SUPPORTING INFORMATION

Exponential growth of functional poly(glutamic acid) dendrimers with varying stereochemistry

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General Methods

Solvents and starting materials were commercial and used as received. All solvents were distilled once prior to usage. THF was stored over KOH and freshly distilled prior to usage. Column chromatography was carried out with 130 – 400 mesh silica gel using the eluents specified. Dialysis of the compounds was achieved using regenerated cellulose dialysis tubes Spectra/Pore Dialysis Membrane MWCO:1000 or MWCO:25000. Compound lyophylization was performed using Christ Alpha 2-4 LDC-1m apparatus. NMR spectra were recorded on a 400 MHz (100.6 MHz for ^{13}C) Bruker AV 400 or on a 300 MHz (75.6 MHz for ^{13}C) Bruker DPX 300 spectrometer at 27 °C using residual protonated solvent signals as internal standard (^{1}H: $\delta(CHCl_3)$ = 7.26 ppm, $\delta(CH_2Cl_2)$ = 5.32 ppm, $\delta((CH_3)_2SO)$ = 2.50 ppm, $\delta(CH_3OH)$ = 3.31 ppm and ^{13}C: $\delta(CHCl_3)$ = 77.16 ppm, $\delta(CH_2Cl_2)$ = 53.80 ppm, $\delta((CH_3)_2SO)$ = 39.52 ppm, $\delta(CH_3OH)$ = 49.00 ppm). Assignments are based on chemical shifts and/or DEPT as well as COSY spectra. Mass spectrometry was performed on Bruker-Esquire 3000 (ESI, ion-trap-MS, potential 4500 V) or Bruker-Apex III (FT-ICR-MS, ESI-HRMS), Finnigan MAT 8200 (EI, double focusing sector field, resolution of 3000, 70 eV ionization), and Waters LCT Premier XE, respectively. TLC was performed on Merck Silica Gel 60 F254 TLC plates with a fluorescent indicator with a 254 nm excitation wavelength. Compounds were visualized under UV light at 254 nm and after exposure to ninhydrin solution. HPLC separations were performed with Shimadzu LC-10A systems equipped with a photodiode array detector (PAD or DAD), specific measuring and system conditions are described for the corresponding substances. UPLC separations were performed with Waters UPLC Acquity equipped with a Waters LCT Premier XE Mass detector for UPLC-HR-MS, with Waters Alliance systems (consisting of a Waters Separations Module 2695, a Waters Diode Array detector 996 and a Waters Mass Detector ZQ 2000), specific measuring and system conditions are described at the corresponding substances. Sodium formate solutions and their observed adduct peaks were used to calibrate over the mass range up to 2000 D and extrapolation was used to cover the higher mass range, causing increasing deviations from the exact mass at masses significantly exceeding 2000 D. GPC measurements in DMF as the mobile phase were performed on PSS columns in a WGE Dr. Bures TAU 2010 column oven at 70 °C, using a WGE Dr. Bures Q-2010 HPLC pump and a Knauer Smartline 3800 autosampler. Detection was achieved using a WGE ETA-2020 RI-visco-detector and a Knauer Smartline 2500 UV-detector. Flow-rate was 1.0 mL/min. Columns were calibrated using a Polystyrene Calibration Kit S-L-10 LOT 79, using 2,4-di-*tert*-butyl-4-methoxy-phenol as internal standard. UV-

visible absorption spectra were recorded in quartz cuvettes of 1 mm path length on a Cary 50 Spectrophotometer and a Cary Eclipse Fluorimeter, respectively, each equipped with a Peltier thermostated cell holder at 25 ± 0.05 °C using spectrophotometric grade solvents. Circular dichroism spectra were recorded on a JASCO 710 Spectropolarimeter equipped with a JASCO PTC-423S/15 Peltier thermostated cell holder in spectroscopic grade solvents using Hellma quartz cuvettes of 1 mm path length. Prior to first use, the cuvettes were cleaned with 1:1 mixture of conc. H_2SO_4 / 30% H_2O_2, washed with water and acetonitrile, and a 10 vol-% solution of *silyl-501* (BSTFA: N,O-bis(trimethylsilyl)acetamide, 1%TMSCl) in acetonitrile was added. It was stirred for 10 min at RT and subsequently 20 min at 50 °C, then washed twice with acetonitrile and chloroform. After this silylation procedure, cuvettes were cleaned with aqueous Hellmanex II cuvette cleaning solutions. IR spectra were recorded on a Biorad Excalibur FTS30MX equipped with a Golden Gate ATR Specac.

Synthesis

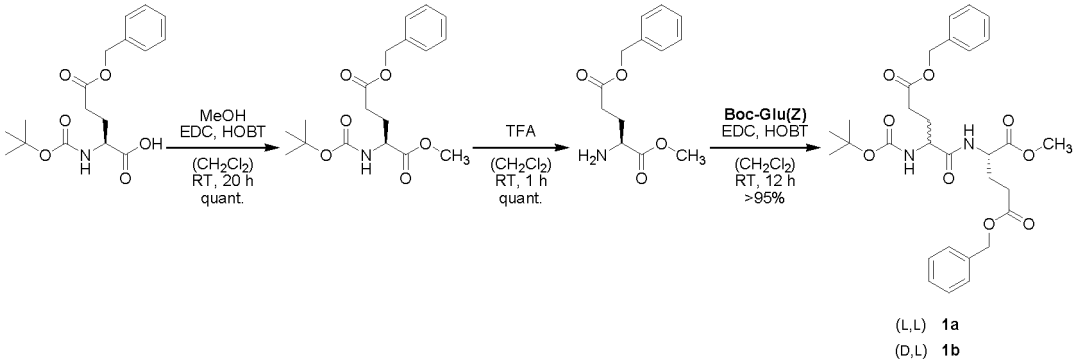
The preparation and characterization of the compounds outlined in Scheme 1 and 2 of the manuscript including additional compounds necessary for the synthesis, are provided below:

General Procedures:

General Procedure for the deprotection of the Boc-group. The respective peptide was dissolved in CH_2Cl_2 or in CH_2Cl_2:CH_3OH 9:1 (depending on solubility) and cooled to 0 °C. TFA (equal amount as the solvent) was added and the solution was allowed to warm to room temperature. After stirring at room temperature until starting material was consumed (TLC monitoring), the solution was concentrated *in vacuo*. When the uncharged, neutralized peptide was the desired product, the solution was extracted with water, saturated aqueous $NaHCO_3$ solution (in case of longer peptides (starting from octamer), CH_3OH was added to assure solubility of the peptide), water, and brine. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated *in vacuo* to yield the crude product in quantitative yield. In case of remaining protected peptide, the procedure was repeated. When the amine salt was the desired product, the reaction mixture was evaporated *in vacuo* and evaporated several times after adding CH_2Cl_2 to remove residual TFA and give the product in quantitative yield.

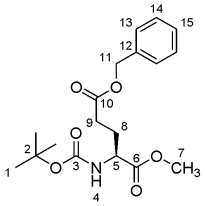
General Procedure for the deprotection of the methyl ester. To a solution of the respective methyl ester protected peptide in water : THF = 1 : 5, a 1 M aqueous solution of LiOH (water : LiOH : THF = 1 : 1 : 5) was added and the reaction mixture stirred at room temperature until starting material was consumed (TLC monitoring). Acetic acid was added to adjust to pH = 5, and the product subsequently extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent evaporated *in vacuo* to give the product in quantitative yield.

General Procedure for the deprotection of the Z-group or benzyl ester. To a solution of the respective Z- or benzyl-protected peptide in ethyl acetate (EA) : CH_3OH (ratio depending on solubility), Pd/C was added and the solution stirred under hydrogen atmosphere at room temperature. The reaction mixture was filtered and evaporated *in vacuo* to give the desired product.



Scheme 1: Synthesis of the dipeptide building blocks Boc-L-Glu(Z)-L-Glu(Z)-Me (**1a**) and Boc-D-Glu(Z)-L-Glu(Z)-Me (**1b**), starting from Boc-L-Glu(Z).

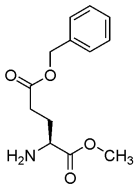
Boc-L-Glu(Z)-Me:



Boc-L-Glu(Z) (1.69 g, 5.00 mmol) and HOBT (0.74 g, 5.50 mmol) were dissolved in CH_2Cl_2:MeOH 1:1 (20 mL) and cooled to 0 °C. To the cold solution, EDC (1.25 g, 6.50 mmol) was added. The solution was allowed to warm to room temperature and stirred for 18 h. Water was added to the reaction mixture and the biphasic system stirred for 20 min.

After phase separation, the organic layer was extracted with aqueous 1 M citric acid solution (1x50 mL), water (1x50 mL), saturated aqueous $NaHCO_3$-solution (1x50 mL), and water (1x50 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give the crude product, which was purified via silica column chromatography (eluent: CH_2Cl_2 : MeOH = 98 : 2) to give 1.74 g (yield: 98%) of the desired product as a pale yellow oil. R_F = 0.80 (CH_2Cl_2 : MeOH = 9 : 1). **HPLC** (125 mm Nucleodur 100-5 C-18, 4.0 mm, Methanol : Water = 70 : 30, 0.8 mL/min, 9.3 MPa, 308 K): t_R = 4.15 min (96.5% peak area). **^{1}H NMR** (400 MHz, DMSO-d_6, 20 °C): δ 7.39 - 7.28 (m, 5 H, 2 $C^{13}H$, 2 $C^{14}H$, $C^{15}H$), 5.09 (s, 2 H, $C^{11}H_2$), 4.02 - 3.90 (m, 1 H, C^5H), 3.62 (s, 3 H, C^7H_3), 2.47 - 2.42 (m, 2 H, C^9H_2), 2.02 - 1.94 (m, 1 H, C^8H), 1.86 - 1.76 (m, 1 H, C^8H), 1.37 (s, 9 H, 3 C^1H_3). **^{13}C NMR** (DMSO-d_6): δ 172.66, 172.05, 155.52, 136.15, 128.42, 127.99, 127.87, 78.31, 65.49, 52.61, 51.82, 29.91, 28.14, 25.90. **EI-MS**: *m/z* = 57 (calcd 57 for $C(CH_3)_3$), 91 (calcd 91 for CH_2Ph), 108 (calcd 108 for OCH_2Ph), 144 (calcd 144 for $C_6H_{10}NO_3$), 160 (calcd 160 for $C_6H_9NO_4$), 192 (calcd 192 for $C_{11}H_{14}NO_2$), 251 (calcd 251 for Boc-L-Glu(Z)-Me - Boc), 292 (calcd 292 for Boc-L-Glu(Z)-Me - (H_3COCO)), 295 (calcd 295 for Boc-L-Glu(Z)-Me - ($C(CH_3)_3$)). **HR-ESI-MS**: *m/z* = 374.157298 (calcd 374.157405 for $C_{18}H_{25}N_1O_6$ + 1 Na^+).

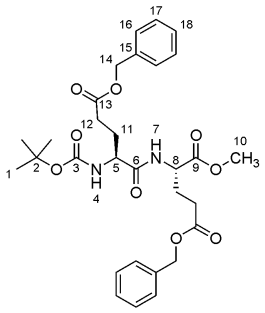
L-Glu(Z)-Me:



$C_{13}H_{17}NO_4$
M = 251.28 g/mol

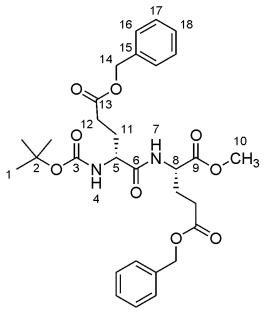
Boc-L-Glu(Z)-Me (2.11 g, 6.00 mmol) was reacted following the general procedure for the deprotection of the Boc-group. TFA (20 mL), CH_2Cl_2 (80 mL). The product was used without further purification and analysis to avoid diketopiperazine-formation. R_F = 0.50 (CH_2Cl_2 : MeOH = 9 : 1).

