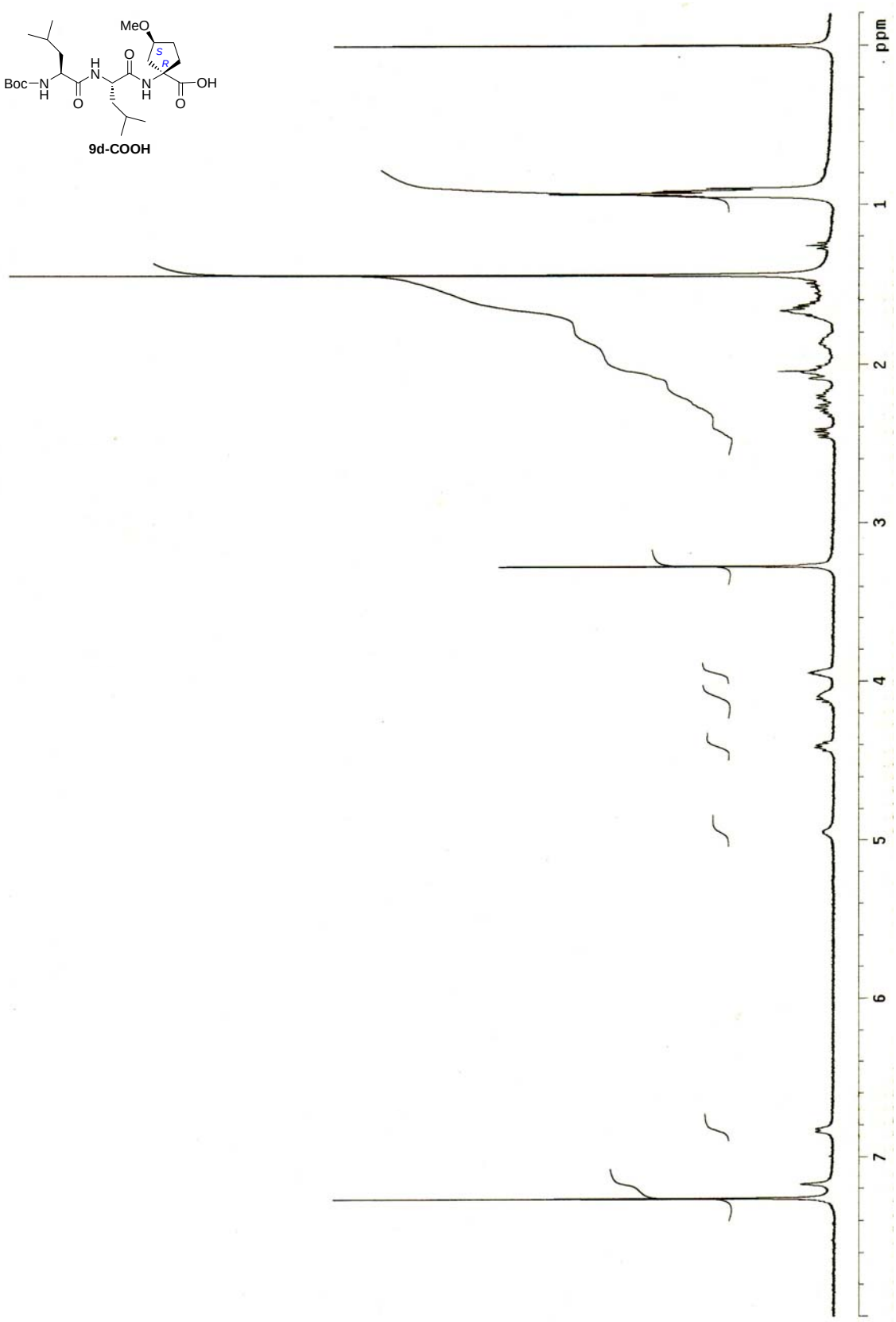
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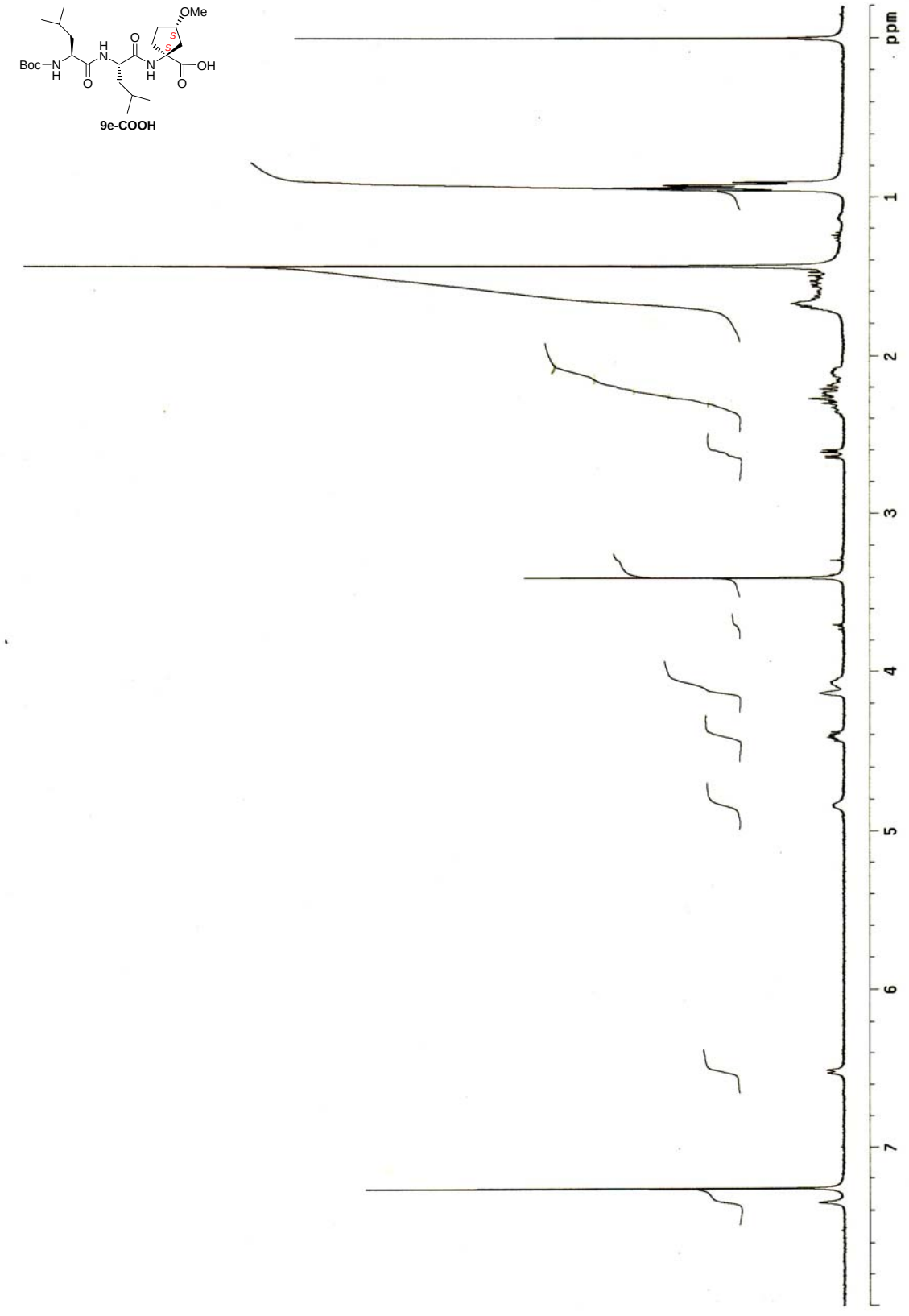
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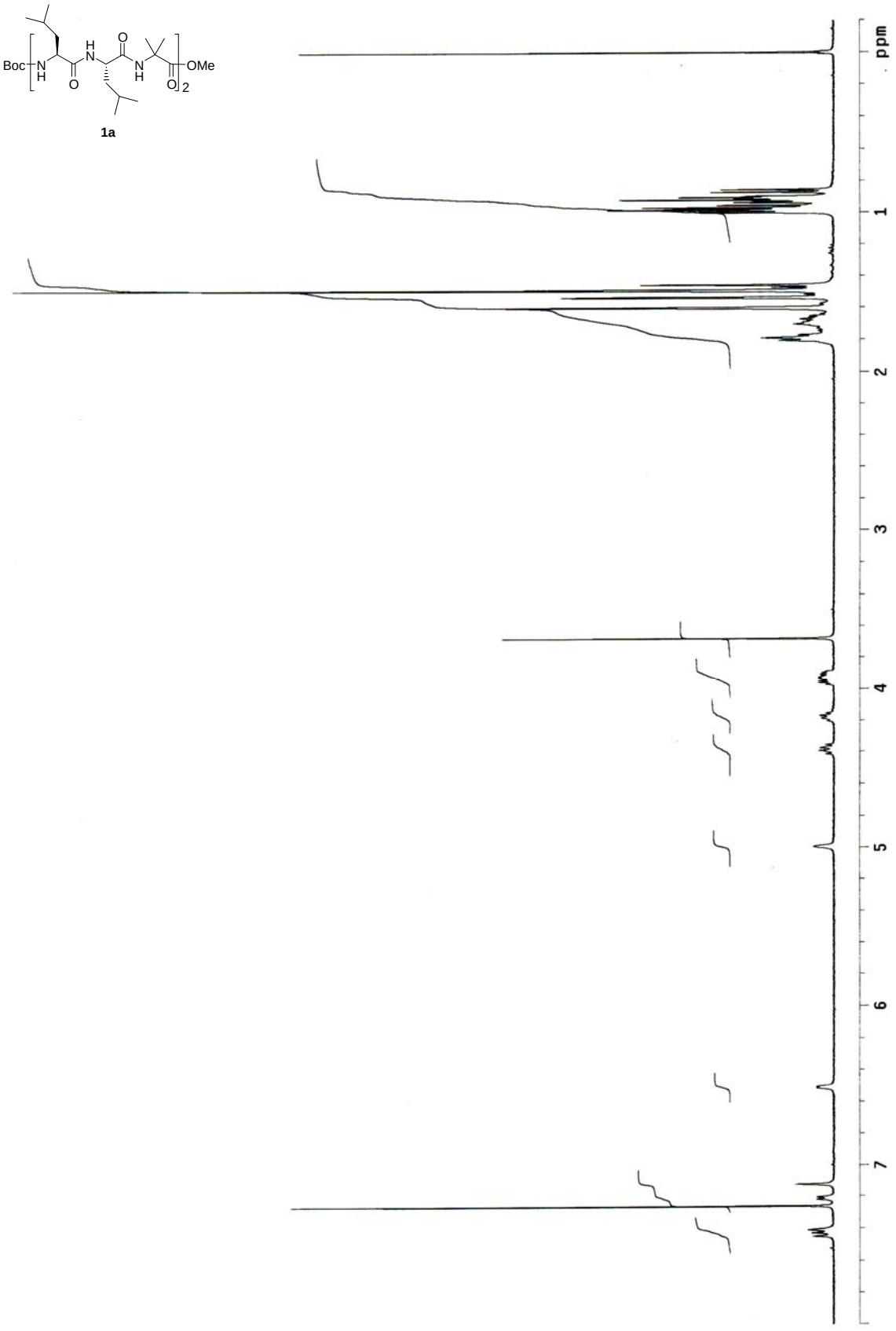
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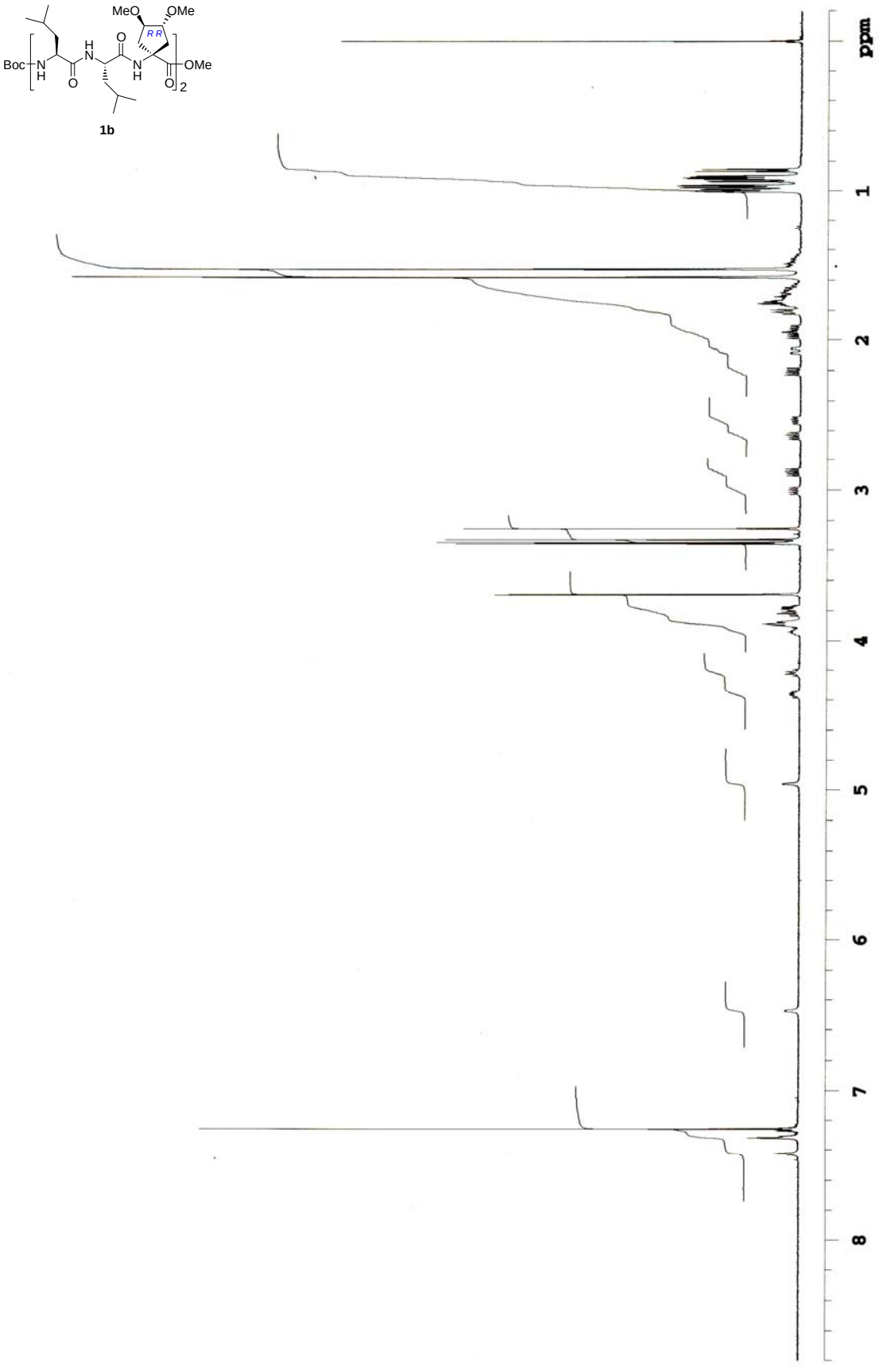
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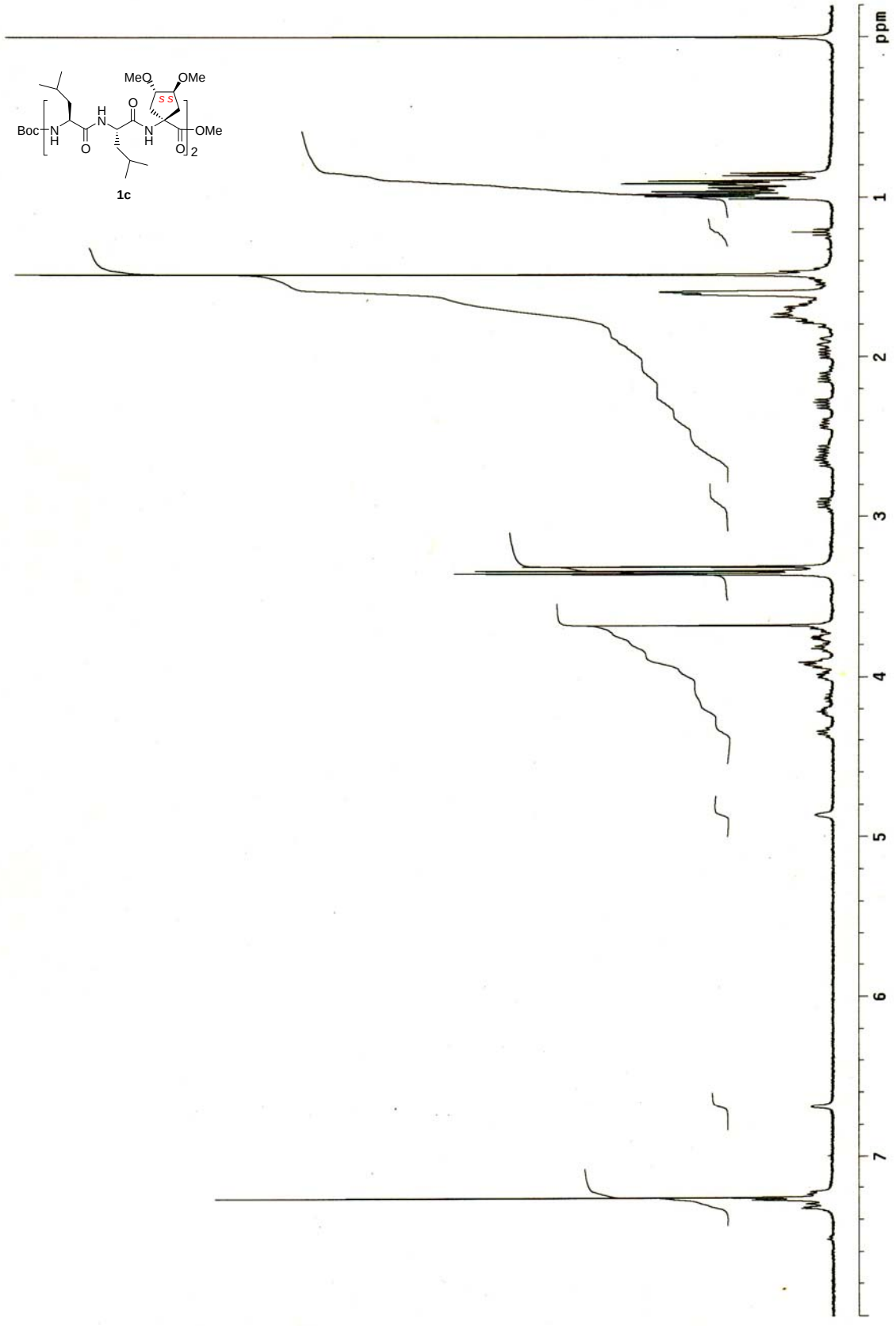
