

**Nanometer-Sized Amino Acids for the Synthesis of Nanometer-Scale Water-Soluble
Molecular Rods of Precise Length**

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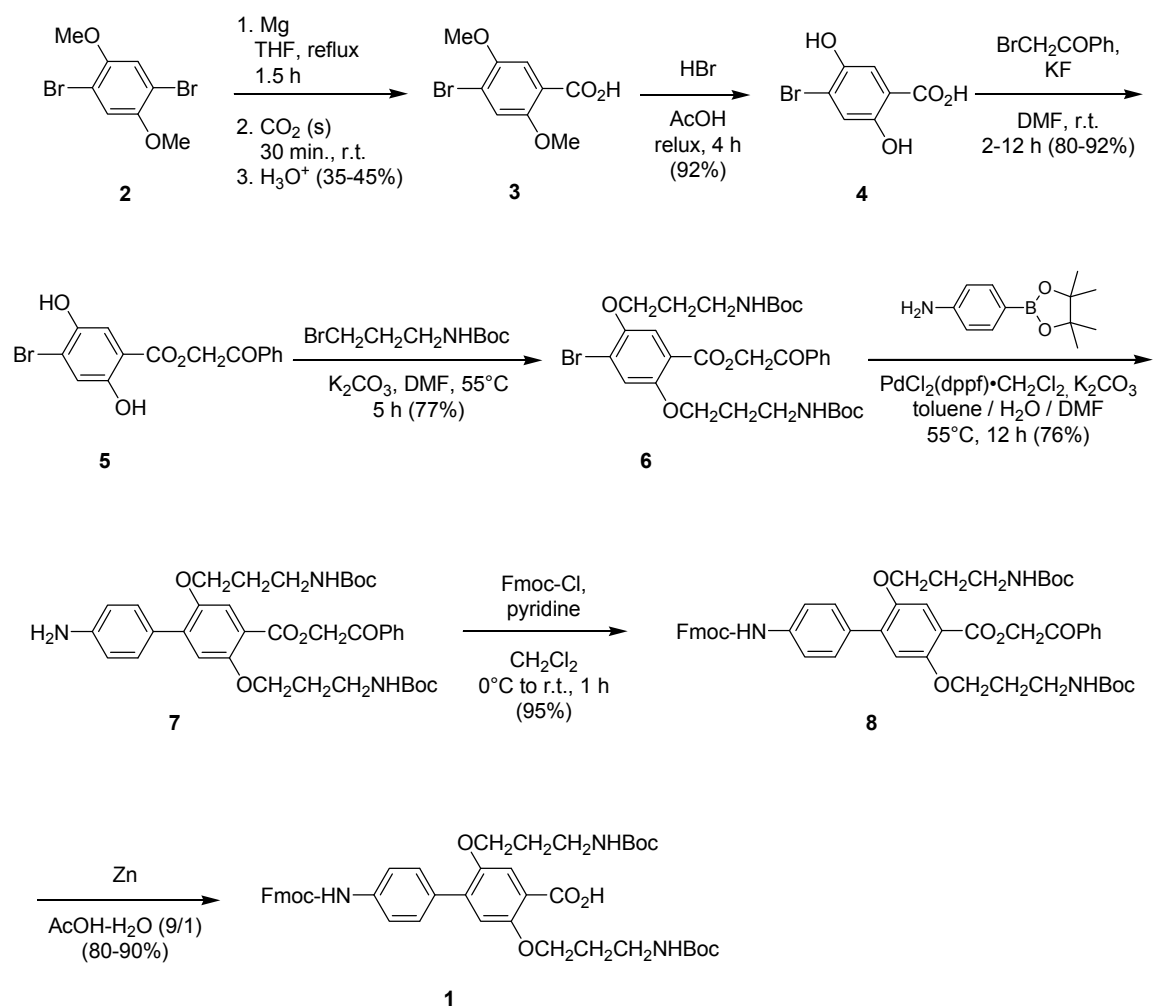
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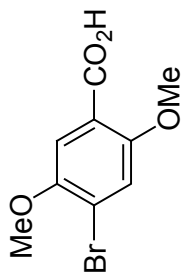
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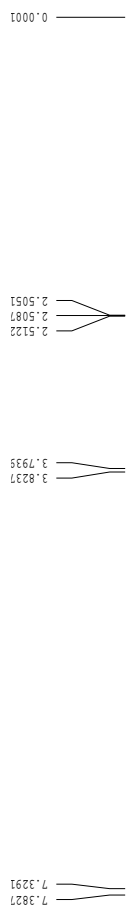
General Procedures. Commercial solvents and reagents were used without further purification, unless otherwise stated. Reactions were carried out under an atmosphere of nitrogen. Solution-phase reactions were monitored by thin-layer chromatography (TLC) and carried out on 250 μm silica gel polyester plates on fluorescent silica gel with UV visualization. Column chromatography was performed on 40–63 μm silica gel (EMD Science) using flash chromatography. Solvents were removed by rotary evaporation. Residual solvents were removed under vacuum (< 0.01 mmHg). Precipitated and recrystallized products were dried under vacuum (< 0.01 mmHg) or by air suction through a filter funnel. High resolution mass spectra were obtained by electrospray ionization (ESI) on a Waters Micromass LCT Premier (instrument variation $\sigma < 5$ ppm). NMR spectra were recorded using a 500 MHz Bruker AVANCETM spectrometer. Chemical shifts are reported in parts per million (ppm) on the δ scale. ^1H and ^{13}C NMR spectra in CD_3SOCD_3 were referenced with TMS ($\delta = 0.00$ ppm); ^1H NMR spectra in D_2O were referenced to HDO at $\delta = 4.80$ ppm. IR spectra were obtained using a Galaxy Series FTIR 5000. HPLC analysis was performed on an analytical RP-HPLC instrument, using a C_{18} column (Alltech, Platinum Rocket, 3 μm packing, 7 mm \times 53 mm).