Boc-L-Glu(Z)-L-Glu(Z)-Me (**1a**):



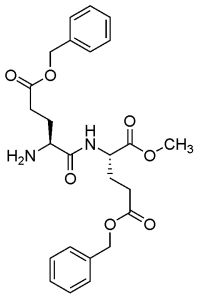
Boc-L-Glu(Z) (7.42 g, 22.00 mmol), HOBT (2.70 g, 20.00 mmol) and L-Glu(Z)-Me (5.03 g, 20.00 mmol) were dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. A concentrated solution of EDC (4.99 g, 26.00 mmol) in CH_2Cl_2 was added. The solution was allowed to warm to room temperature and stirred for 48 h. The reaction mixture was extracted with aqueous 1 M citric acid solution (1x20 mL), water (1x20 mL), saturated aqueous $NaHCO_3$-solution (1x20 mL), and water (1x20 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The crude product was purified via silica column chromatography (eluent: PE : EA = 2 : 1) to give 11.20 g (yield: 98%) of the desired product as a colorless oil. R_F = 0.80 (CH_2Cl_2 : MeOH = 9 : 1). **UPLC-HRMS**: ((2.1x100 mm HSS T3 1.8µm, acetonitrile : water Grad 40 95A): t_R = 4.69 min (>99.9% peak area, ESI(+): 571.27 (**1a** + 1 H^+)). **GPC** (DMF): M_n = 546 g/mol, M_w = 556 g/mol, M_p = 562 g/mol, PDI = 1.02. **^{1}H NMR** (300 MHz, $CDCl_3$, 20 °C): δ 7.37 - 7.30 (m, 10 H, 4 $C^{16}H$, 4 $C^{17}H$, 2 $C^{18}H$), 6.87 (d, ^3J(H,H) = 7.4 Hz, 1 H, N^7H), 5.22 (d, ^3J(H,H) = 7.4 Hz, 1 H, N^4H), 5.13 (s, 2 H, $C^{14}H_2$), 5.11 (s, 2 H, $C^{14}H_2$), 4.60 (dt, ^3J(H,H) = 8.0 Hz, ^3J(H,H) = 5.0 Hz, 1 H, C^8H), 4.25 - 4.14 (m, 1 H, C^5H), 3.71 (s, 3 H, $C^{10}H_3$), 2.62 - 2.35 (m, 4 H, 2 $C^{12}H_2$), 2.34 - 1.85 (m, 4 H, 2 $C^{11}H_2$), 1.42 (s, 9 H, 3 C^1H_3). **^{13}C NMR** ($CDCl_3$): δ 173.28, 172.58, 171.97, 171, 60, 155.21, 135.78, 128.71, 128.45, 128.41, 66.60, 52.55, 51.63, 30.39, 30.15, 28.26, 27.85, 27.12. **HR-ESI-MS**: *m/z* = 571.2650 (calcd 571.2656 for $C_{30}H_{38}N_2O_9$ + 1 Na^+).

Boc-D-Glu(Z)-L-Glu(Z)-Me (**1b**):



Boc-D-Glu(Z) (2.13 g, 6.30 mmol), HOBT (0.89 g, 6.60 mmol), and L-Glu(Z)-Me (1.51 g, 6.00 mmol) were dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. A concentrated solution of EDC (1.50 g, 7.80 mmol) in CH_2Cl_2 (20 mL) was added drop wise. The solution was allowed to warm to room temperature and stirred for 14 h. Water was added to the solution and the resulting biphasic system stirred for 10 min. After phase separation, the organic layer was dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The crude product was purified via silica column chromatography (eluent: CH_2Cl_2 : MeOH = 95 : 5) to give 3.38 g (yield: 99%) of **1b** as an yellow oil. The yellow color was removed by extraction of this oil with PE. R_F = 0.80 (CH_2Cl_2 : MeOH = 9 : 1). **HPLC**: (125 mm Nucleodur 100-5 C-18, 2.0 mm, Methanol : Water = 70 : 30, 0.2 mL/min, 11.9 MPa, 308 K): t_R = 9.99 min (96.6% peak area, **1b**). **GPC** (DMF): M_n = 546 g/mol, M_w = 556 g/mol, M_p = 562 g/mol, PDI = 1.02. **^{1}H NMR** (400 MHz, DMSO-d_6, 20 °C): δ 8.23 (d, ^3J(H,H) = 6.9 Hz, 1 H, N^7H), 7.39 - 7.31 (m, 10 H, 4 C^{16}H, 4 C^{17}H, 2 C^{18}H), 6.91 (d, ^3J(H,H) = 7.9 Hz, 1 H, N^4H), 5.08 (s, 4 H, 2 C$^{14}H_2$), 4.31 - 4.25 (m, 1 H, C^8H), 4.00 - 3.86 (m, 1 H, C^5H), 3.60 (s, 3 H, C$^{10}H_3$), 2.43 - 2.37 (m, 4 H, 2 C$^{12}H_2$), 2.06 - 1.75 (m, 4 H, 2 C$^{11}H_2$), 1.36 (s, 9 H, 3 C$^1H_3$). **^{13}C NMR** (DMSO-d_6): δ 172.18, 171.99, 171, 86, 171.78, 155.21, 136.18, 136.08, 128.39, 127.97, 127.94, 127.88, 127.81, 78.20, 65.49, 65.41, 53.55, 51.89, 51.01, 29.94, 29.69, 28.09, 27.09, 25.91. **EI-MS**: *m/z* = 57 (calcd 57 for $C(CH_3)_3$), 91 (calcd 91 for CH_2Ph), 108 (calcd 108 for OCH_2Ph), 192 (calcd 191 for $C_{11}H_{13}NO_2$), 236 (calcd 236 for $C_{12}H_{14}NO_4$), 292 (calcd 292 for $C_{16}H_{22}NO_4$), 362 (calcd 362 for $C_{18}H_{22}N_2O_6$), 514 (calcd 513 for **1b** -($C(CH_3)_3$)), 570 (calcd 570 for **1b**). **HR-ESI-MS**: *m/z* = 593.246646 (calcd 593.246951 for $C_{30}H_{38}N_2O_9$ + 1 Na^+).

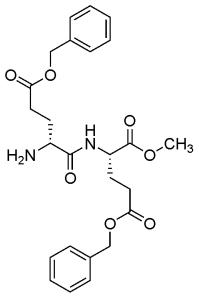
L-Glu(Z)-L-Glu(Z)-Me (**2a**):



$C_{25}H_{30}N_2O_7$
M = 470.51 g/mol

1a (6.59 g, 11.55 mmol) was reacted following the general procedure for the deprotection of the Boc-group. TFA (17 mL), CH_2Cl_2 (17 mL). The product was used without further purification and analysis to avoid diketopiperazine-formation. R_F = 0.50 (CH_2Cl_2 : MeOH = 9 : 1). **^{1}H NMR** (300 MHz, $CDCl_3$, 20 °C): δ 7.71 (d, ^3J(H,H) = 8.2 Hz, 1 H, N*H*), 7.37 - 7.30 (m, 10 H, Ar-*H*), 5.10 (s, 4 H, CH_2), 4.60 (dt, ^3J(H,H) = 8.1 Hz, ^3J(H,H) = 5.5 Hz, 1 H, C*H*), 3.71 (s, 3 H, CH_3), 3.49 - 3.40 (m, 1 H, C*H*), 2.52 - 1.75 (m, 8 H, CH_2). **^{13}C NMR** ($CDCl_3$): δ 173.19, 172.45, 172.19, 135.79, 135.73, 128.59, 128.31, 128.27, 66.56, 66.46, 54.41, 52.48, 51.33, 30.72, 30.37, 30.10, 27.23.

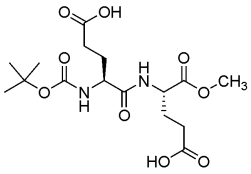
D-Glu(Z)-L-Glu(Z)-Me (**2b**):



$C_{25}H_{30}N_2O_7$
M = 470.51 g/mol

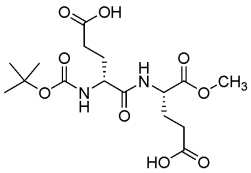
1b (2.40 g, 4.20 mmol) was reacted following the general procedure for the deprotection of the Boc-group. TFA (50 mL), CH_2Cl_2 (50 mL). The product was used without further purification and analysis to avoid diketopiperazine-formation. R_F = 0.50 (CH_2Cl_2 : MeOH = 9 : 1).

Boc-L-Glu-L-Glu-Me (**3a**):



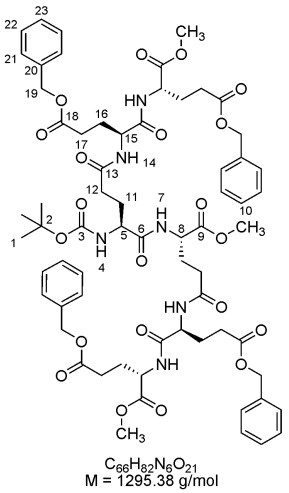
1a (3.14 g, 5.50 mmol) was reacted following the general procedure for the deprotection of the Z-group or benzyl ester. EA (20 mL), Pd/C (260 mg), reaction time: 2.5 h, hydrogen pressure: 5 bar. The product was obtained in quantitative yield and was used without further purification. **^{1}H NMR** (300 MHz, $CDCl_3$, 20 °C): δ 7.54 - 7.53 (m, 1 H, N*H*), 5.64 – 5.62 (m, 1 H, N*H*), 4.65 – 4.63 (m, 1 H, C*H*), 4.40 – 4.38 (m, 1 H, C*H*), 3.75 (s, 3 H, CH_3), 2.52 - 1.90 (m, 8 H, CH_2), 1.44 (s, 9 H, CH_3). **HR-ESI-MS**: *m/z* = 391.1530 (calcd 391.1717 for $C_{16}H_{26}N_2O_9$ + 1 H^+).

Boc-D-Glu-L-Glu-Me (**3b**):



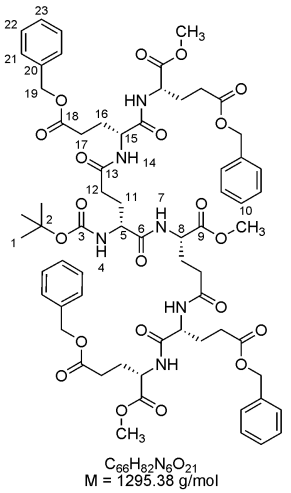
1b (0.80 g, 0.14 mmol) was reacted following the general procedure for the deprotection of the Z-group or benzyl ester. MeOH (20 mL), Pd/C (80 mg), reaction time: 2.5 h, hydrogen pressure: 5 bar. The product was obtained in quantitative yield and was used without further purification. **HR-ESI-MS**: *m/z* = 389.1517 (calcd 389.1560 for $C_{16}H_{24}N_2O_9$ - 1 H^+).