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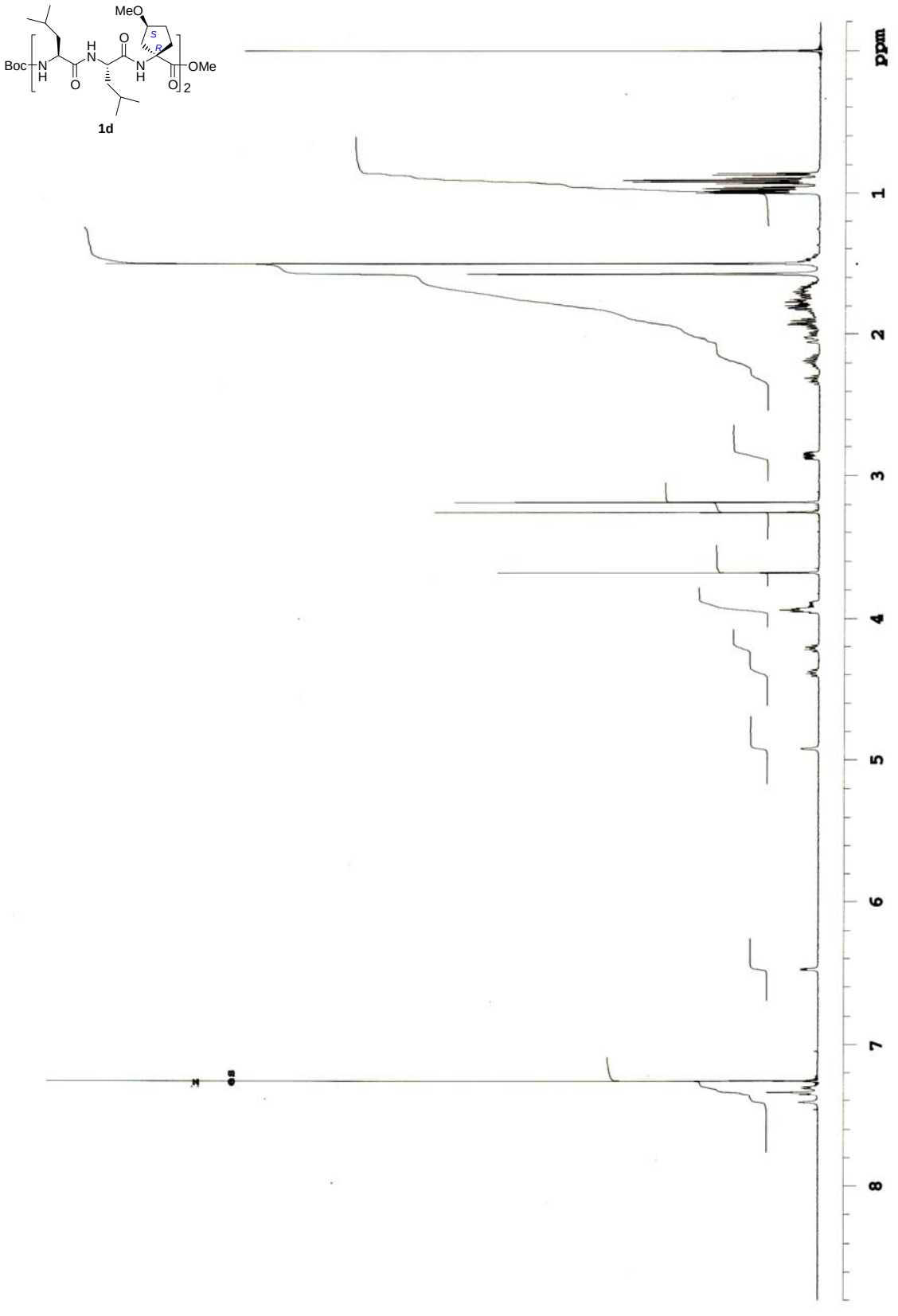
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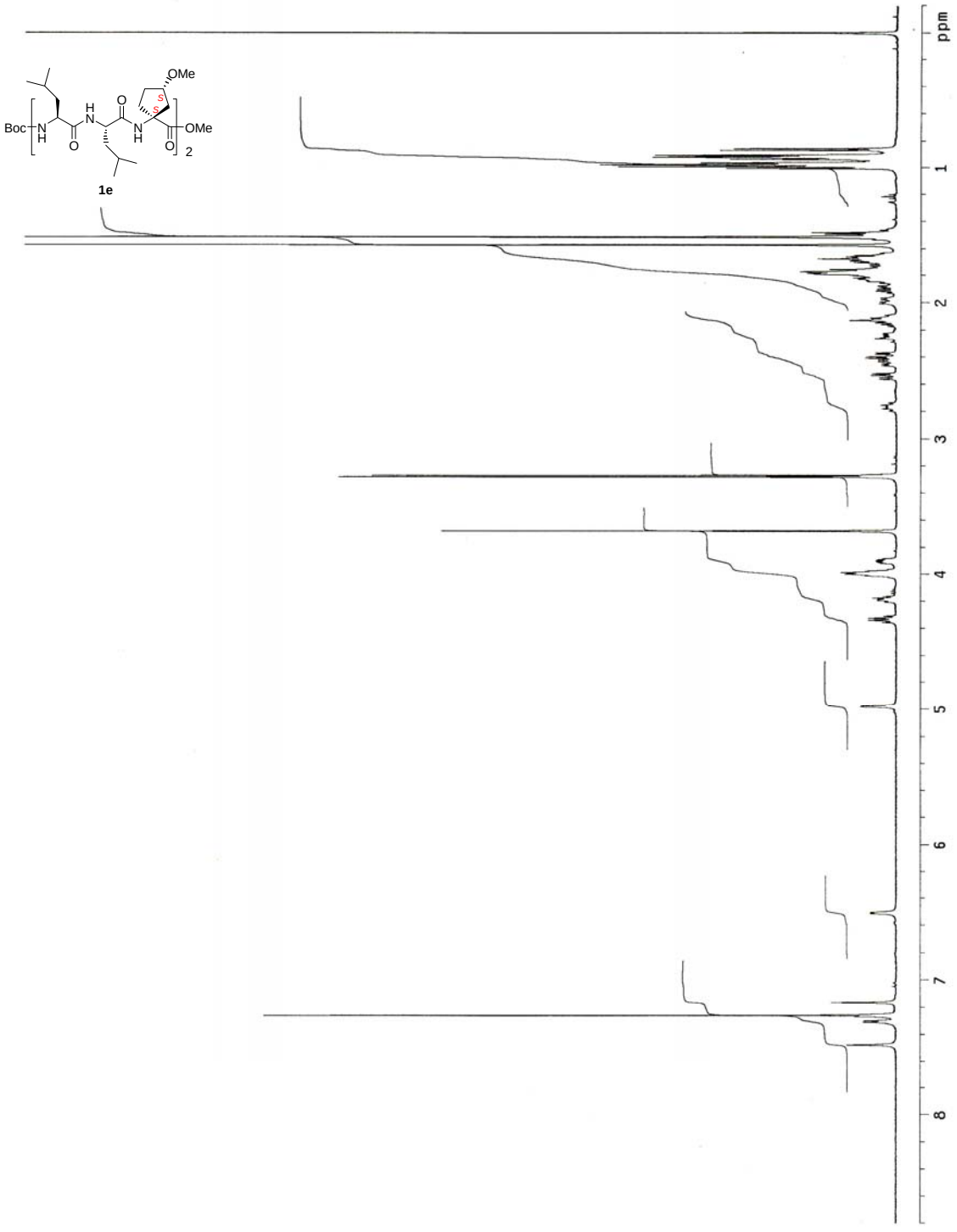
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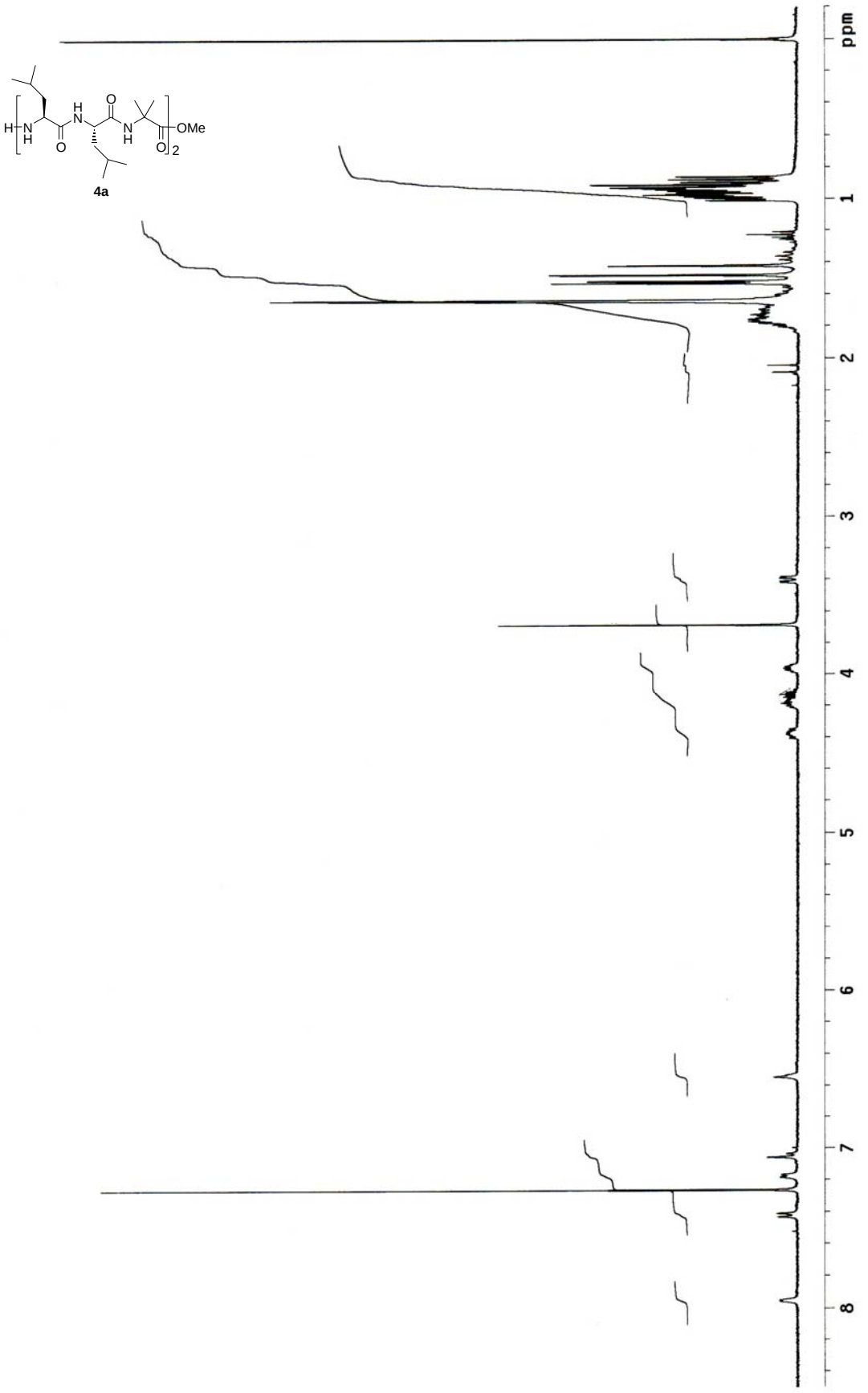
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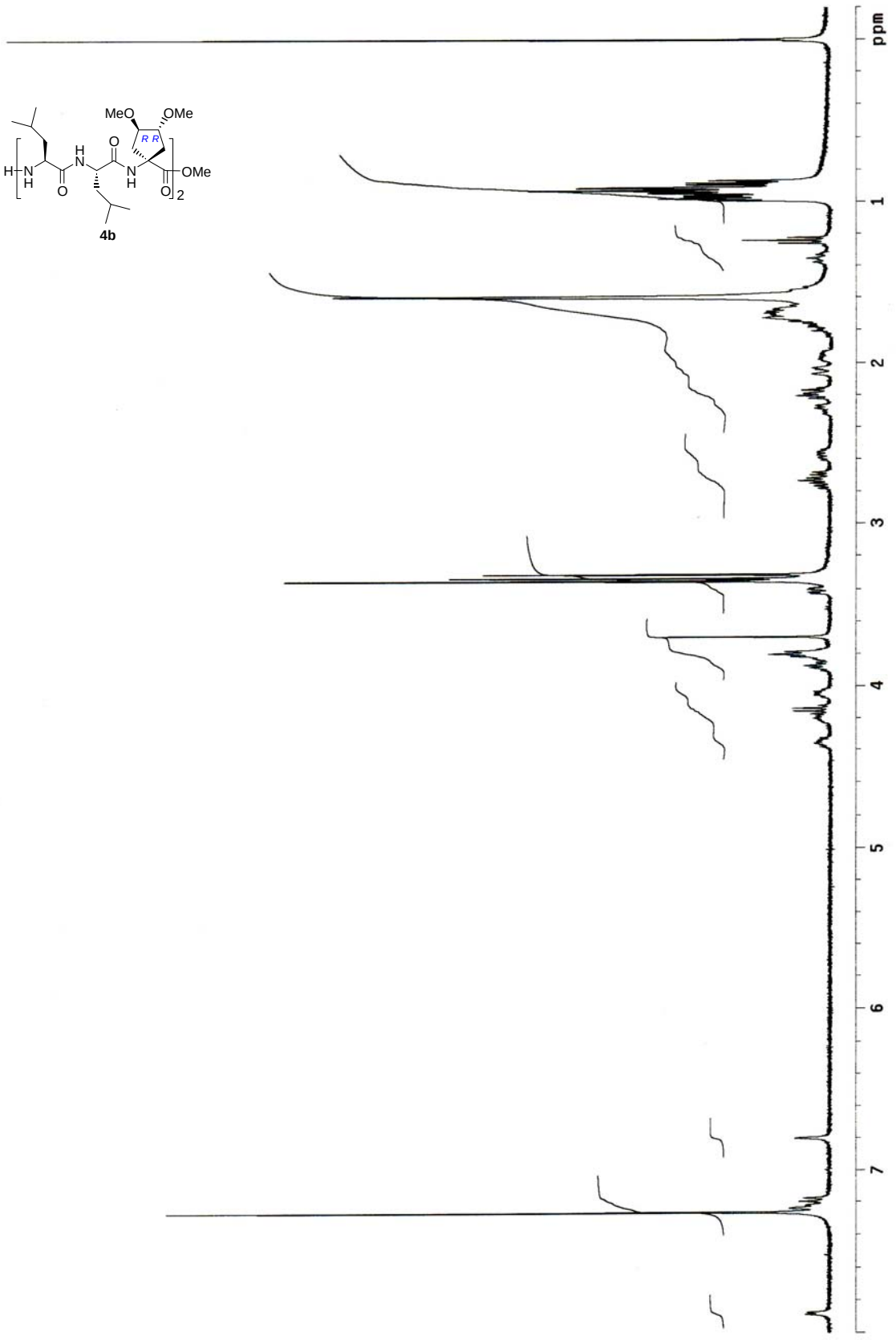