Fmoc-Abc^{2K(Boc)}-OH (1) Synthetic Scheme.

¹H spectrum
ppm



4-bromo-2,5-dimethoxybenzoic acid (**3**)



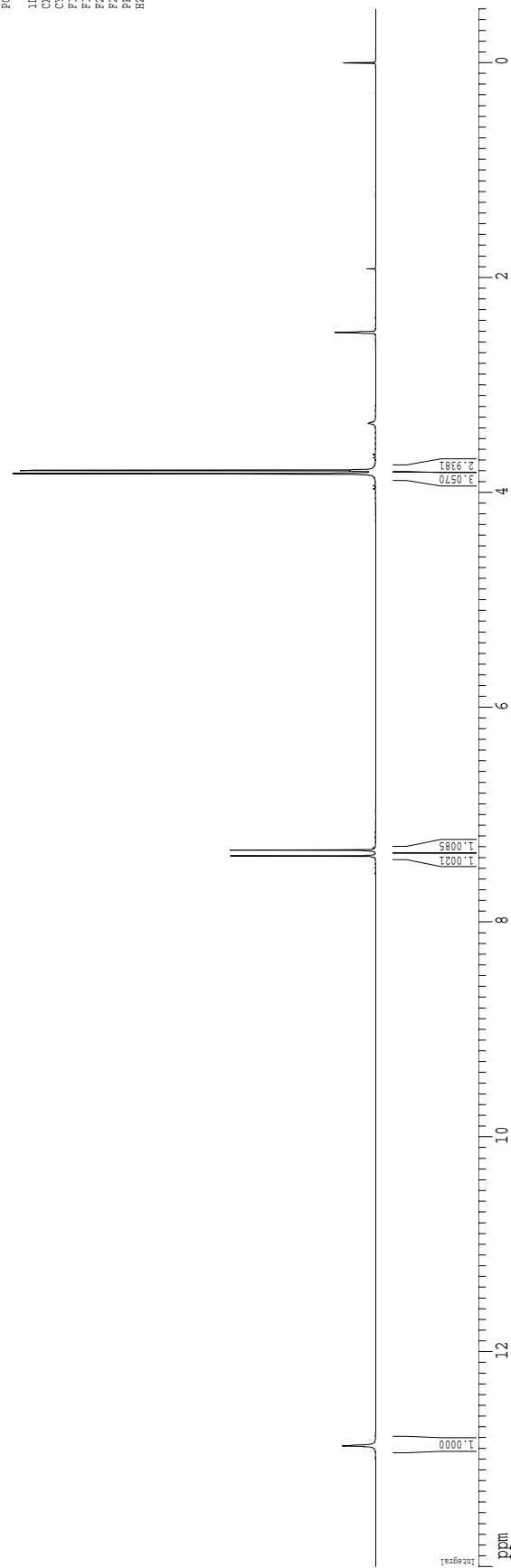