Boc-G2-*all*-L-Glu(Z)-Me (**4a**):



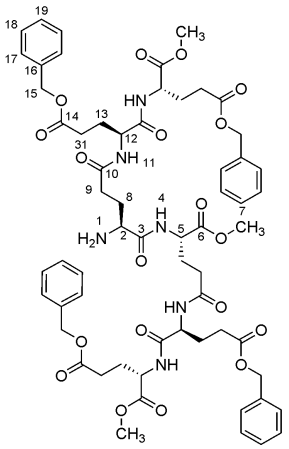
3a (2.15 g, 5.50 mmol), **2a** (5.44 g, 11.55 mmol), and HOBT (0.74 g, 5.50 mmol) were dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. To the cold solution EDC (3.16 g, 16.50 mmol) was added. The solution was allowed to warm to room temperature and stirred under TLC monitoring. After completion of the reaction, water was added and the biphasic system stirred for 10 minutes. After phase separation, the organic layer was extracted with aqueous 1 M citric acid solution (1x20 mL), water (1x20 mL), saturated aqueous $NaHCO_3$-solution (1x20 mL), and water (1x20 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated *in vacuo*, to give the crude product, which was dissolved in CH_2Cl_2 and precipitated in Et_2O. The purified crude product was further purified via silica column chromatography (eluent: CH_2Cl_2 : MeOH = 95 : 5). The white solid was dissolved in CH_2Cl_2 : MeOH and precipitated in ice-cold Et_2O, to give 6.57 g (92%) of the desired product as a white powder. R_F = 0.60 (CH_2Cl_2 : MeOH = 9 : 1). **UPLC-HRMS**: ((2.1x100 mm HSS T3 1.8µm, acetonitrile : water Grad 60 95A): t_R = 3.54 min (>99.9% peak area, ESI(+): 1317.42 (**4a** + 1 Na^+)). **GPC** (DMF): M_n = 1684 g/mol, M_w = 1709 g/mol, M_p = 1717 g/mol, PDI = 1.01. **^{1}H NMR** (300 MHz, $CDCl_3$, 20 °C): δ 8.29 (d, ^3J(H,H) = 8.3 Hz, 1 H, N*H*), 7.57 (d, ^3J(H,H) = 7.2 Hz, 1 H, N*H*), 7.30 - 7. 17 (m, 20 H, Ar-*H*), 6.99 (d, ^3J(H,H) = 6.6 Hz, 2 H, N*H*), 6.79 (d, ^3J(H,H) = 6.8 Hz, 1 H, N*H*), 5.17 – 5.08 (m, 8 H, CH_2), 5.02 – 4.97 (m, 1 H, N*H*), 4.59 - 4.28 (m, 5 H, C*H*), 3.79 - 3.69 (m, 1 H, C*H*), 3.58 – 3.55 (3xs, 9 H, CH_3), 2.49 - 1.61 (m, 24 H, CH_2), 1.27 (s, 9 H, CH_3). **HR-ESI-MS**: *m/z* = 1317.4174 (calcd 1317.5431 for $C_{66}H_{82}N_6O_{21}$ + 1 Na^+).

Boc-G2-D-(*alt*)-L-Glu(Z)-Me (**4b**):



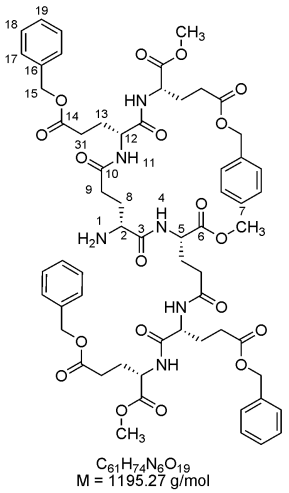
3b (0.55 g, 1.40 mmol), **2b** (1.37 g, 2.90 mmol), and HOBT (0.19 g, 1.40 mmol) were dissolved in CH_2Cl_2 (40 mL) and cooled to 0 °C. To the cold solution, EDC (0.81 g, 4.20 mmol) was added. The solution was allowed to warm to room temperature and stirred under TLC monitoring. After completion of the reaction, water was added and the biphasic system stirred for 10 minutes. After phase separation, the organic layer was extracted with aqueous 1 M citric acid solution (1x20 mL), water (1x20 mL), saturated aqueous $NaHCO_3$-solution (1x20 mL), and water (1x20 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated *in vacuo*, to give the crude product, which was dissolved in CH_2Cl_2 and precipitated in Et_2O. The purified crude product was further purified via silica column chromatography (eluent: CH_2Cl_2 : MeOH = 9 : 1) to give 1.72 g (yield:95%) of the desired product as white powder. R_F = 0.60 (CH_2Cl_2 : MeOH = 9 : 1). **UPLC-HRMS**: ((2.1x100 mm BEH Phenyl 1.7µm, acetonitrile : water Grad 40 95A): t_R = 5.08 min (>99.9% peak area, ESI(+): 1317.55 (**4b** + 1 Na^+)). **GPC** (DMF): M_n = 1655 g/mol, M_w = 1677 g/mol, M_p = 1690 g/mol, PDI = 1.01. **^{1}H NMR** (300 MHz, $CDCl_3$, 20 °C): δ 7.63 (d, ^3J(H,H) = 7.9 Hz, 1 H, N*H*), 7.44 (d, ^3J(H,H) = 7.9 Hz, 1 H, N*H*), 7.39 - 7. 14 (m, 23 H, 4 $C^{21-23}H$, 3 N*H*), 5.72 – 5.70 (m, 1 H, N*H*), 5.10 – 5.07 (m, 8 H, 4 $C^{19}H_2$), 4.67 - 4.43 (m, 5 H, 3 C^8H, 2 $C^{15}H$), 4.21 - 4.10 (m, 1 H, C^5H), 3.68 – 3.66 (3xs, 9 H, 3 $C^{10}H_3$), 2.61 - 1.73 (m, 24 H, 2 $C^{11-12}H_2$, 1.39 (s, 9 H, 3 C^1H_3). **^{13}C NMR** ($CDCl_3$): δ 172.41, 171.33, 172.17, 172.14, 172.02, 172.03, 135.91, 135.86, 135.77, 128.65, 128.62, 128.39, 128.35, 128.31, 128.28, 128.24, 80.22, 66.65, 66.54, 66.46, 52.66, 52.58, 52.51, 51.84, 51.74, 51.62, 30.64, 30.54, 30.47, 30.39, 28.36, 26.77. **HR-ESI-MS**: *m/z* = 1295.5606 (calcd 1295.5606 for $C_{66}H_{82}N_6O_{21}$ + 1 H^+).

G2-*all*-L-Glu(Z)-Me (**5a**):



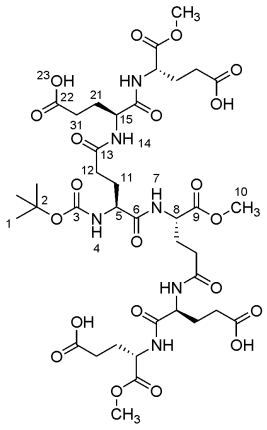
4a (0.33 g, 0.25 mmol) was reacted following the general procedure for the deprotection of the Boc-group. TFA (3.0 mL), CH_2Cl_2 (6.0 mL). The product was used without further purification. R_F = 0.22 (CH_2Cl_2 : MeOH = 9 : 1). **UPLC-HRMS**: ((2.1x100 mm BEH Phenyl 1.7µm, acetonitrile : water Grad 40 95A): t_R = 5.48 min (>99.9% peak area, ESI(+): 1195.51 (**5a** + 1 H^+)). **HR-ESI-MS**: *m/z* = 1195.5051 (calcd 1195.5087 for $C_{61}H_{74}N_6O_{19}$ + 1 H^+).

G2-D-(*alt*)-L-Glu(Z)-Me (**5b**):



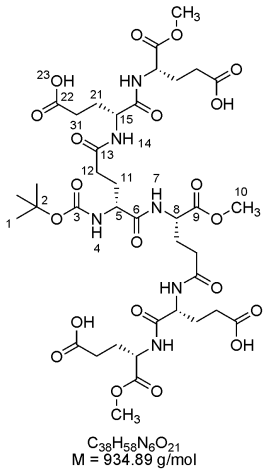
4b (0.32 g, 0.25 mmol) was reacted following the general procedure for the deprotection of the Boc-group. TFA (2.0 mL), CH_2Cl_2 (4.0 mL). The crude product was dissolved in CH_2Cl_2 and precipitated in Et_2O to give the pure product. R_F = 0.22 (CH_2Cl_2 : MeOH = 9 : 1).

Boc-G2-*all*-L-Glu-Me (**6a**):



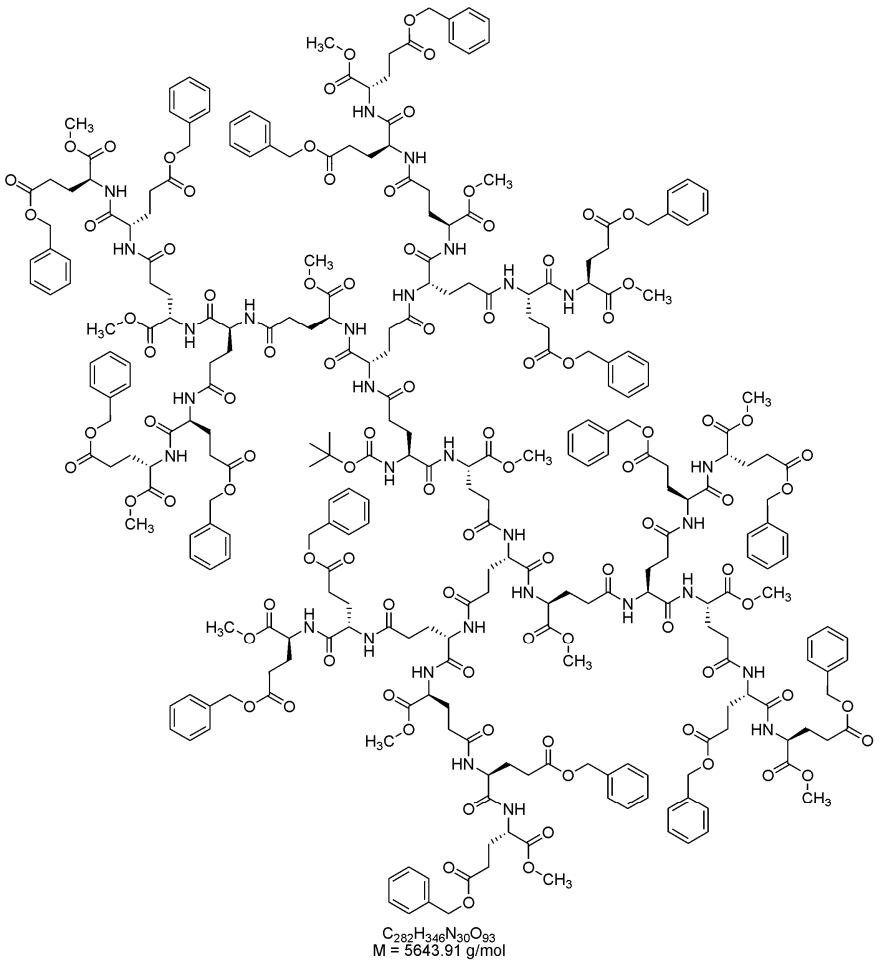
4a (0.26 g, 0.20 mmol) was reacted following the general procedure for the deprotection of the Z-group or benzyl ester. THF (Please note that Z deprotection was performed in THF as hydrogenation in MeOH led to partial esterification of the free carboxylic acid functionalities) (60 mL), Pd/C (25 mg), reaction time: 6 h, hydrogen pressure: 5 bar. The product was obtained in quantitative yield and was used without further purification. $R_F = 0.10$ (CH_2Cl_2 : MeOH = 9 : 1). **HR-ESI-MS**: *m/z* = 935.3724 (calcd 935.3733 for $C_{38}H_{58}N_6O_{21}$ + 1 H^+).