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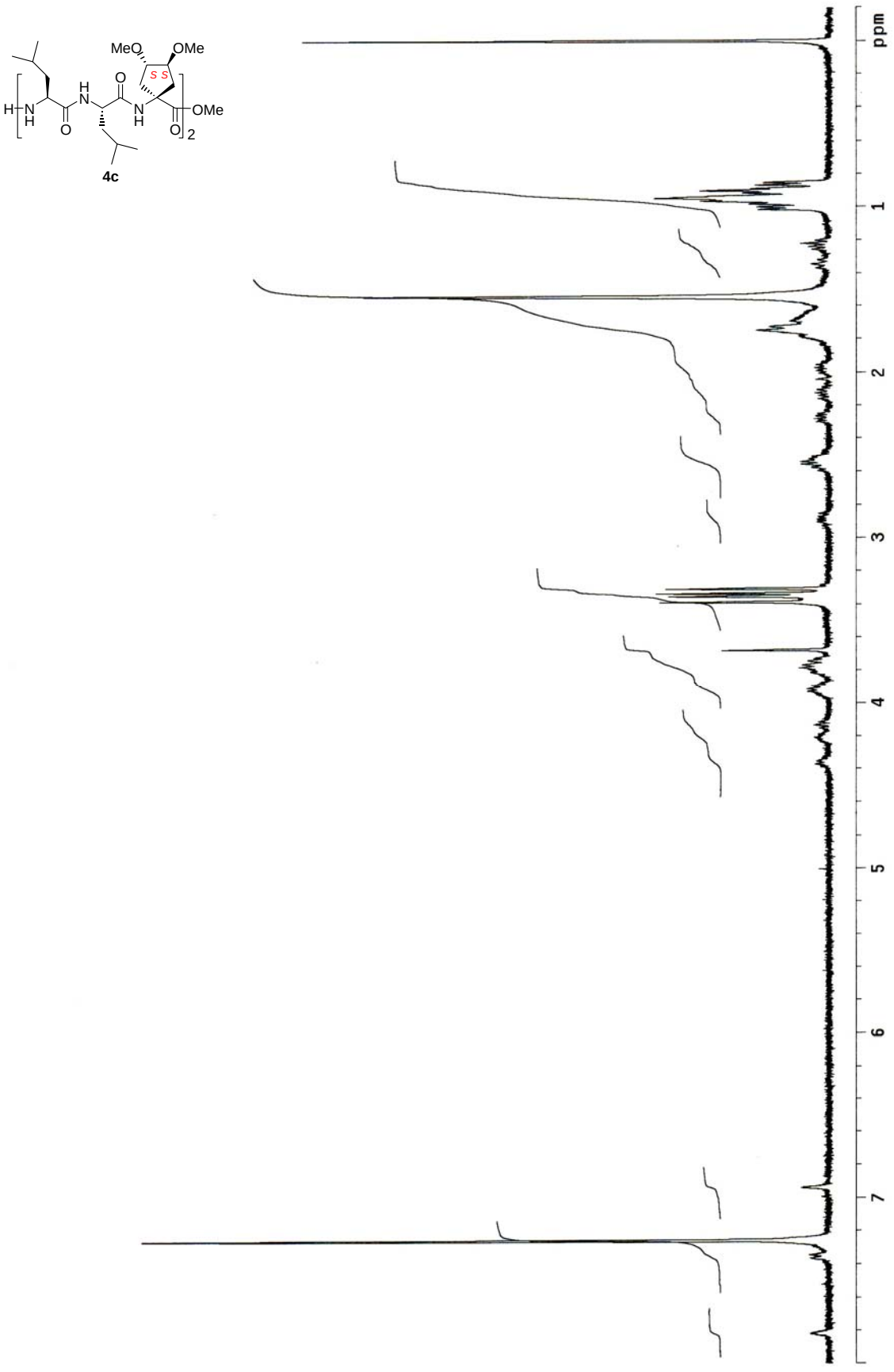
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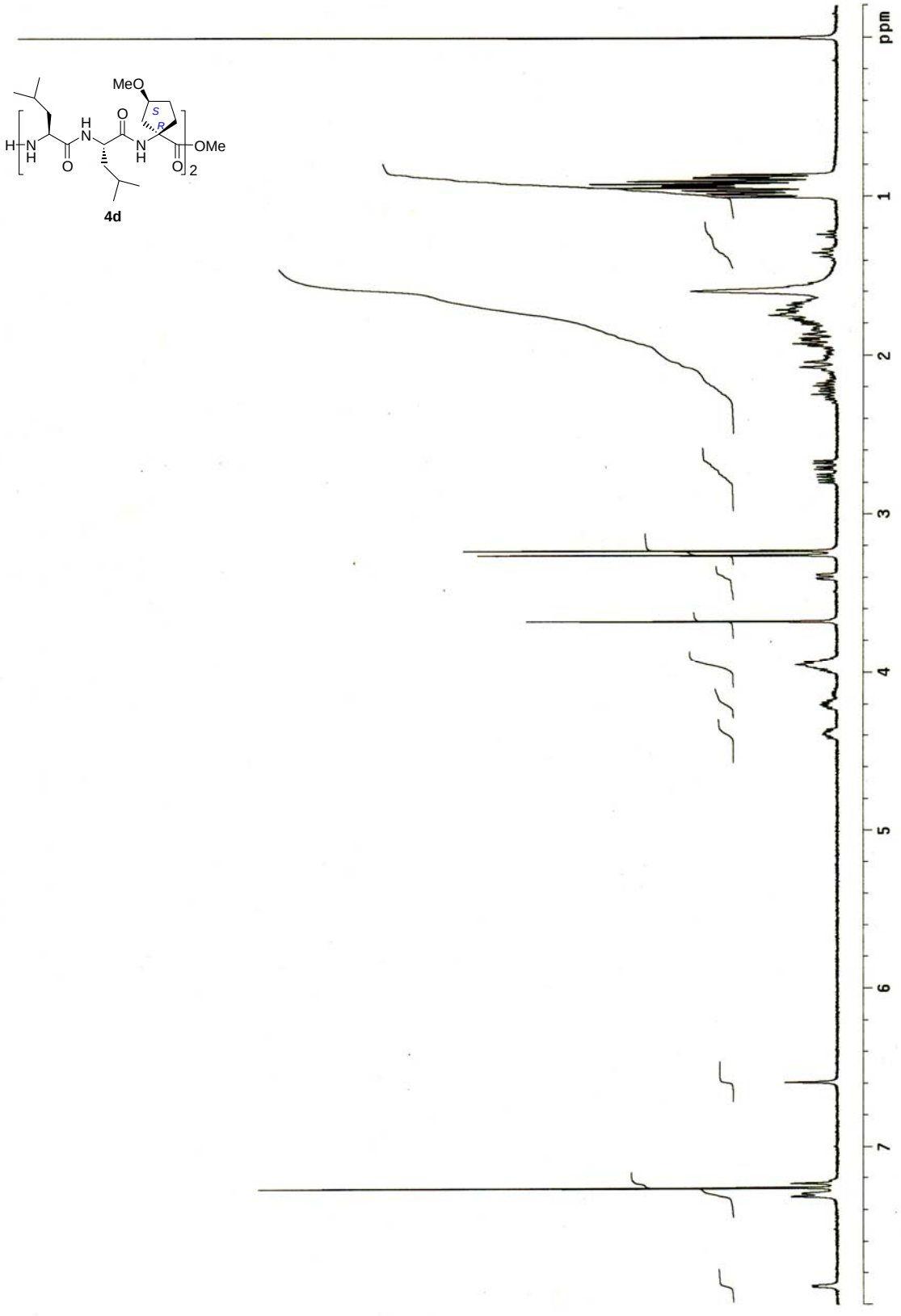
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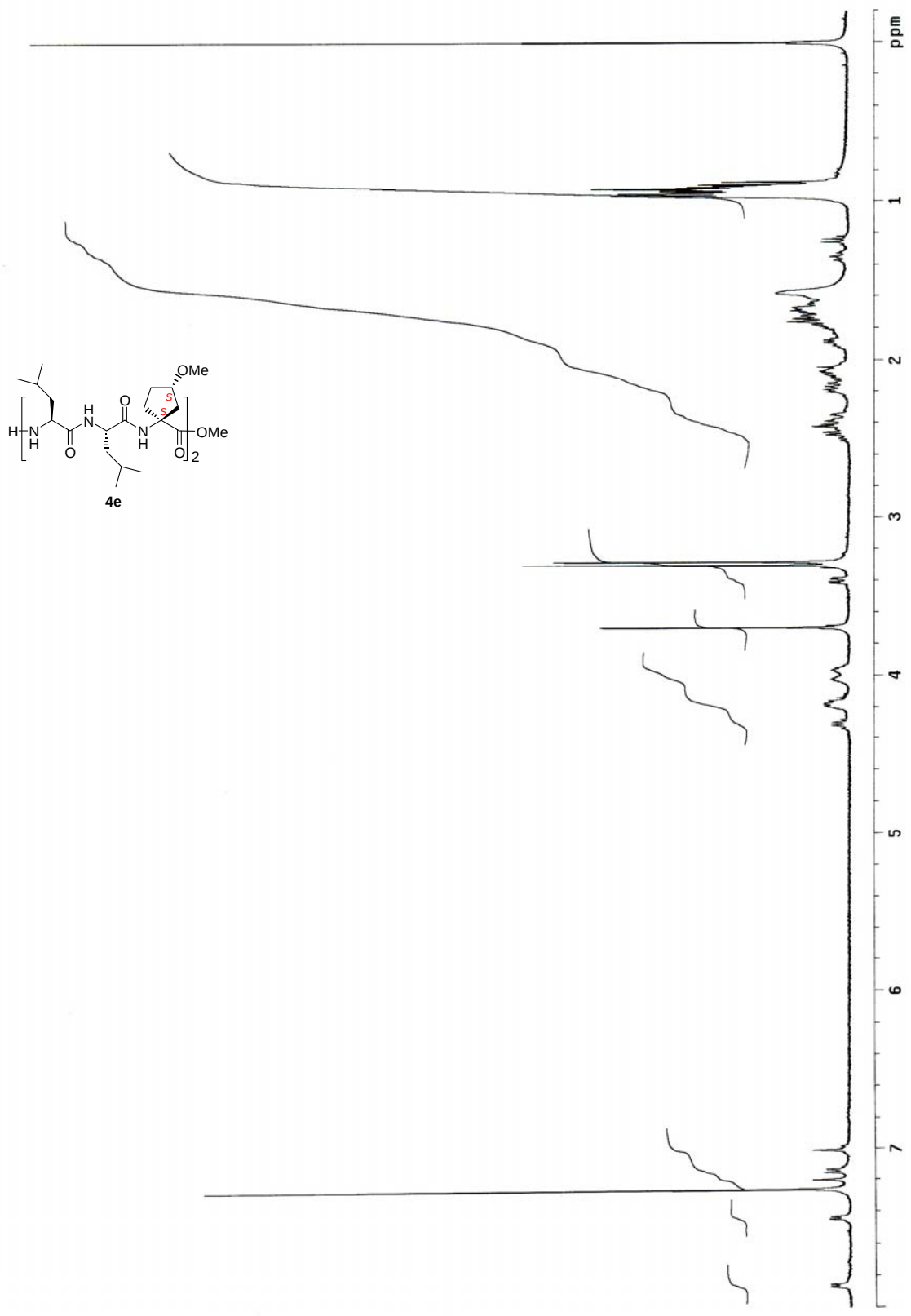
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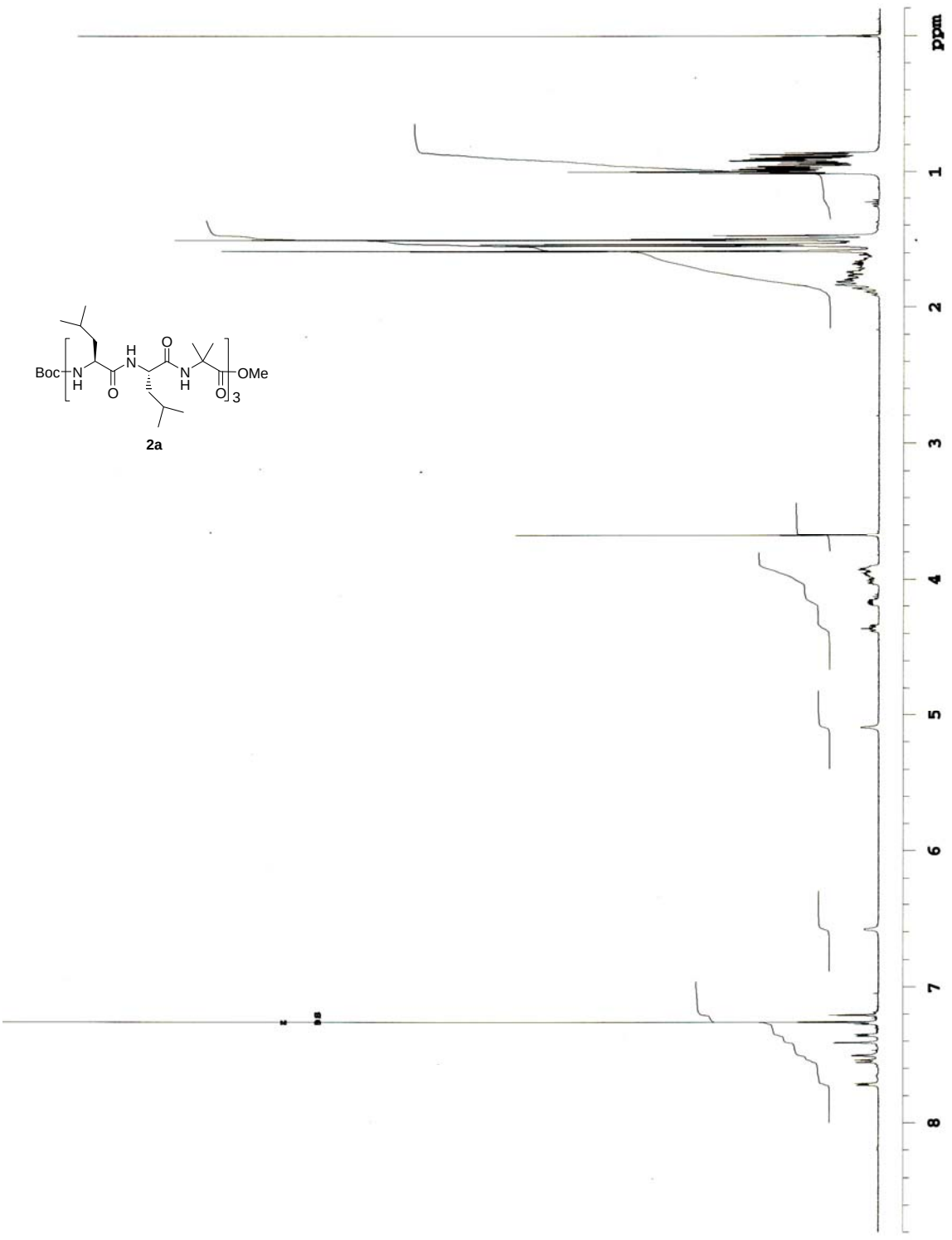