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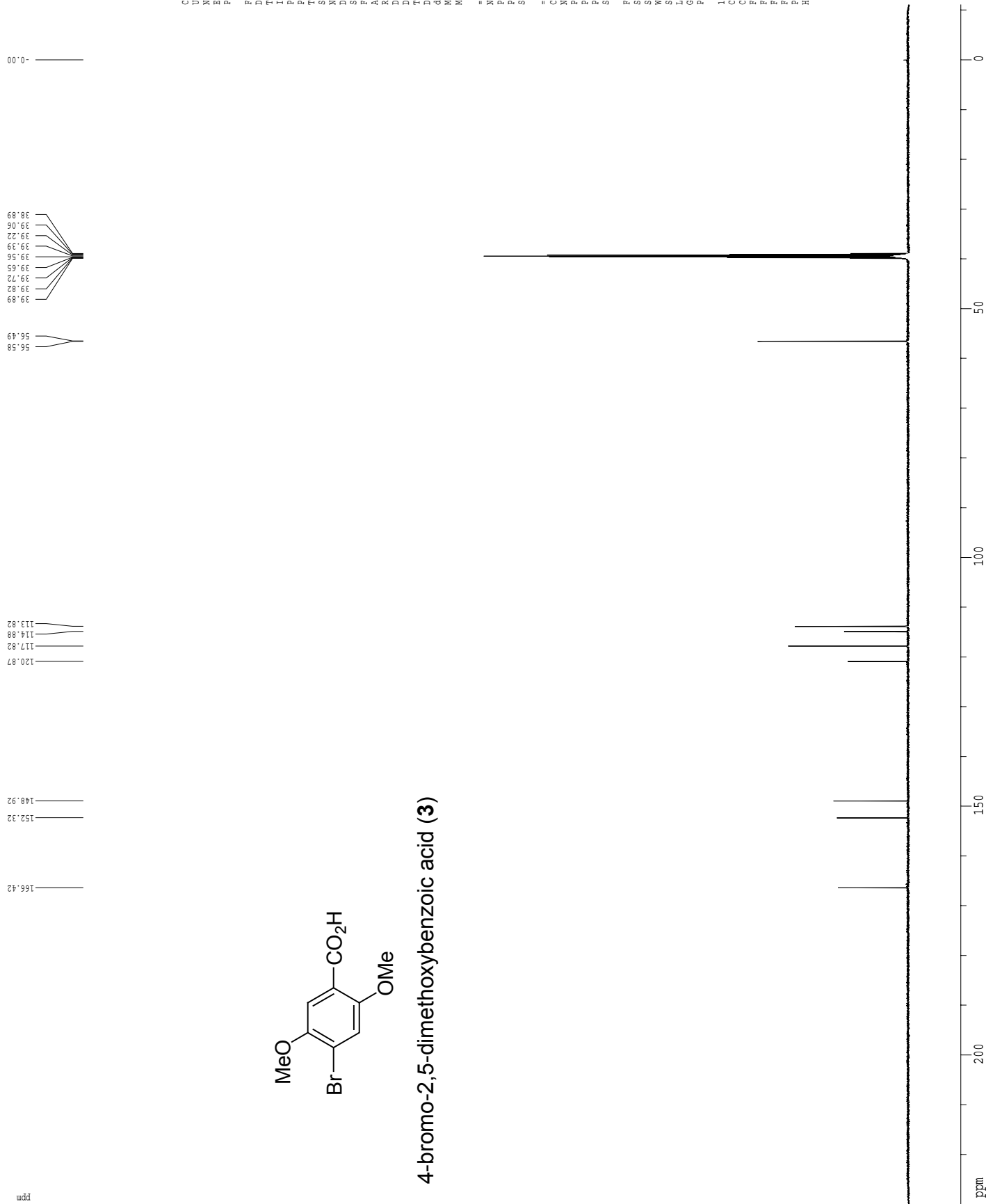
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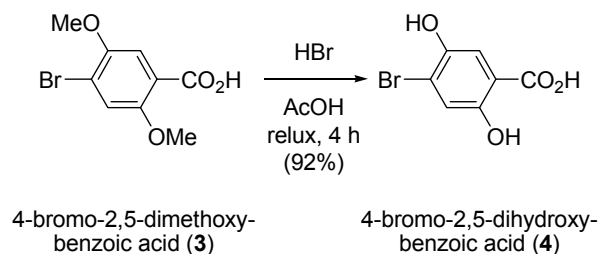