Boc-G2-D-(*alt*)-L-Glu-Me (**6b**):



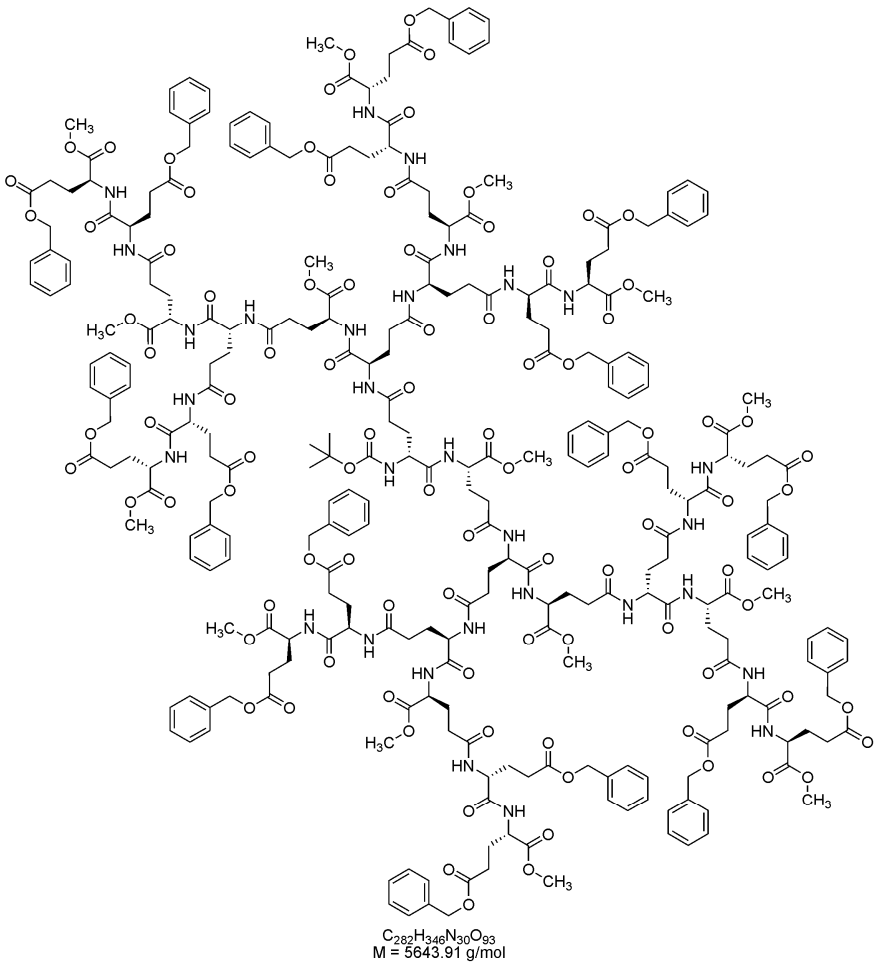
4b (0.10 g, 0.08 mmol) was reacted following the general procedure for the deprotection of the Z-group or benzyl ester. THF (Please note that Z deprotection was performed in THF as hydrogenation in MeOH led to partial esterification of the free carboxylic acid functionalities) (60 mL), Pd/C (25 mg), reaction time: 6 h, hydrogen pressure: 5 bar. The product was obtained in quantitative yield and was used without further purification. $R_F = 0.10$ (CH_2Cl_2 : MeOH = 9 : 1). **UPLC-HRMS**: ((2.1x100 mm BEH Phenyl 1.7µm, acetonitrile : water Grad 20 50A): $t_R = 2.75$ min (>99.9% peak area, ESI(+): 934.42 (**6b** + 1 H^+)). **^{1}H NMR** (300 MHz, CD_3OD, 20 °C): δ 4.50 – 4.32 (m, 5 H, C*H*), 4.10 – 4.05 (m, 1 H, C*H*), 3.72 (s, 9 H, CH_3), 2.61 - 1.74 (m, 24 H, CH_2), 1.45 (s, 9 H, CH_3). **HR-ESI-MS**: *m/z* = 933.3750 (calcd 933.3577 for $C_{38}H_{58}N_6O_{21}$ - 1 H^+).

Boc-G4-*all*-L-Glu(Z)-Me (**7a**):



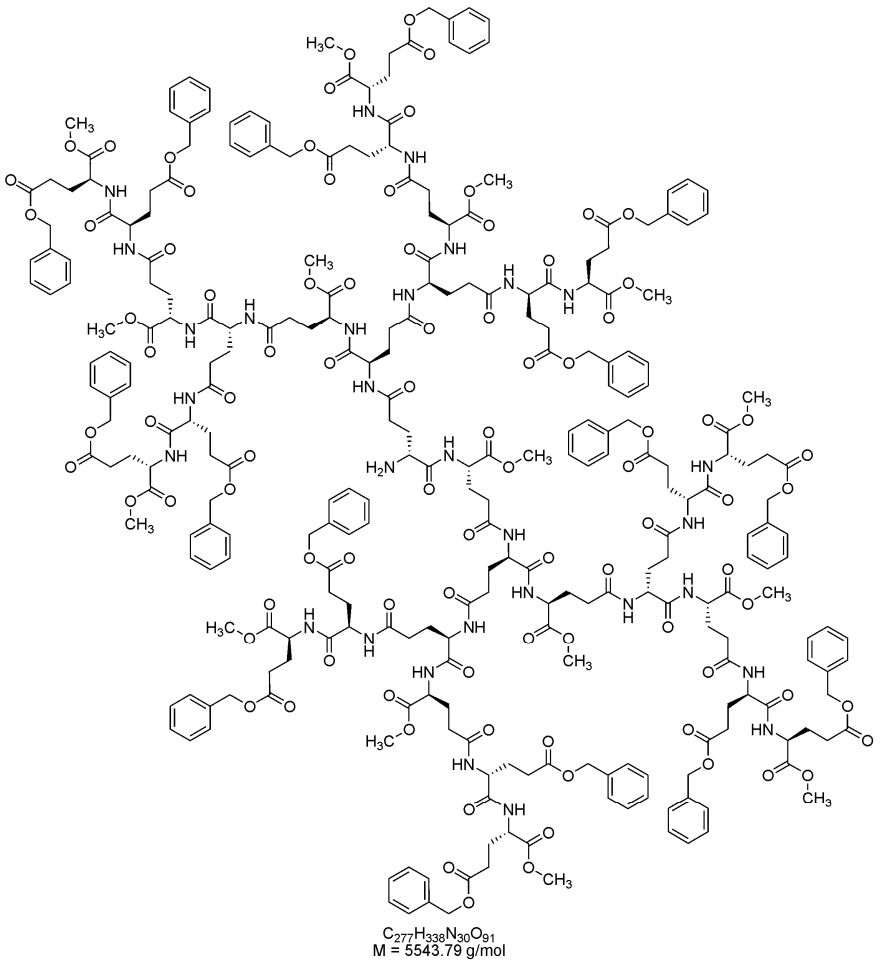
6a (0.19 g, 0.20 mmol), **5a** (1.02 g, 0.85 mmol), and HOBT (0.05 g, 0.40 mmol) were dissolved in DMF (15 mL) and cooled to 0 °C. To the cold solution EDC (0.23 g, 1.20 mmol) was added. The solution was allowed to warm to room temperature and stirred for 3 days. The reaction was monitored by GPC. The solution was precipitated in Et_2O. The precipitate was extensively washed with Et_2O and MeOH (TLC monitoring). The remaining white powder was extracted with EA, until GPC displayed pure product. This procedure afforded 0.95 g (yield: 84%) of the desired product as a white powder. **GPC** (DMF): M_n = 5552 g/mol, M_w = 5744 g/mol, M_p = 6009 g/mol, PDI = 1.04. **^{1}H NMR** (300 MHz, DMSO-d_6, 20 °C): δ 8.49 – 7.85 (m, 30 H, N*H*), 7.41 – 7.25 (m, 80 H, Ar-*H*), 5.08 (s, 32 H, CH_2), 4.37 – 4.12 (m, 29 H, C*H*), 3.90 – 3.89 (m, 1 H, C*H*), 3.62 – 3.51 (m, 45 H, CH_3), 2.48 - 1.59 (m, 120 H, CH_2), 1.33 (s, 9 H, CH_3). **ESI-MS**: *m/z* = 5661.21 (calcd 5663.32 for $C_{282}H_{346}N_{30}O_{93}$ + 1 Na^+), 2844.56 (calcd 2843.15 for $C_{282}H_{346}N_{30}O_{93}$ + 2 Na^+).

Boc-G4-D-(*alt*)-L-Glu(Z)-Me (**7b**):



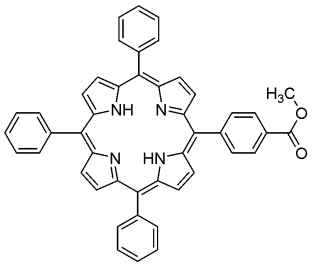
6b (0.19 g, 0.20 mmol), **5b** (1.02 g, 0.85 mmol), and HOBT (0.05 g, 0.40 mmol) were dissolved in DMF (15 mL) and cooled to 0 °C. To the cold solution EDC (0.23 g, 1.20 mmol) was added. The solution was allowed to warm to room temperature and stirred for 3 days. The reaction was monitored by GPC. The solution was precipitated in Et_2O. The precipitate was extensively washed with Et_2O and MeOH (TLC monitoring). The remaining white powder was extracted with EA, until GPC displayed pure product. This procedure afforded 1.03 g (yield: 91%) of the desired product as a white powder. **GPC** (DMF): M_n = 5706 g/mol, M_w = 5827 g/mol, M_p = 5939 g/mol, PDI = 1.02. **^{1}H NMR** (300 MHz, DMSO-d_6, 20 °C): δ 8.47 – 7.88 (m, 30 H, N*H*), 7.40 – 7.25 (m, 80 H, Ar-*H*), 5.06 (s, 32 H, CH_2), 4.40 – 4.13 (m, 29 H, C*H*), 3.90 – 3.89 (m, 1 H, C*H*), 3.65 – 3.51 (m, 45 H, CH_3), 2.46 - 1.63 (m, 120 H, CH_2), 1.35 (s, 9 H, CH_3). **ESI-MS**: *m/z* = 5661.23 (calcd 5663.32 for $C_{282}H_{346}N_{30}O_{93}$ + 1 Na^+), 2844.55 (calcd 2843.15 for $C_{282}H_{346}N_{30}O_{93}$ + 2 Na^+).

G4-D-(*alt*)-L-Glu(Z)-Me:



7b (0.10 g, 0.02 mmol) was reacted following the general procedure for the deprotection of the Boc-group. TFA (3.0 mL), CH_2Cl_2 (3.0 mL). The crude product was dissolved in CH_2Cl_2 and precipitated in Et_2O to give the pure product. In case of anion exchange, the product was dissolved in DMF, NEt_3 (0.075 mL, 30 eq) was added and the solution precipitated in Et_2O. The solid was washed with Et_2O to give the product in quantitative yield. The product was used immediately in the subsequent coupling reaction as described on page S20. **^{1}H NMR** (300 MHz, DMSO-d_6, 20 °C): δ 8.45 – 7.92 (m, 29 H, N*H*), 7.40 – 7.25 (m, 80 H, Ar-*H*), 5.10 –5.01 (m, 32 H, CH_2), 4.40 – 4.13 (m, 29 H, C*H*), 3.62 – 3.47 (m, 45 H, CH_3), 2.45 - 1.63 (m, 120 H, CH_2).