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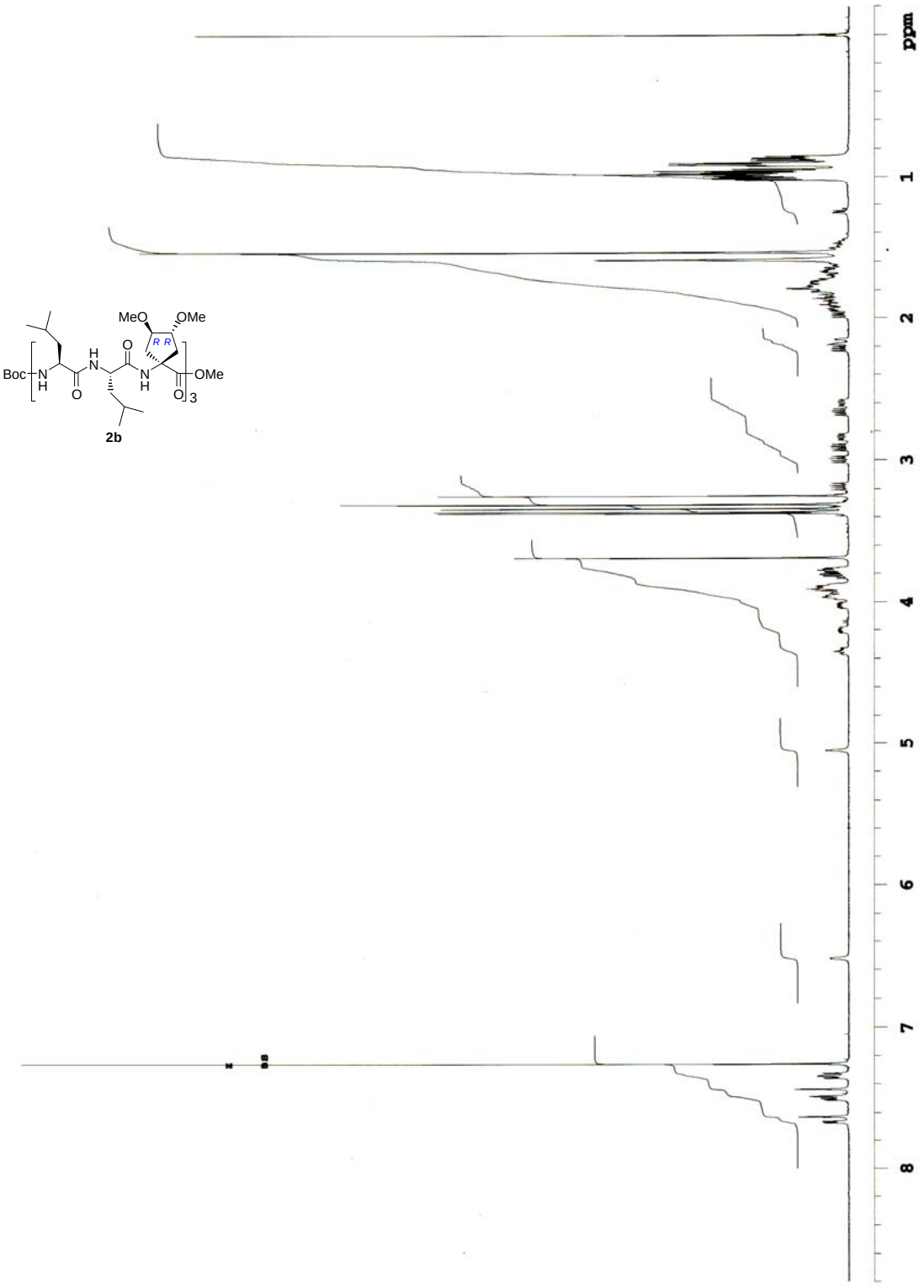
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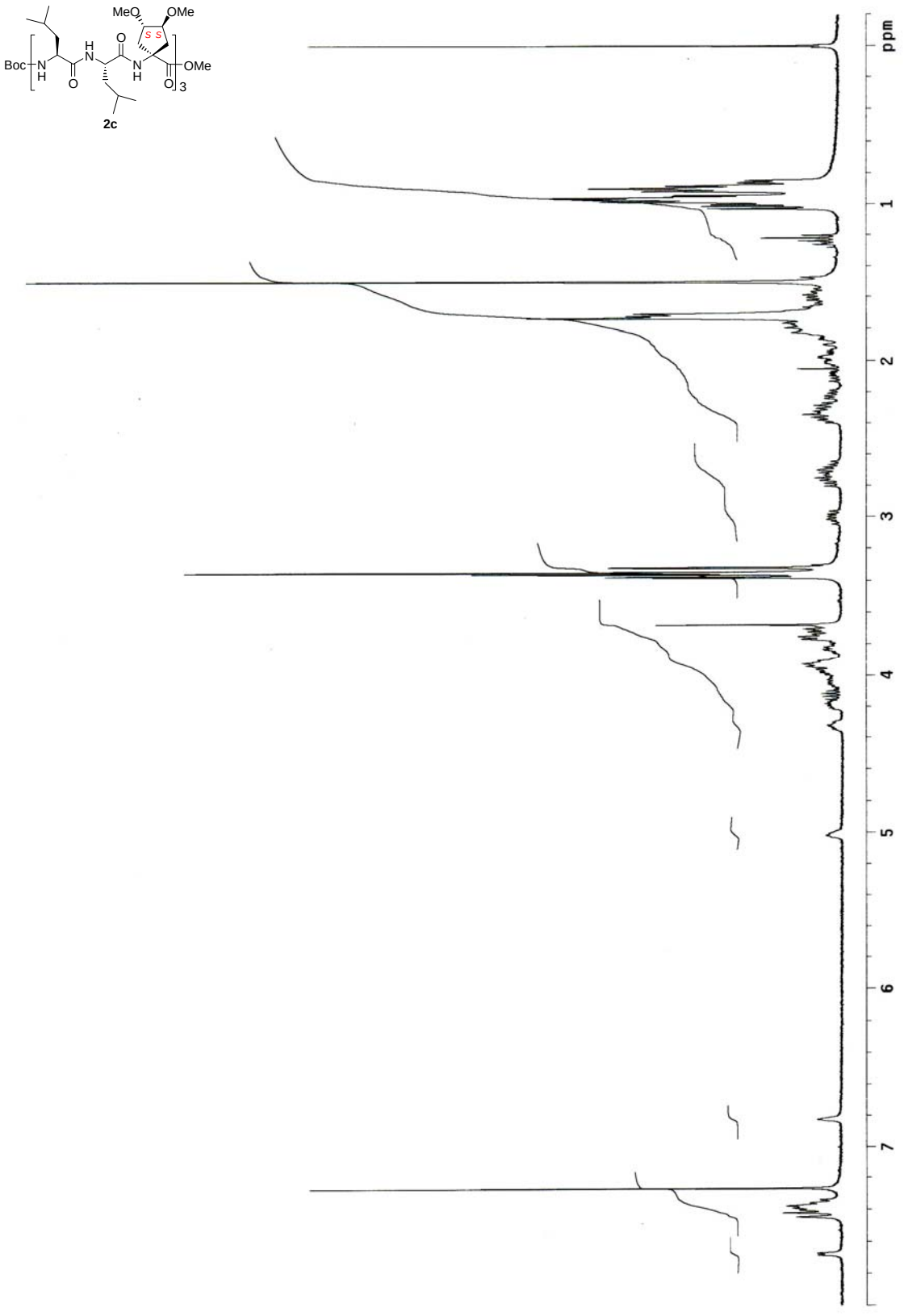
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Boc
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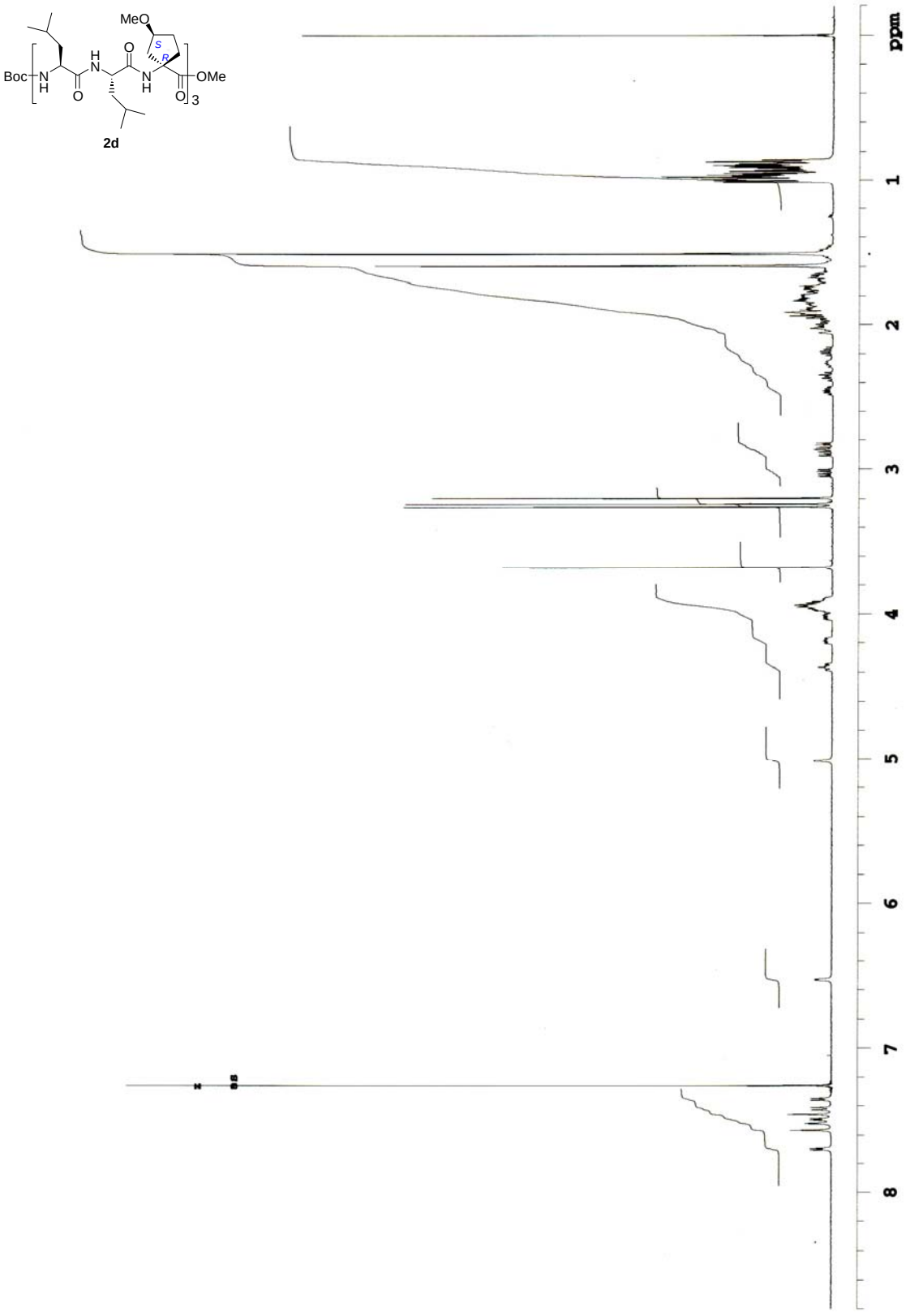
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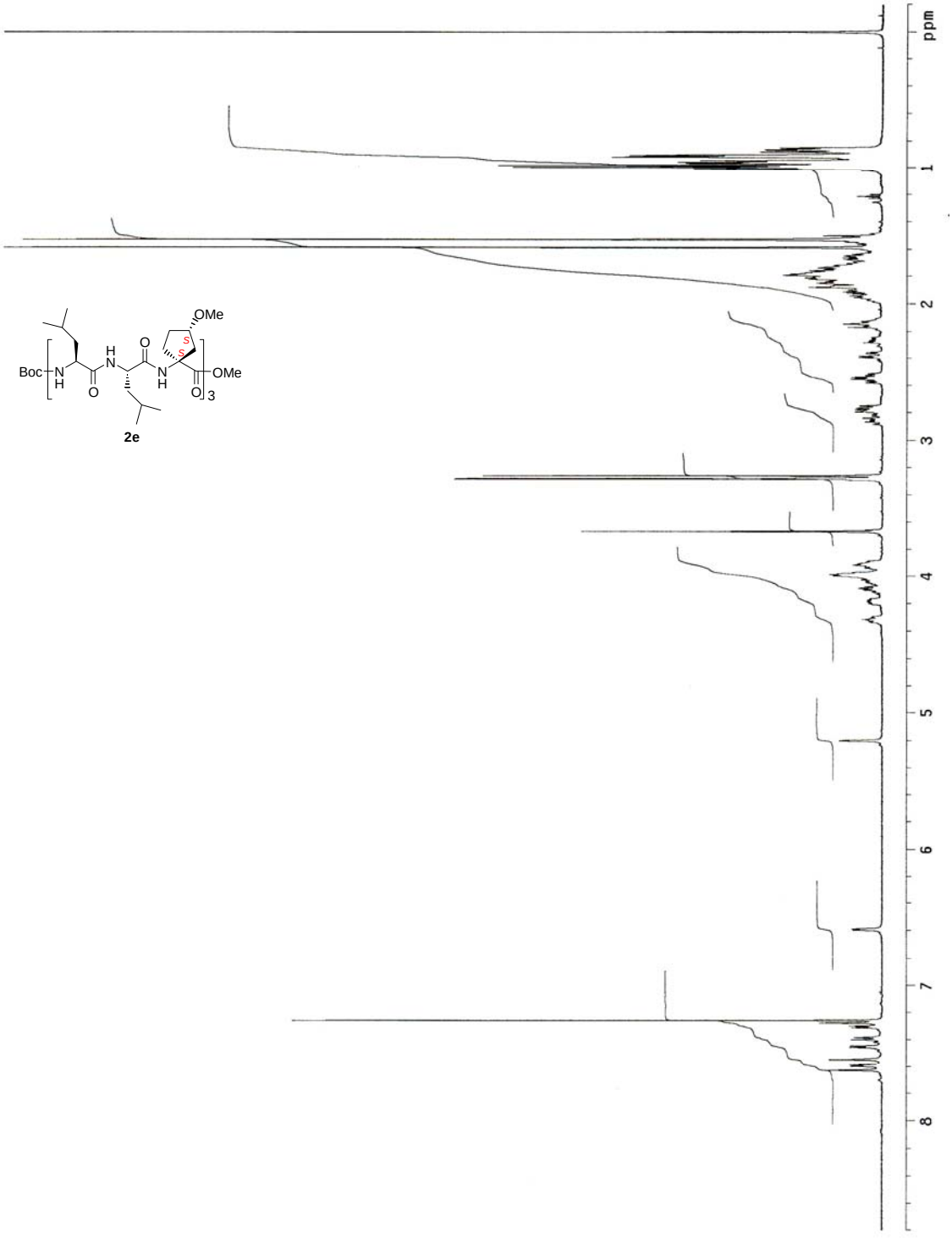
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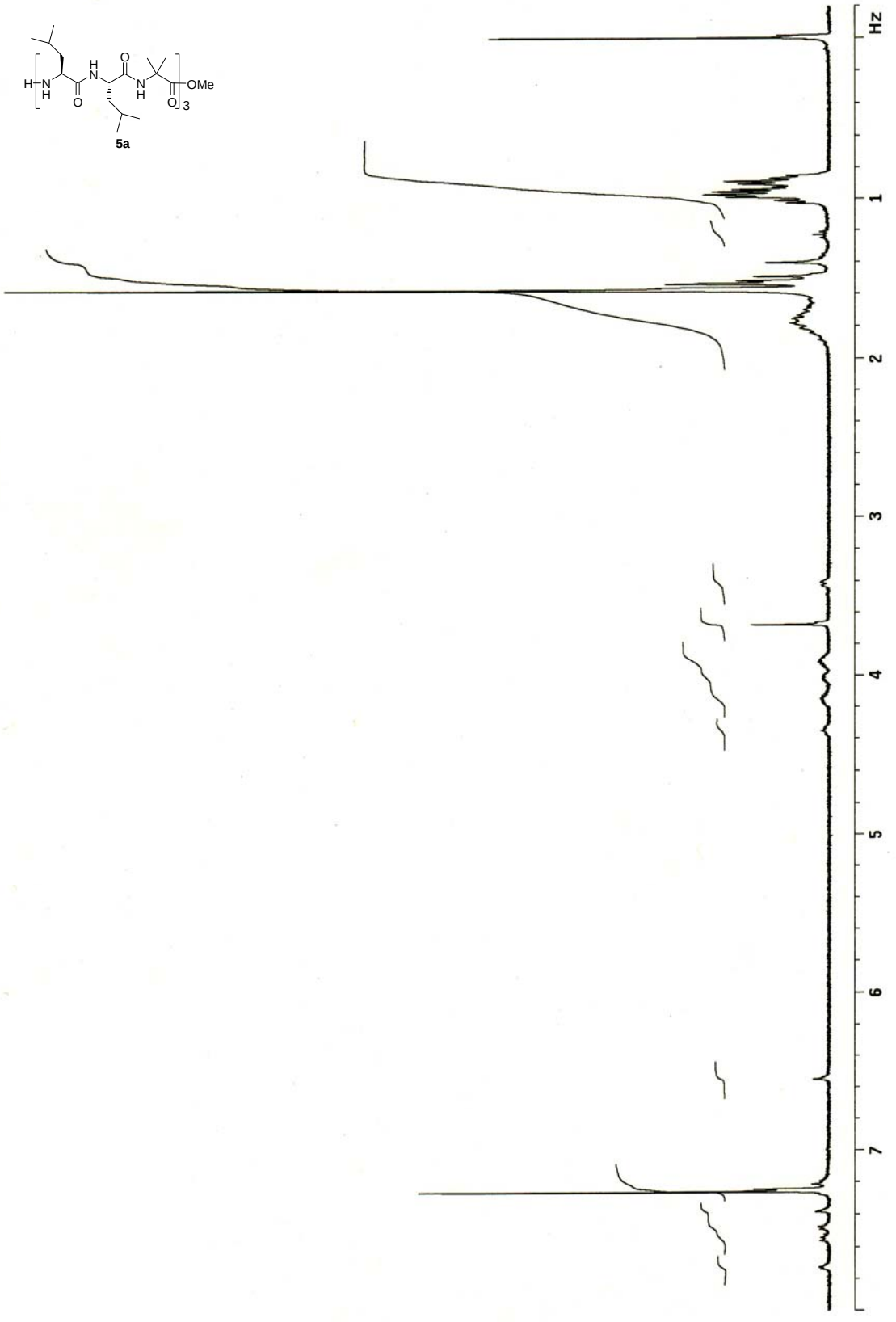
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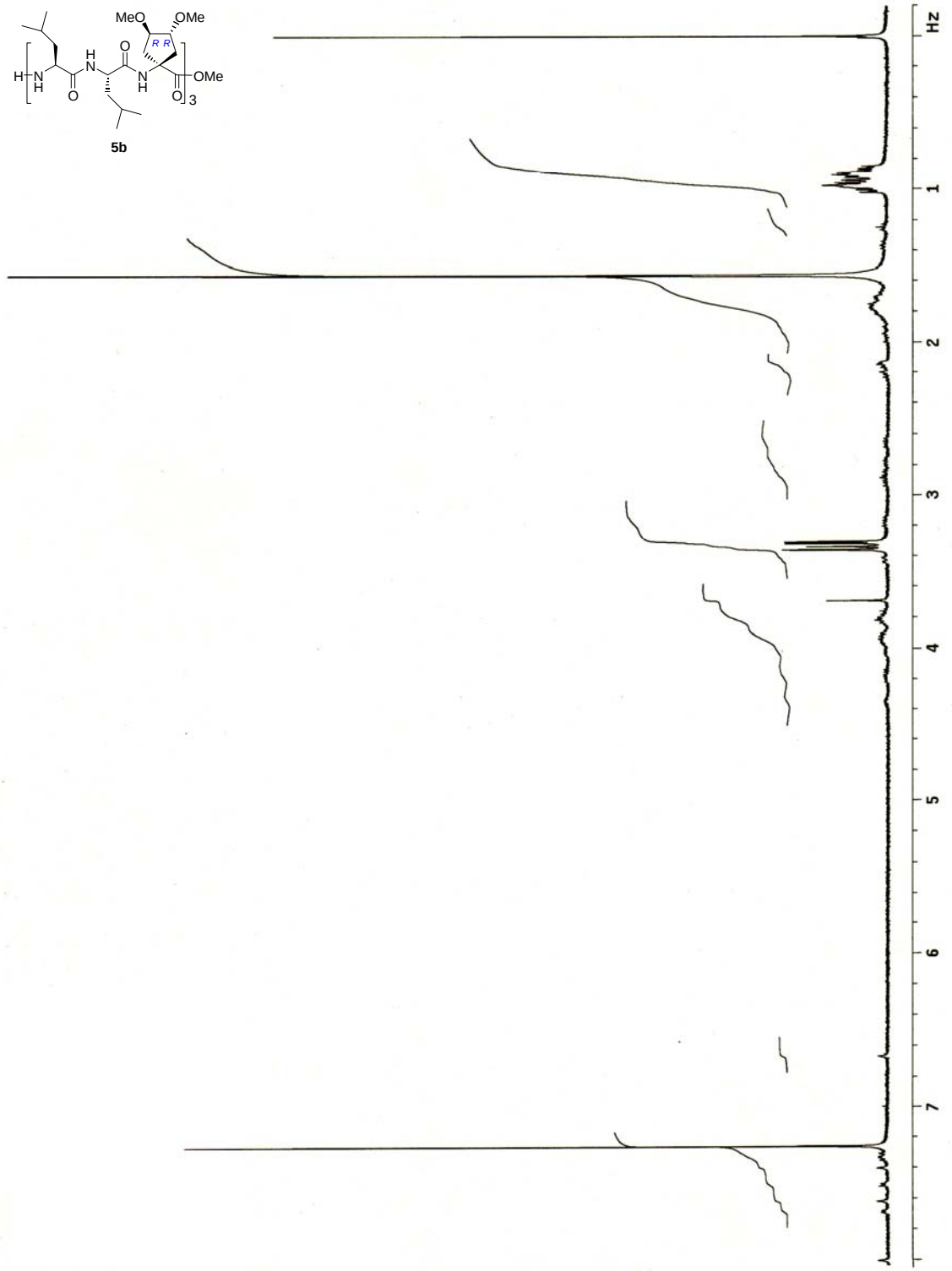
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Hz
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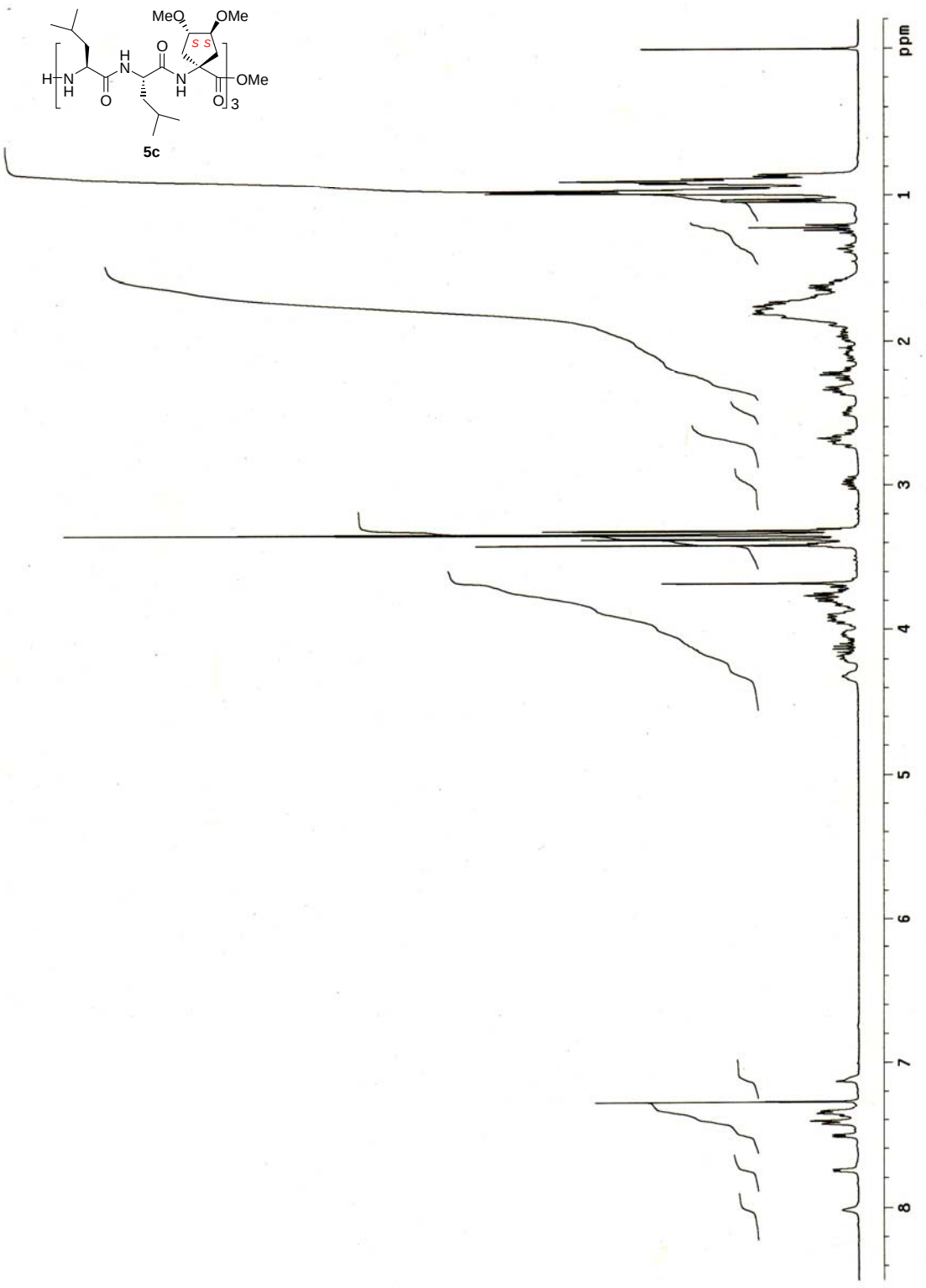