5-(4'-Carboxymethylphenyl)-10,15,20-triphenylporphyrin:[1]

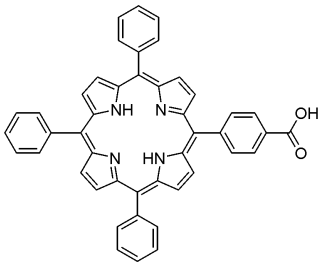


$C_{46}H_{32}N_4O_2$
M = 672.77 g/mol

Benzaldehyde (4.6 mL, 45.0 mmol) and methyl 4-formylbenzoate (2.5 g, 15.0 mmol) were dissolved in propionic acid : nitrobenzene = 5 : 1 (400 mL) and heated to 140 °C. Pyrrole (4.2 mL, 60.0 mmol) was added dropwise and the solution was stirred for 3 h. After standing over night, the solvent was removed *in vacuo*. The dark purple solid was dissolved in CH_2Cl_2 and stirred with saturated aqueous $NaHCO_3$-solution. The resulting emulsion was filtered through an alox plug. The solution was evaporated *in vacuo*. Purification was achieved via repetitive silica column chromatography and afforded 1.14 g (yield: 11%) of the desired product as a dark purple solid. $R_F = 0.60$ (EA : PE = 7 : 3 + 0.1 vol-% NEt_3). **^{1}H NMR** (300 MHz, $CDCl_3$, 20 °C): δ 8.91 – 8.87 (m, 6 H, Ar-*H*), 8.83 (d, ^3J(H,H) = 4.8 Hz, 2 H, Ar-*H*), 8.50 – 8.45 (m, 2 H, Ar-*H*), 8.36 – 8.32 (m, 2 H, Ar-*H*), 8.27 – 8.22 (m, 6 H, Ar-*H*), 7.81 – 7.74 (m, 9 H, Ar-*H*), 4.13 (s, 3 H, C*H*$_3$), -2.73 (2 H, N*H*). **^{13}C NMR** (DMSO-d_6): δ 167.49, 147.20, 142.21, 142.18, 134.73, 134.70, 129.70, 128.07, 127.93, 126.87, 120.73, 120.53, 118.68, 52.58. **ESI-MS**: *m/z* = 673.28 (M + 1 H^+). **HR-ESI-MS**: *m/z* = 673.2480 (calcd 673.2604 for $C_{46}H_{32}N_4O_2$ + 1 H^+).

[1] (a) D. Huang, S. Matile, N. Berova and K. Nakanishi, *Heterocycles*, 1996, **42**, 723-736. (b) S. Matile, N. Berova, K. Nakanishi, J. Fleischhauer and R.W. Woody, *J. Am. Chem. Soc.*, 1996, **118**, 5198-5206.

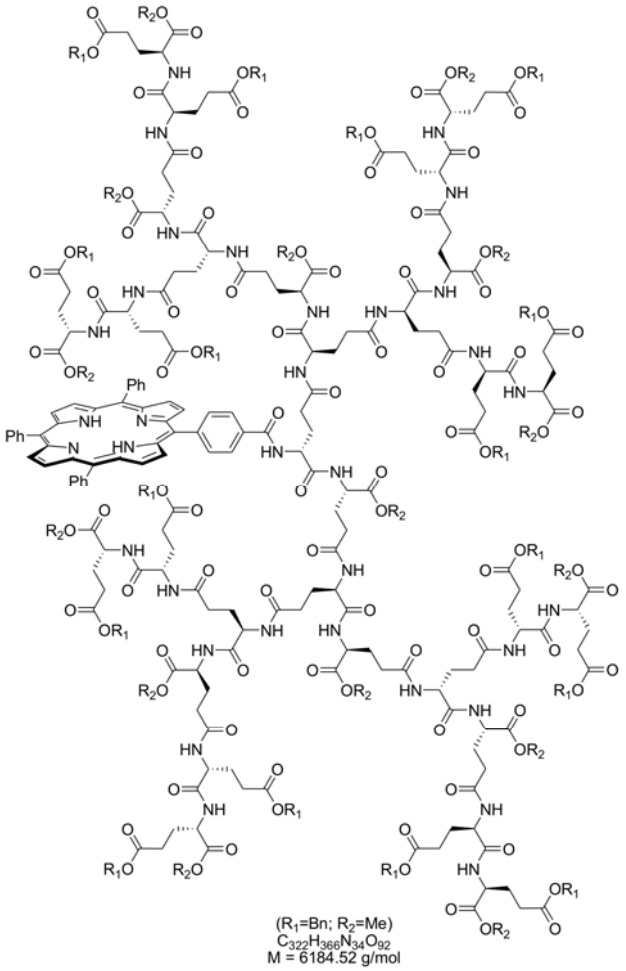
5-(4'-Carboxyphenyl)-10,15,20-triphenylporphyrin:[1]



$C_{45}H_{30}N_4O_2$
M = 658.75 g/mol

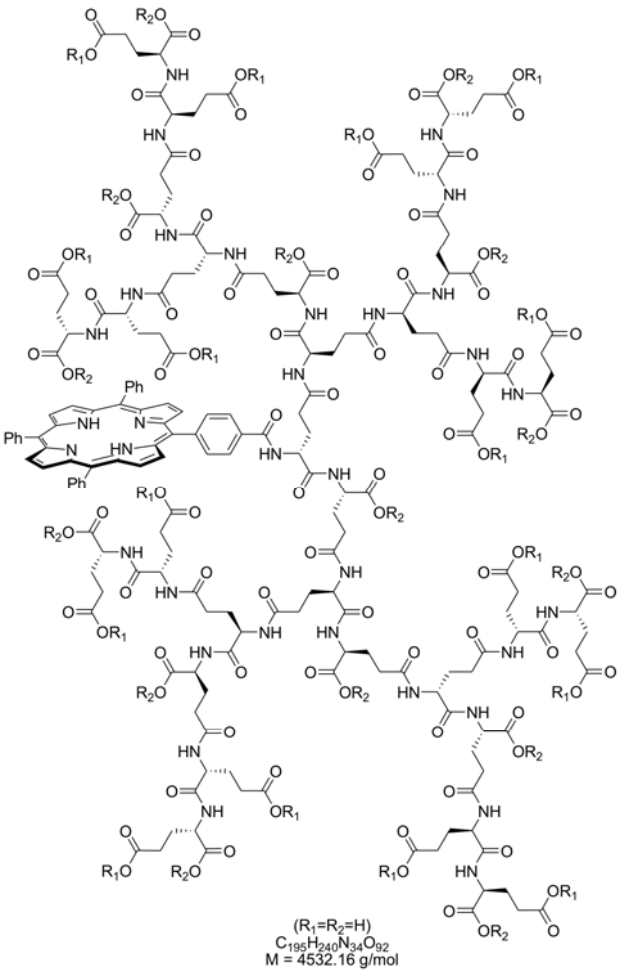
5-(4'-Carboxymethylphenyl)-10,15,20-triphenylporporphyrin (1.04 g, 1.55 mmol) was refluxed in aqueous 2 M NaOH : EtOH : THF = 2 : 2 : 1 (200 mL) for 2 h. The organic solvents were removed *in vacuo* and the basic aqueous suspension acidified with acetic acid. The aqueous layer was extracted with CH_2Cl_2. The united organic layers were evaporated *in vacuo* and the remaining purple solid was dried under vacuum at 150 °C, to give the desired product in quantitative yield. R_F = 0.40 (CH_2Cl_2 : MeOH = 95 : 5 + 0.1 vol-% HOAc). **UPLC-MS**: ((2.1x100 mm BEH HILIC 1.7µm, acetonitrile : water Grad 5 15A): t_R = 10.95 min (>99.9% peak area, ESI(+): 660.00 (M + 1 H^+). **^{1}H NMR** (300 MHz, $CDCl_3$, 20 °C): δ 8.79 (br s, 8 H, Ar-*H*), 8.38 (d, ^3J(H,H) = 8.3 Hz, 2 H, Ar-*H*), 8.24 (d, ^3J(H,H) = 8.3 Hz, 2 H, Ar-*H*), 8.16 – 8.13 (m, 6 H, Ar-*H*), 7.72 – 7.66 (m, 9 H, Ar-*H*).

Porphyrin-G4- D-(*alt*)-L-Glu(Z)-Me (**8**):



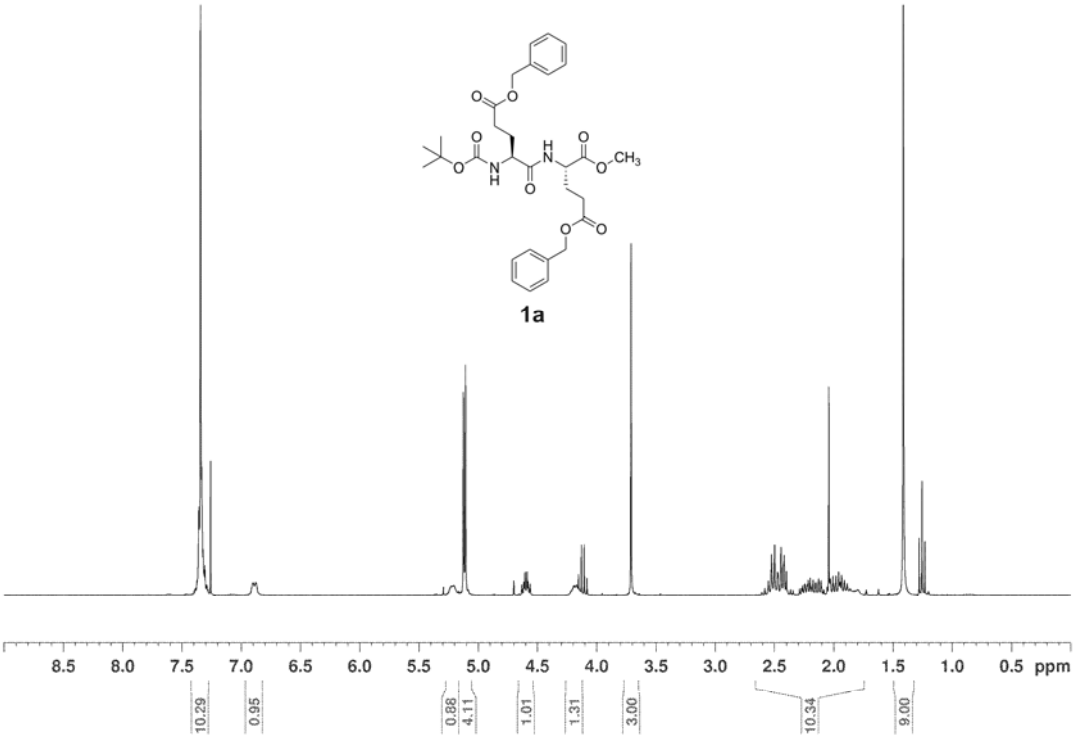
5-(4'-Carboxyphenyl)-10,15,20-triphenylporphyrin (0.006 g, 0.008 mmol) and HOBT (0.004 g, 0.032 mmol), dissolved in a small amount of DMF (1 mL) were cooled to 0 °C and EDC (0.003 g, 0.016 mmol) was added. The solution was stirred at room temperature for 10 minutes. Boc-deprotected **7b**, freshly prepared as described on page S17 (0.022 g, 0.004 mmol), dissolved in 0.2 mL DMF and NEt_3 (0.002 mL) were added to the solution. After stirring for 4 days, the solvents were removed *in vacuo*. Washing of the remaining purple solid with H_2O and acetone (3x) afforded 0.021 g (yield: 91%) of the desired product as dark red solid. **GPC** (DMF): M_n = 4989 g/mol, M_w = 5689 g/mol, M_p = 5961 g/mol, PDI = 1.14. **^{1}H NMR** (300 MHz, DMSO-d_6, 20 °C): δ 8.95 – 8.80 (m, 7 H, Ar-*H*), 8.60 – 7.78 (m, 50 H, Ar-*H*, N*H*), 7.40 – 7.19 (m, 80 H, Ar-*H*), 5.08 – 5.00 (m, 32 H, CH_2), 4.42 – 4.12 (m, 30 H, C*H*), 3.62 – 3.46 (m, 45 H, CH_3), 2.45 - 1.60 (m, 120 H, CH_2).