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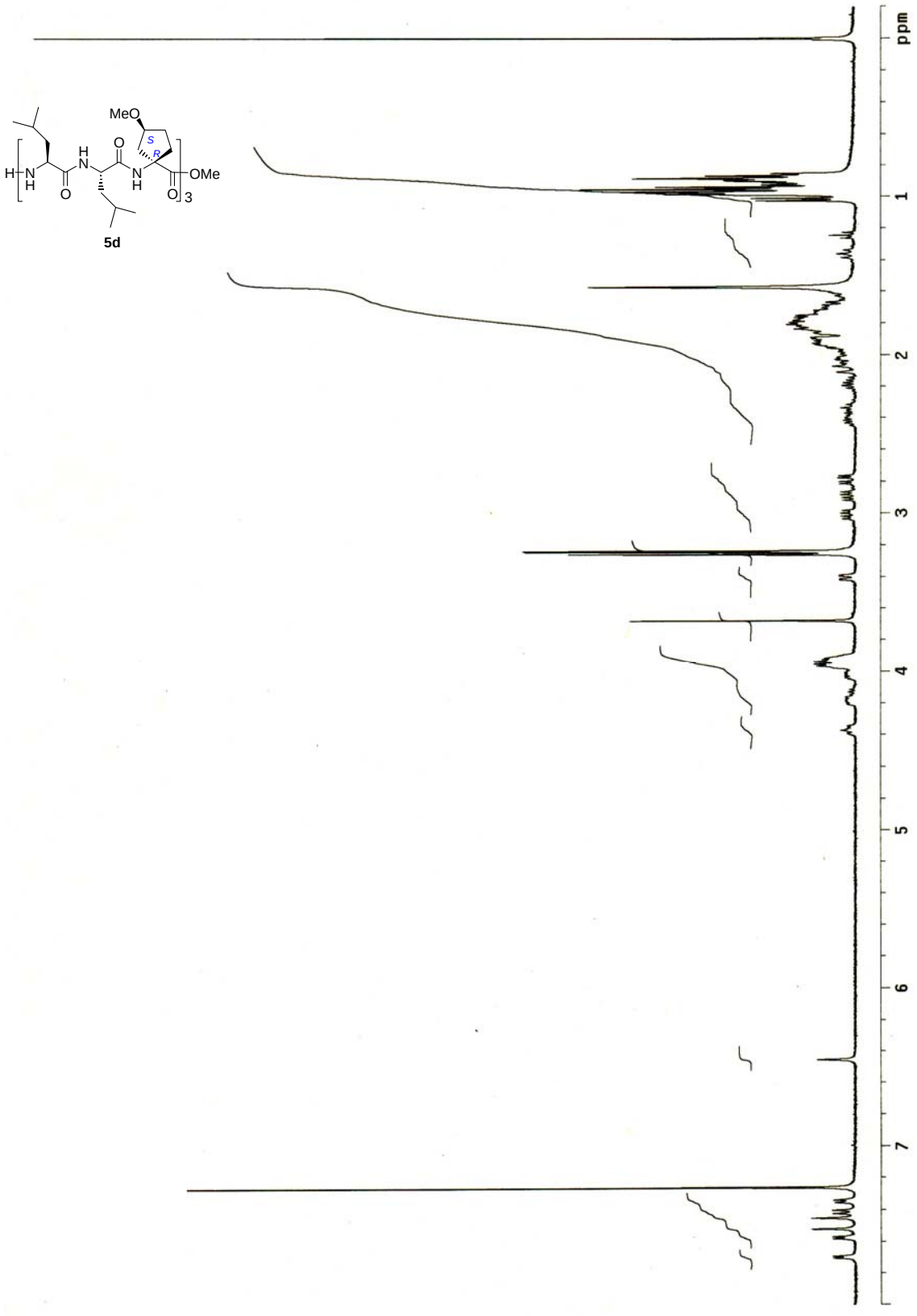
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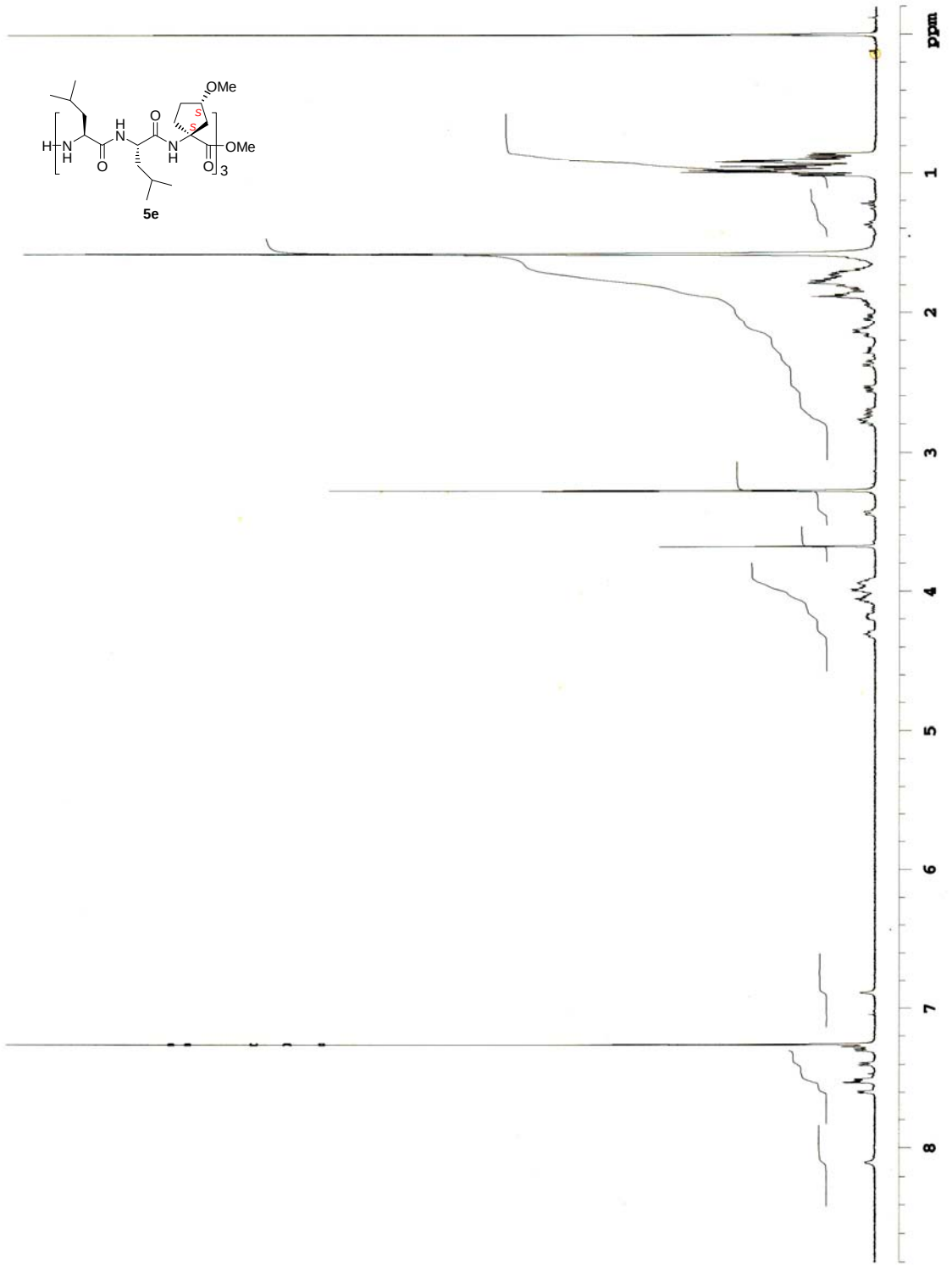
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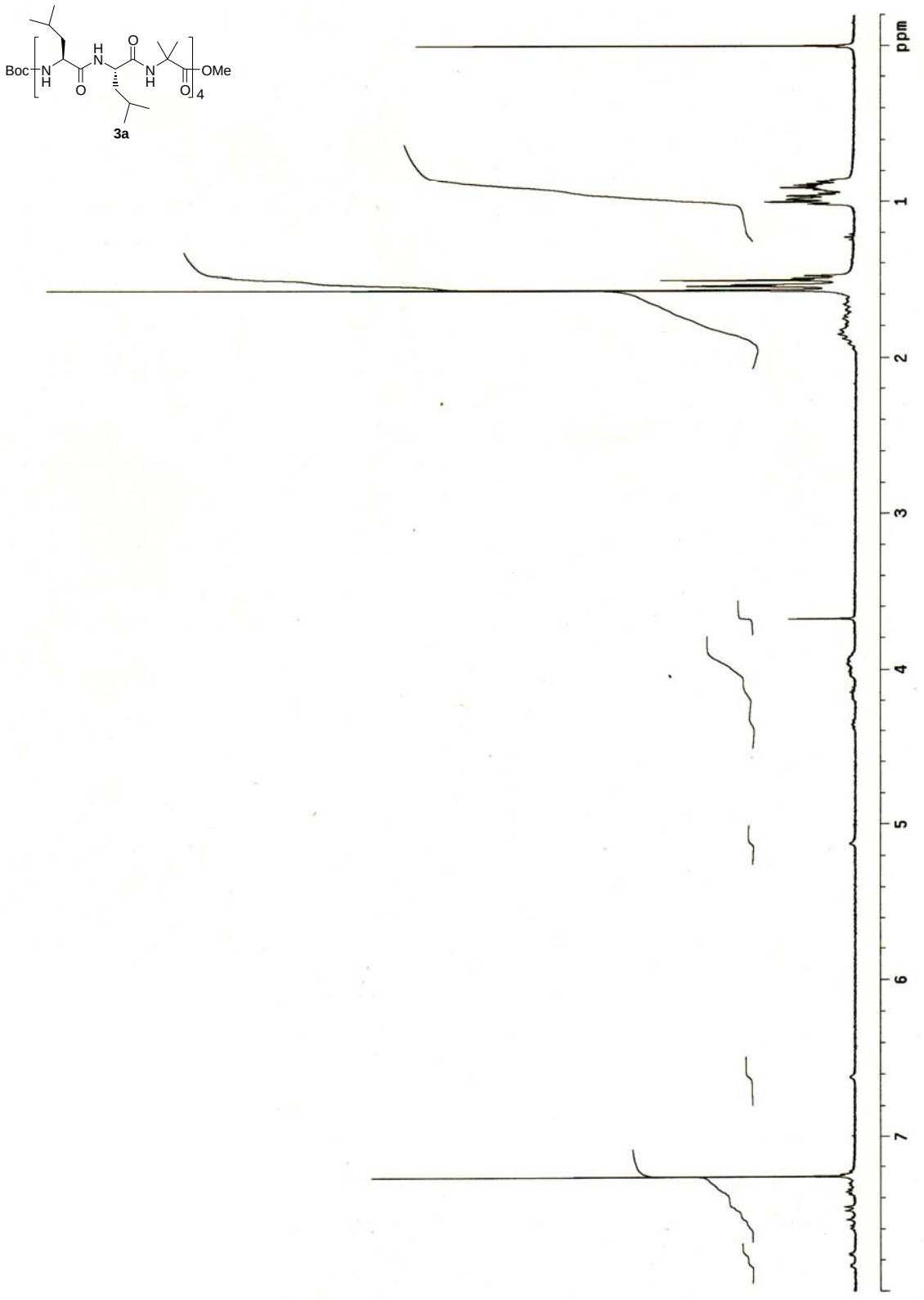
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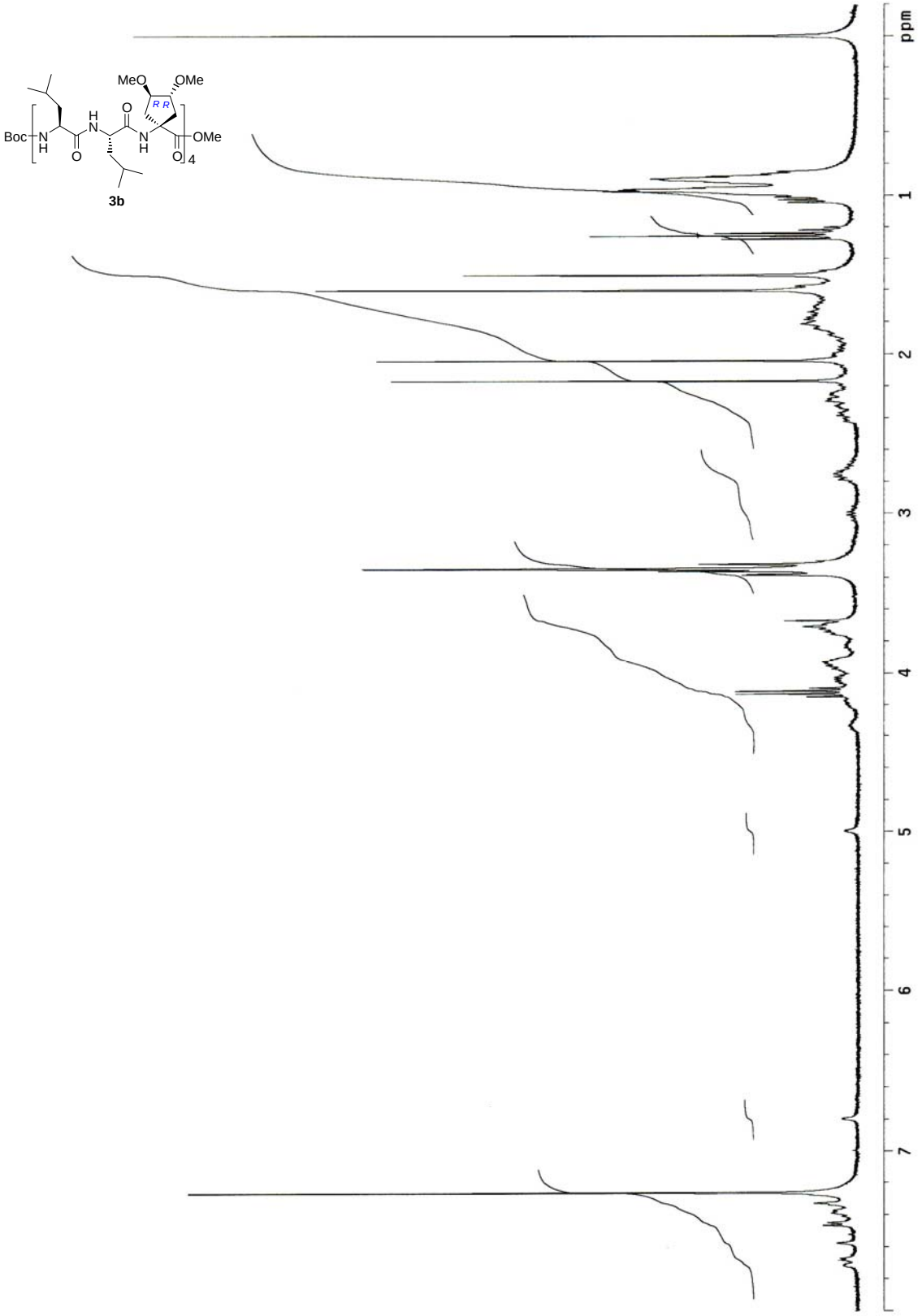
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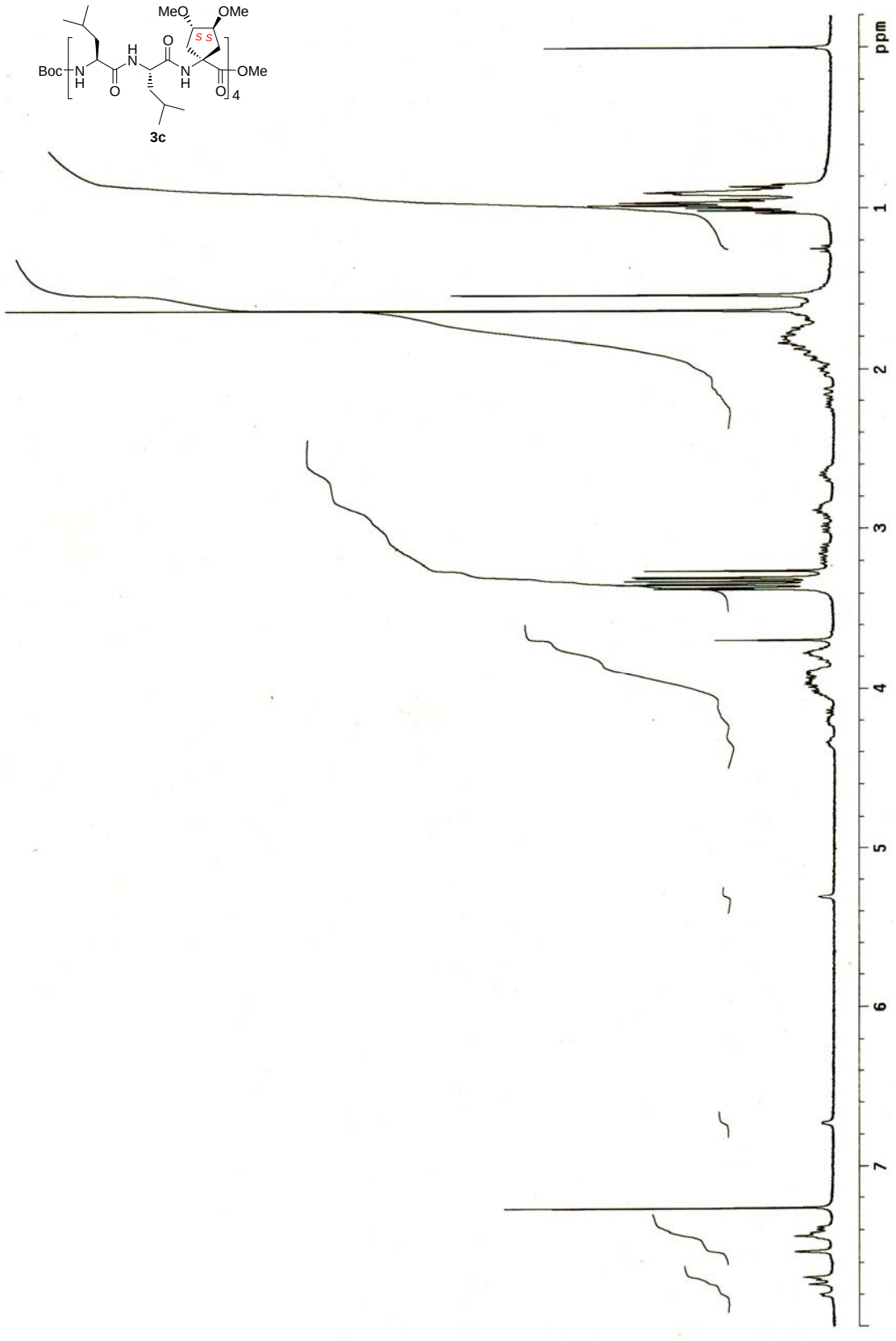
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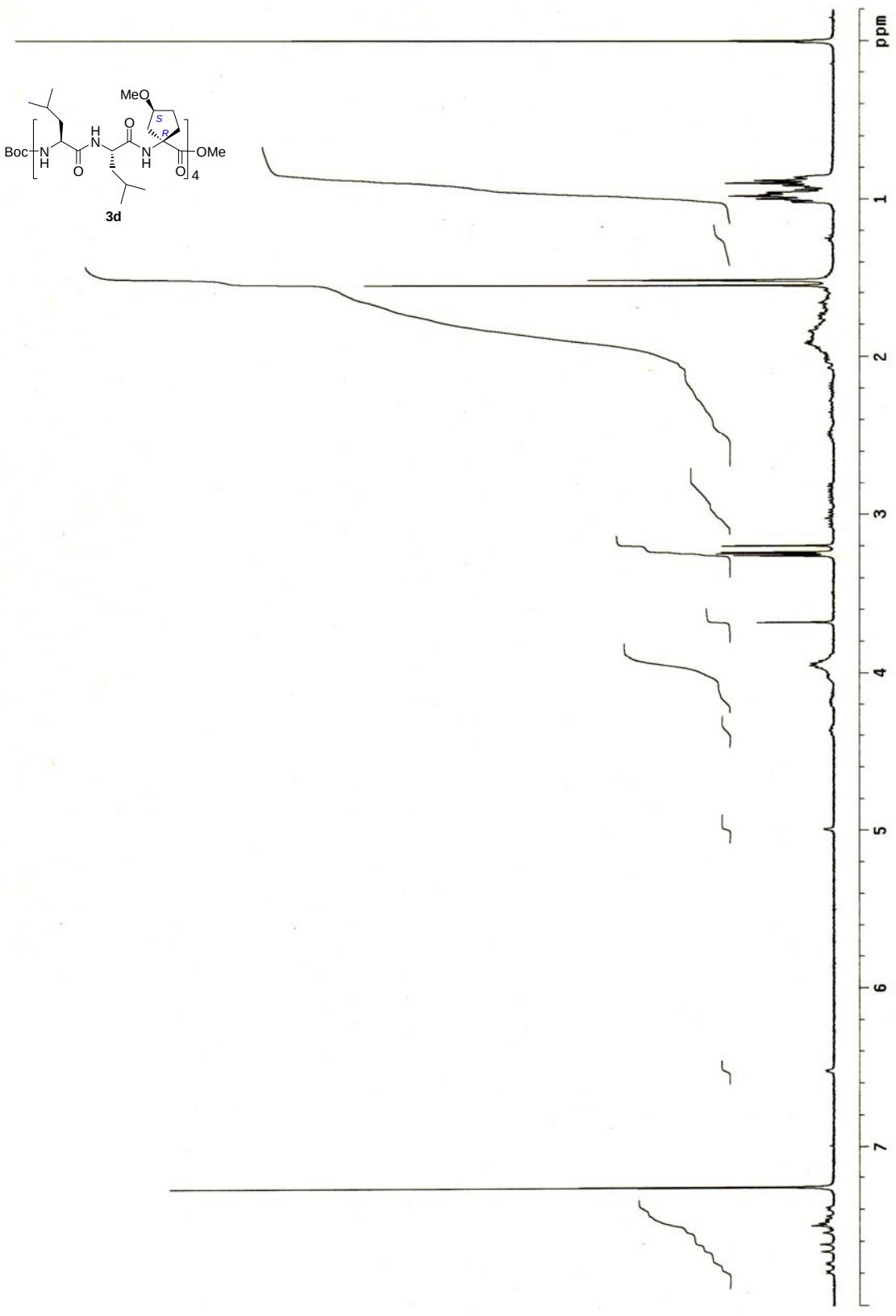
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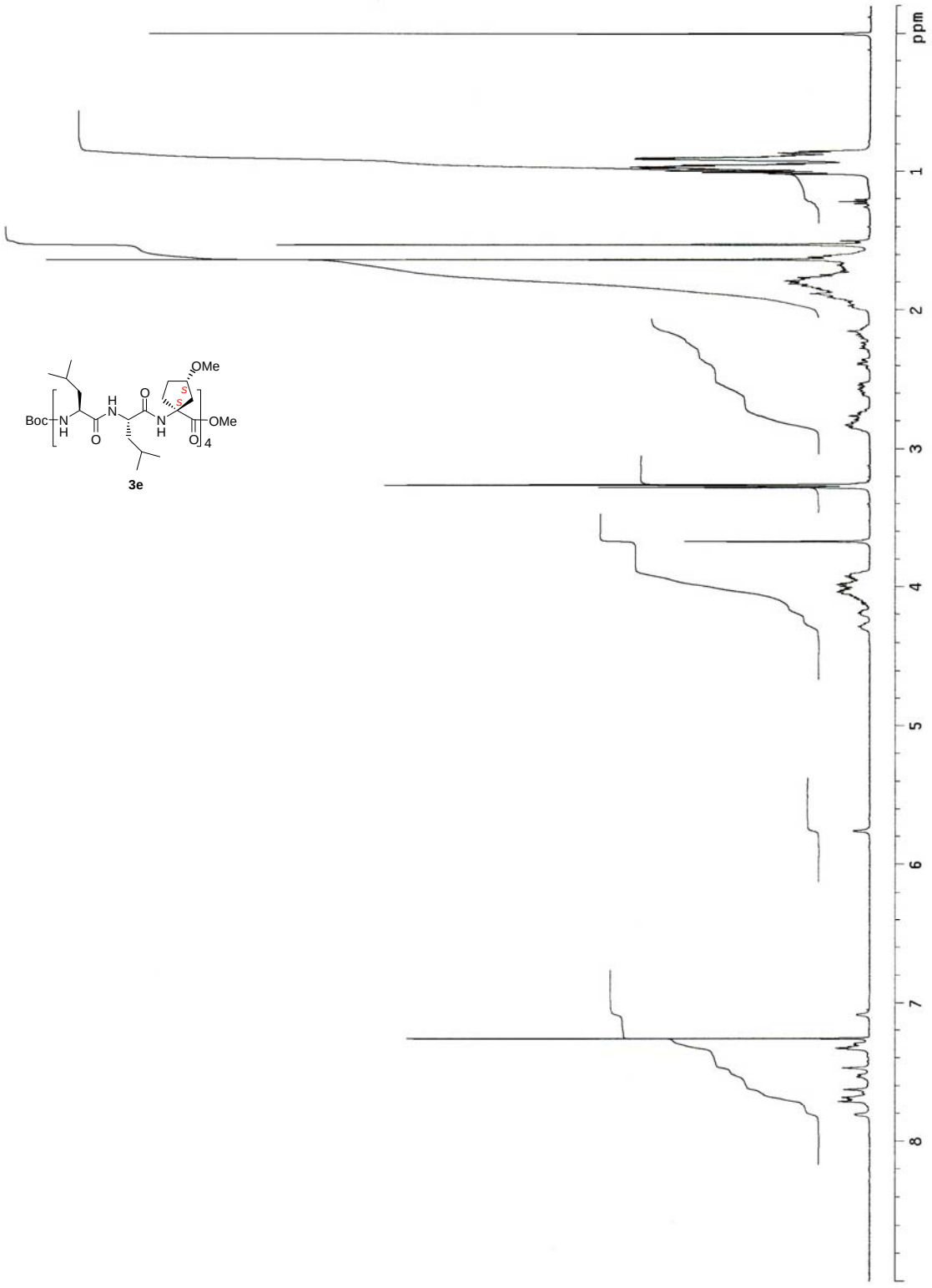
OMe
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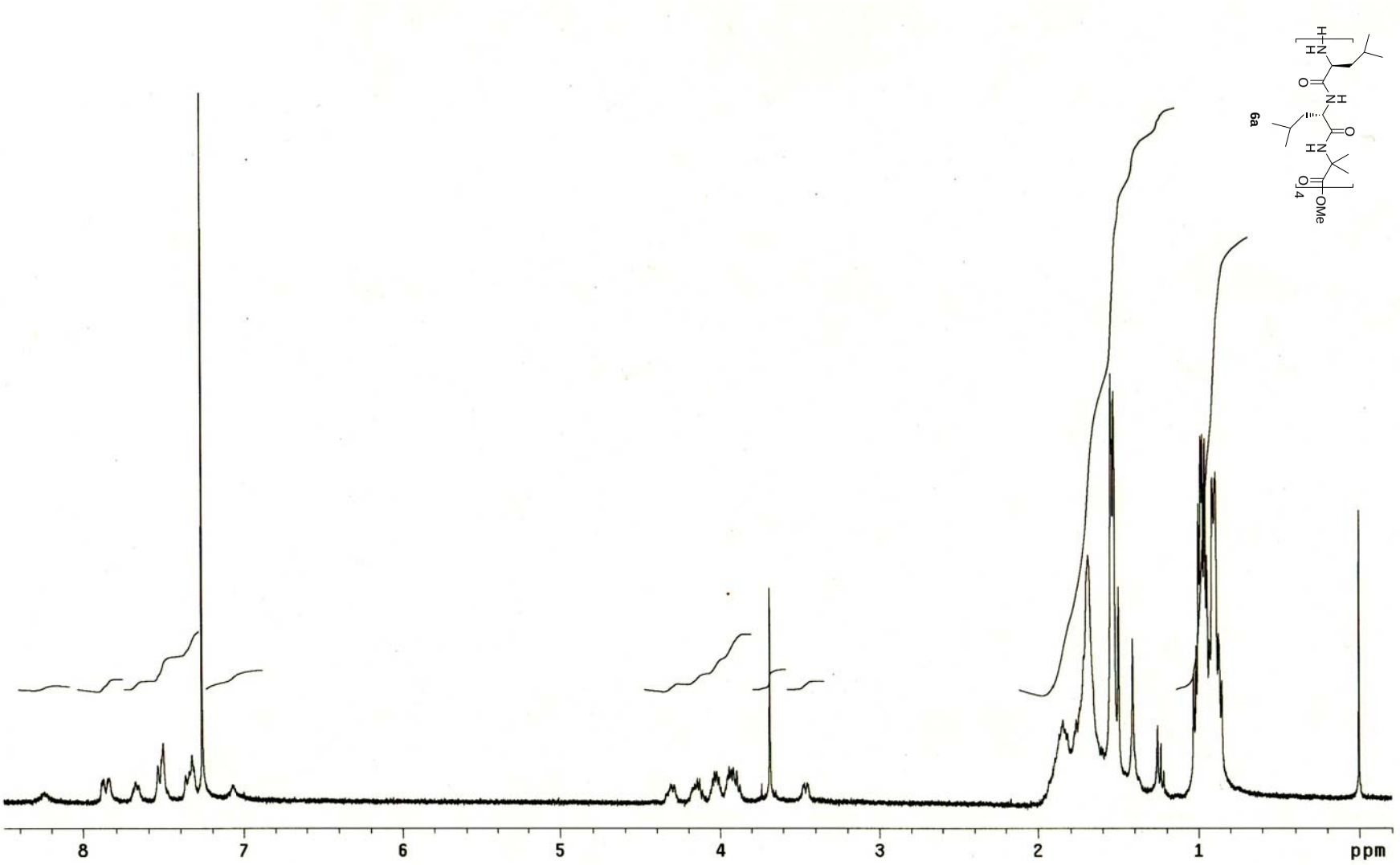
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ppm