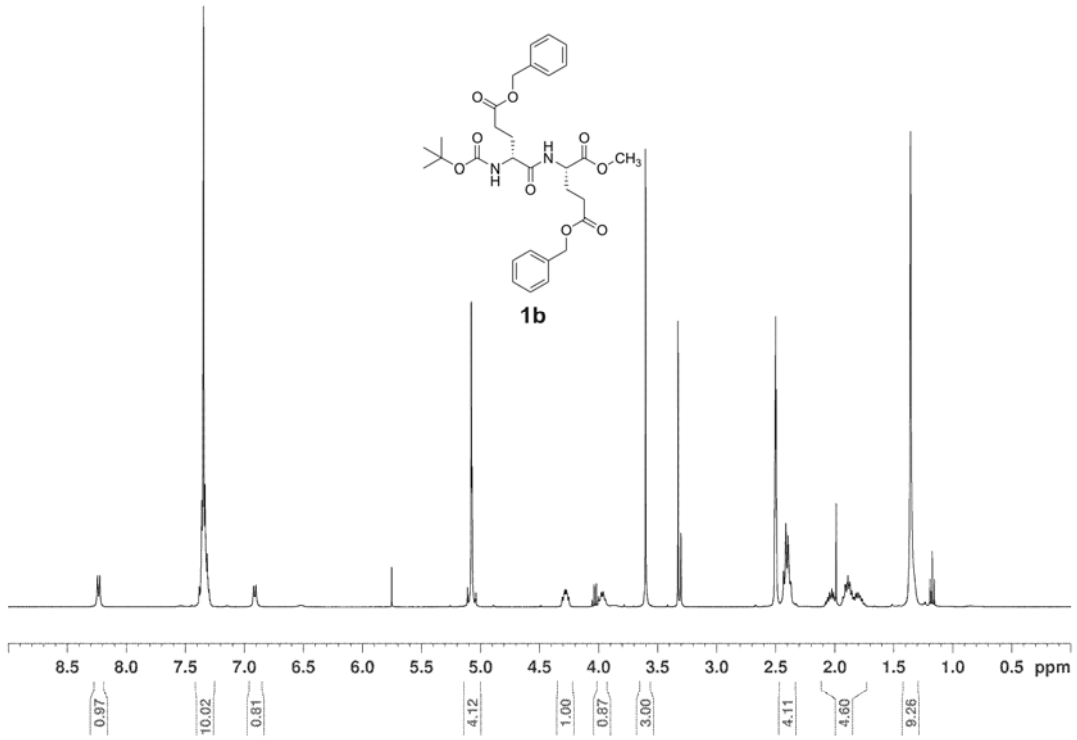
Porphyrin-G4- D-(*alt*)-L-Glu (**9**):

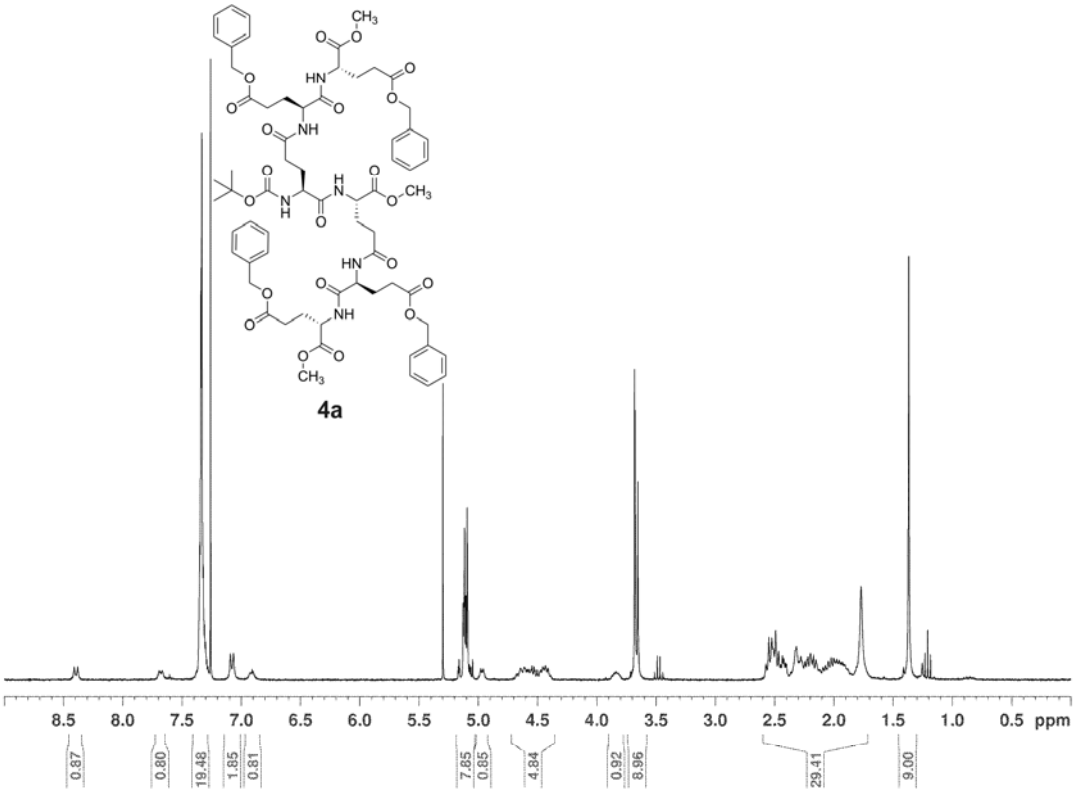


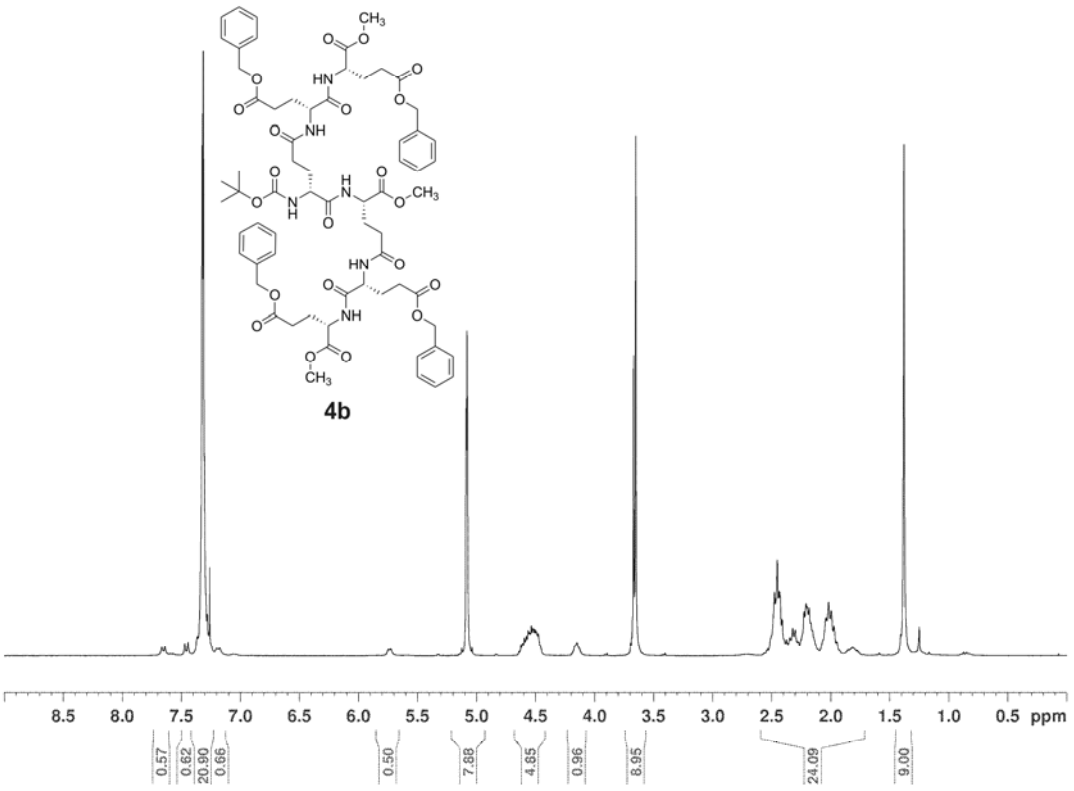
8 (0.015 g, 0.003 mmol) was reacted following the general procedure for the deprotection of the methyl ester. Reaction was achieved in DMF. After 1 h, the reaction mixture was concentrated *in vacuo*. The reaction mixture was dialyzed in water (MWCO 1000 g/mol) to afford the desired product as a dark red solid. **GPC** (DMF): M_n = 5692 g/mol, M_w = 6028 g/mol, M_p = 6484 g/mol, PDI = 1.06.

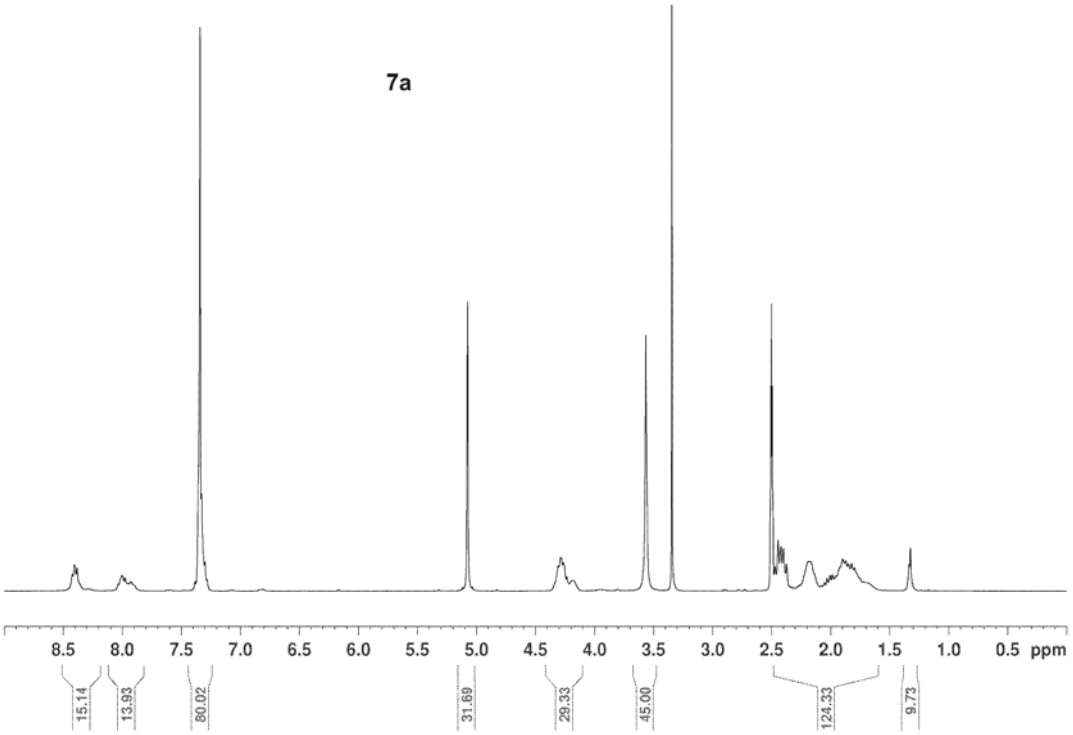
Appendix (copies of ^{1}H-NMR, ESI-MS, and GPC data)

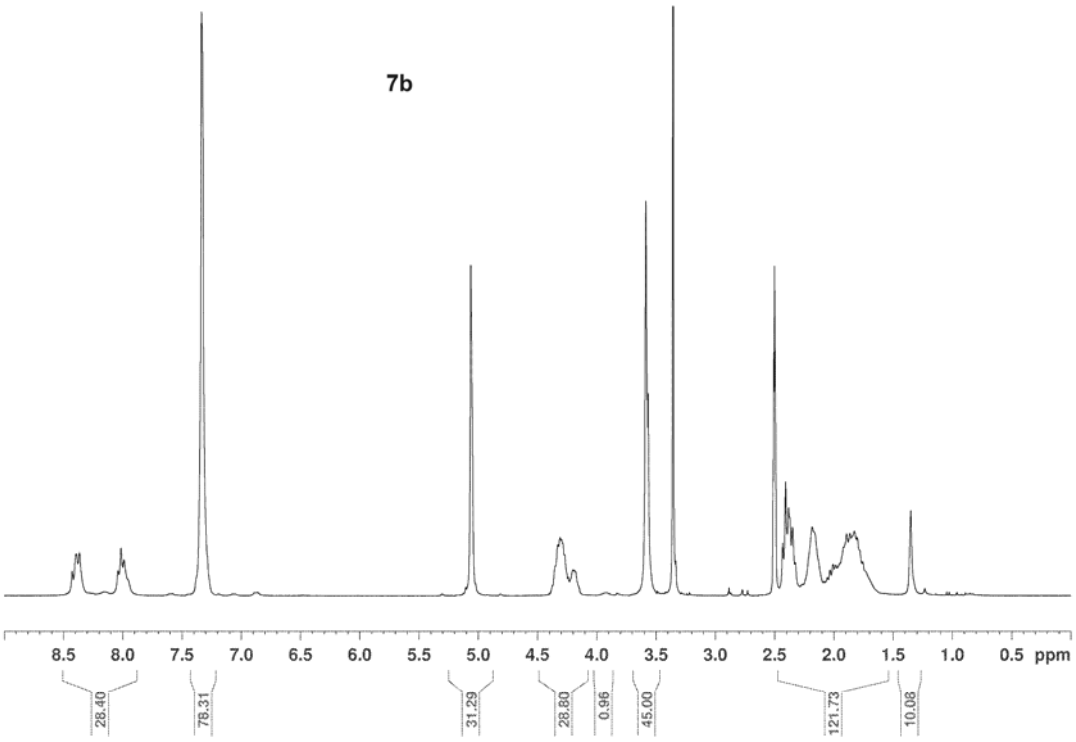


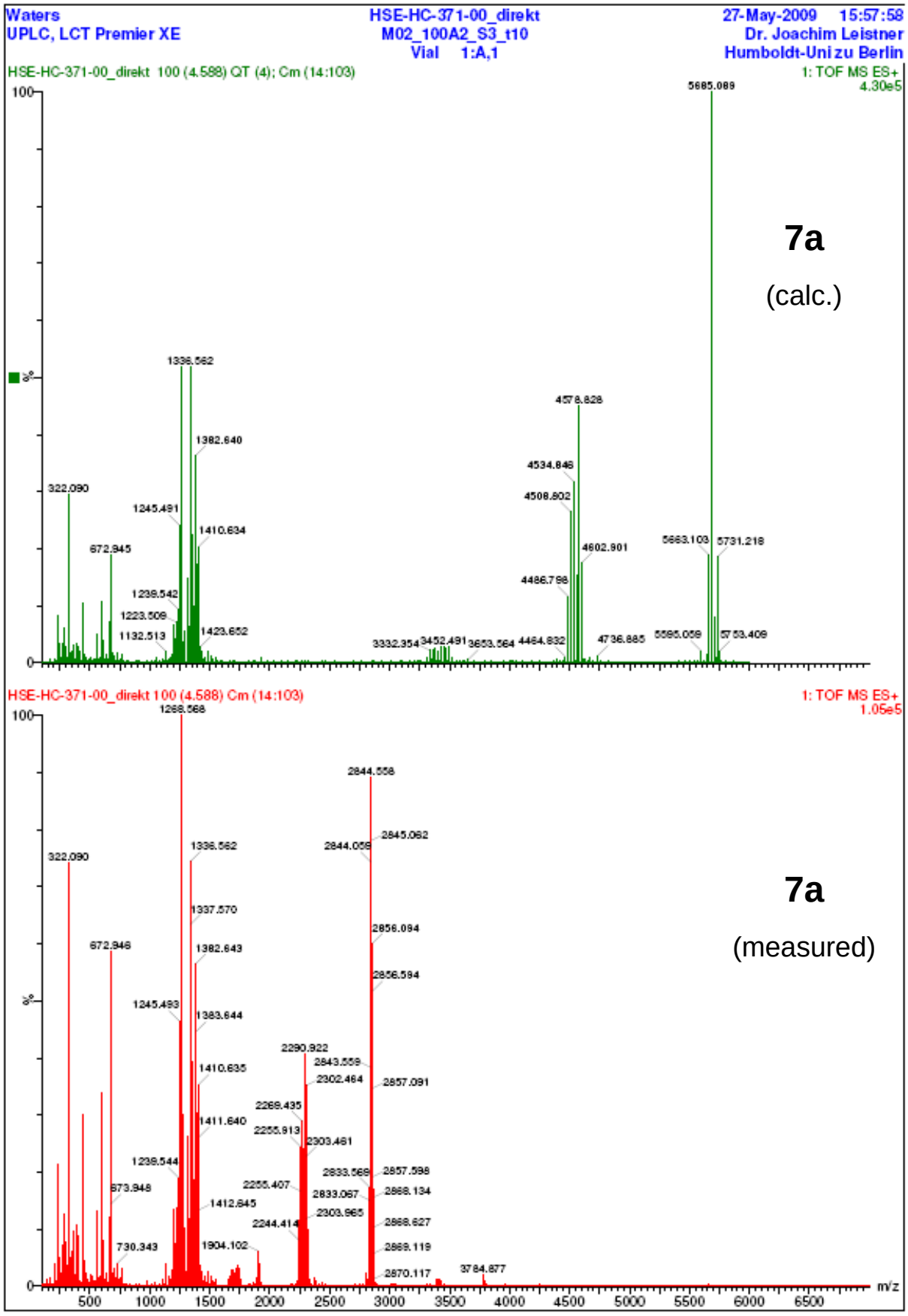










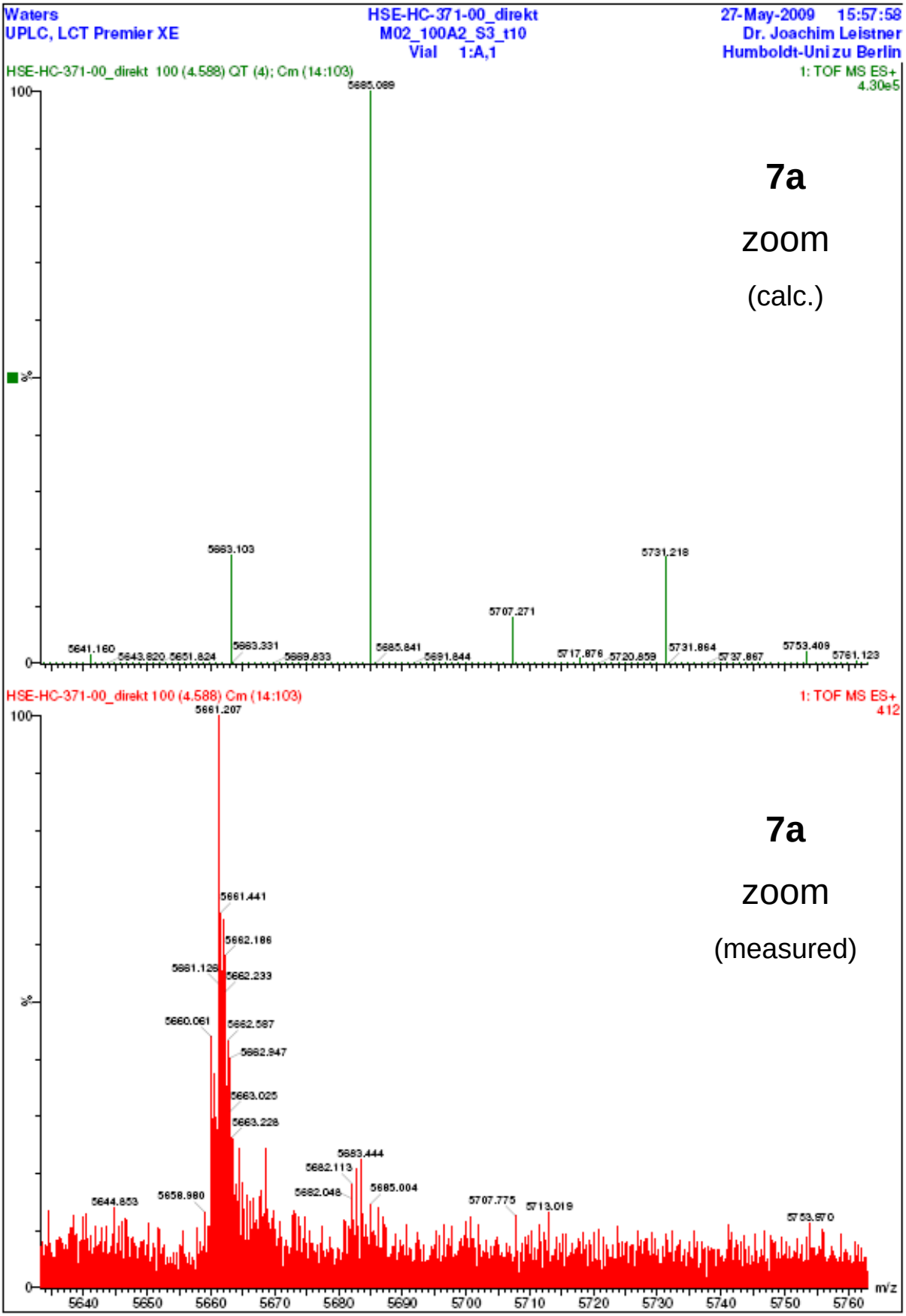


7a

(calc.)