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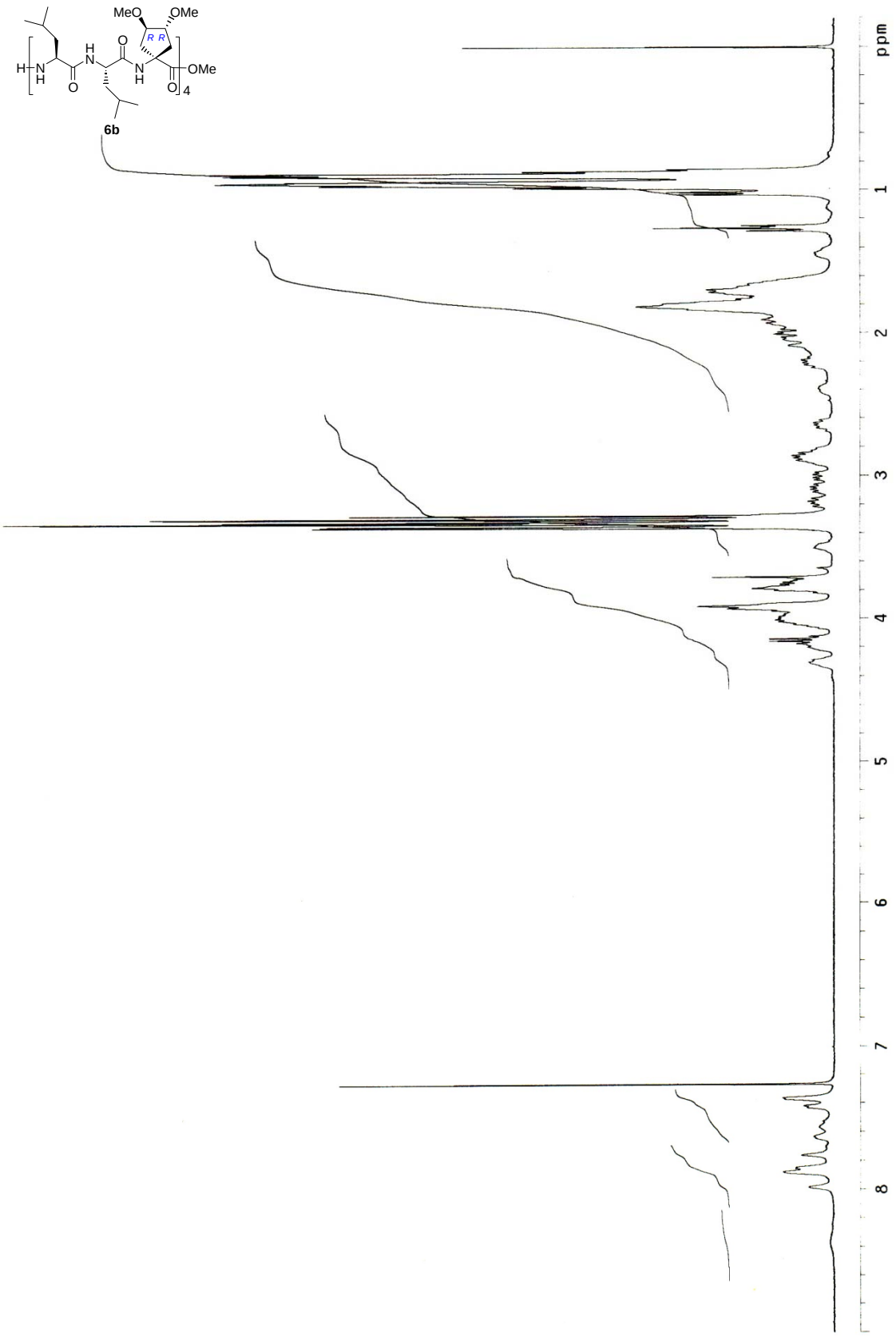
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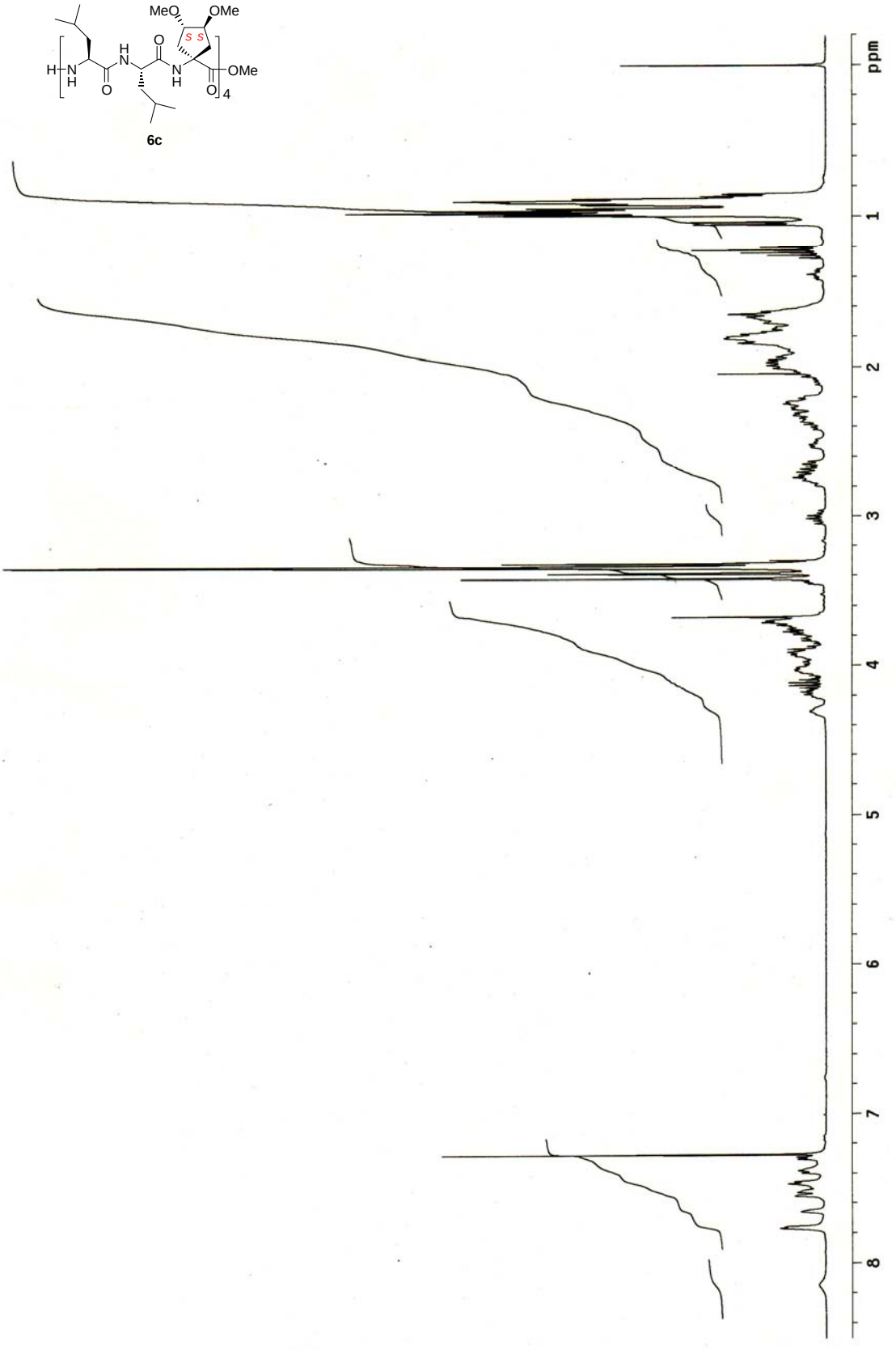
MeO
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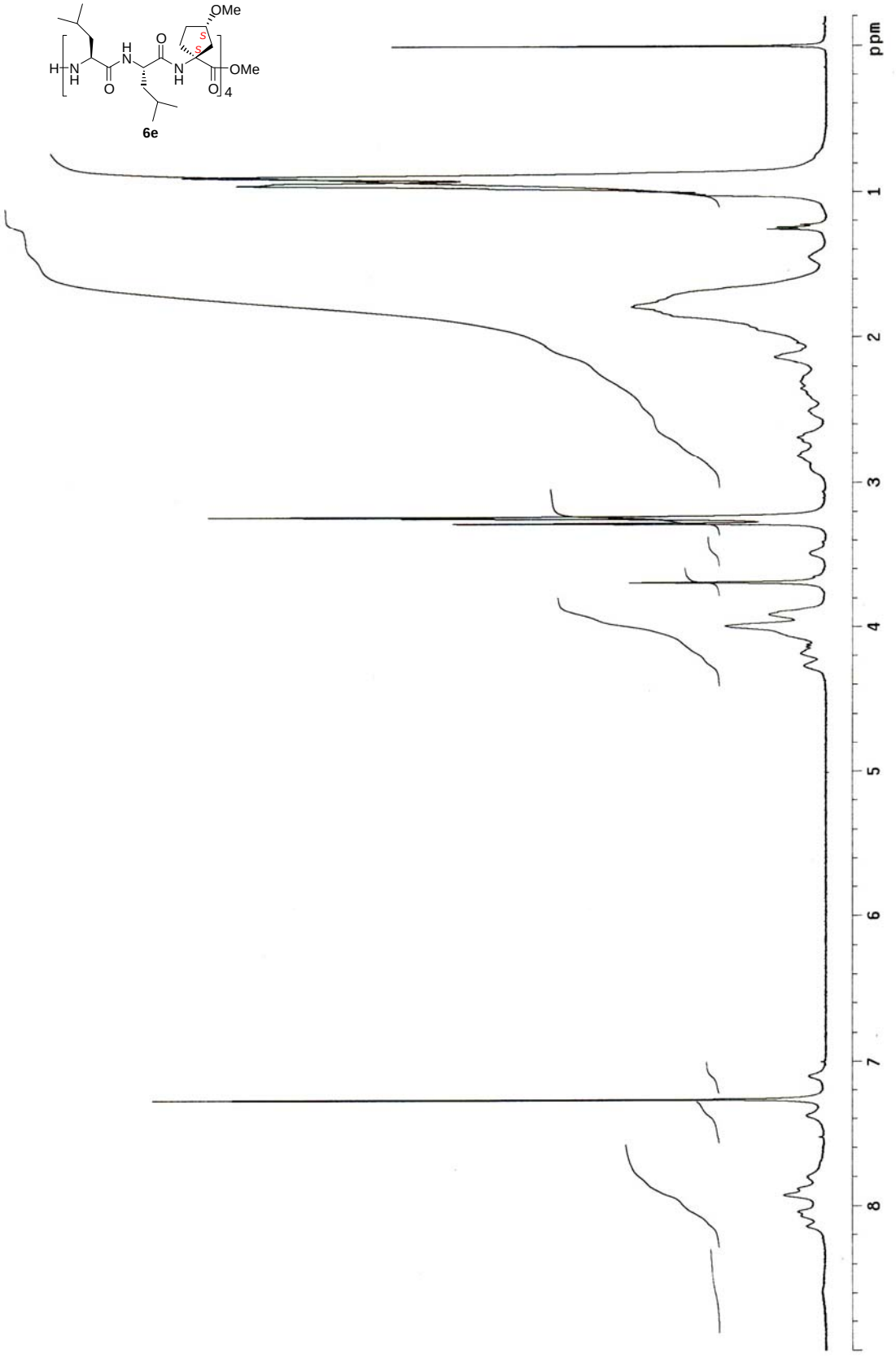
OMe
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ppm
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