7a

(measured)



7a

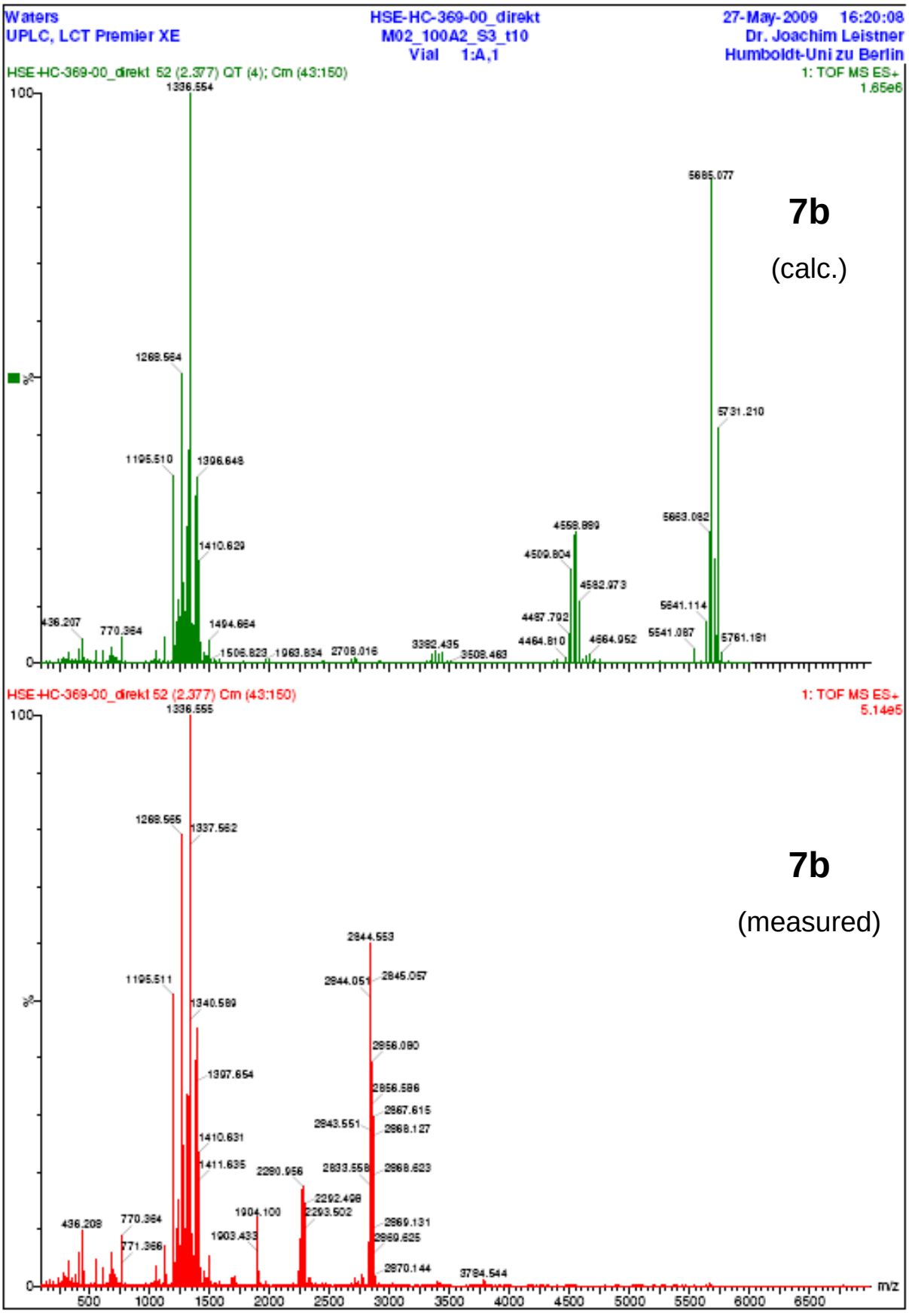
zoom

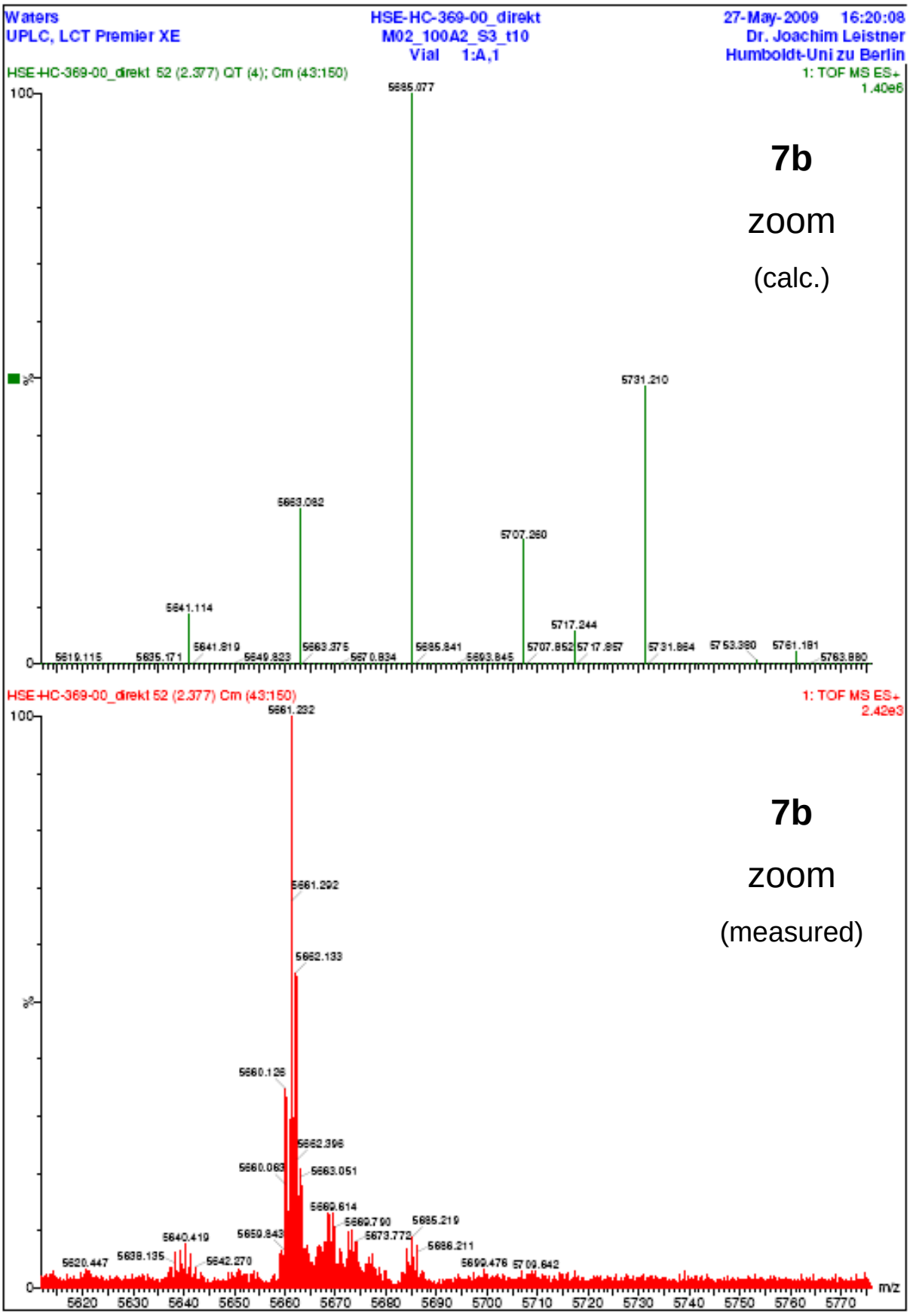
(calc.)

7a

zoom

(measured)





7b

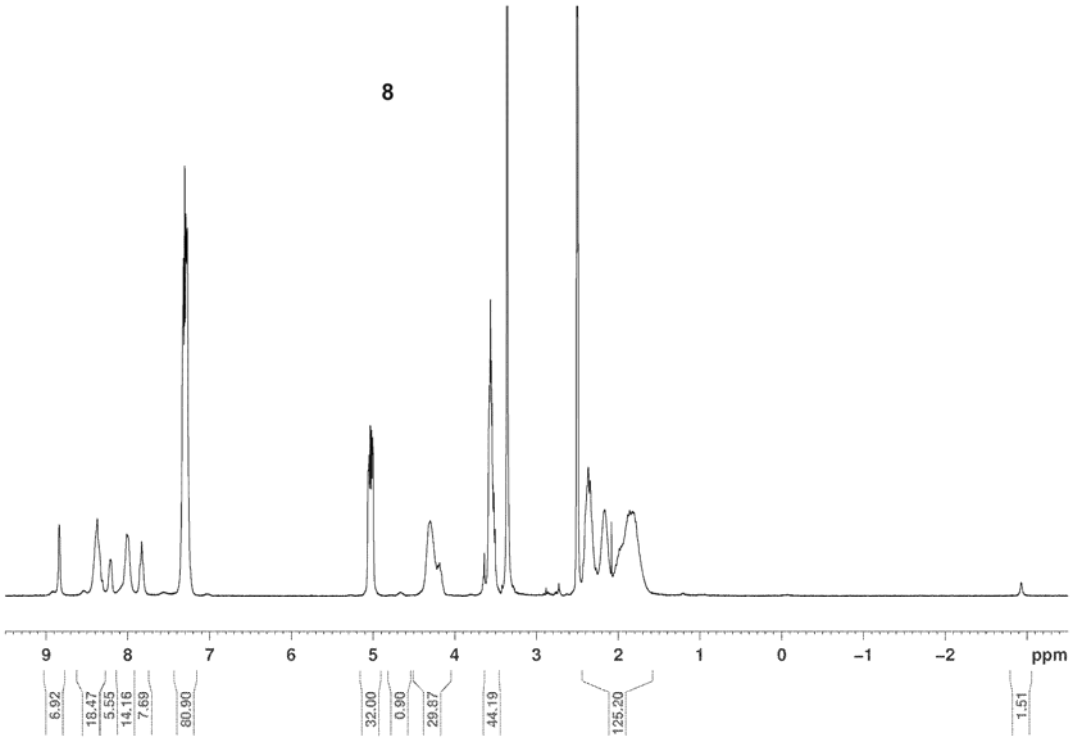
zoom

(calc.)

7b

zoom

(measured)



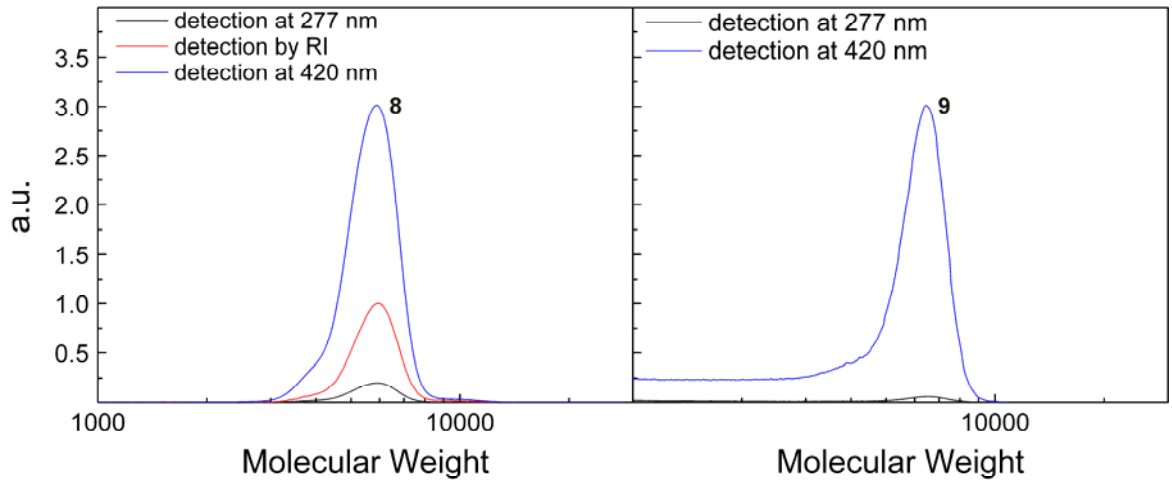


Figure 1: GPC-traces of protected porphyrin labeled D,L-dendrimer **8** and of saponified porphyrin labeled D,L-dendrimer **9** (GPC in DMF at 70 °C, calibrated with polystyrene standards, relative intensities of UV signals at different wavelengths are normalized to the corresponding RI signal; in the case of **9**, the respective RI signal is not detectable, hence the relative intensities of UV signals at different wavelengths are normalized to RI signal of added standard; absolute intensities of **8** and **9** are normalized to the detection at 420 nm).