^{13}C spectrum with ^1H decoupling

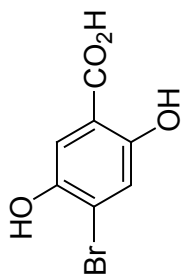
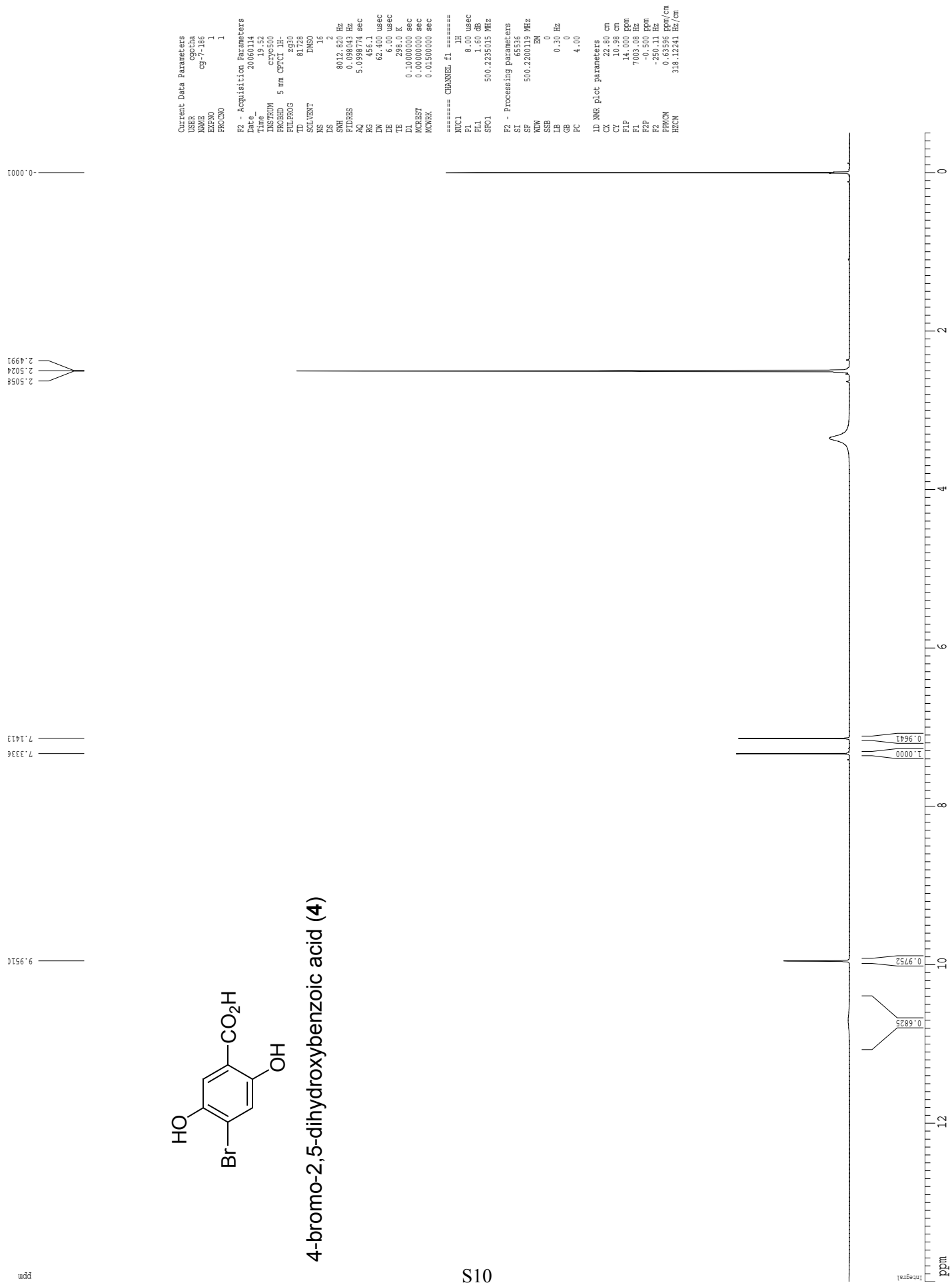
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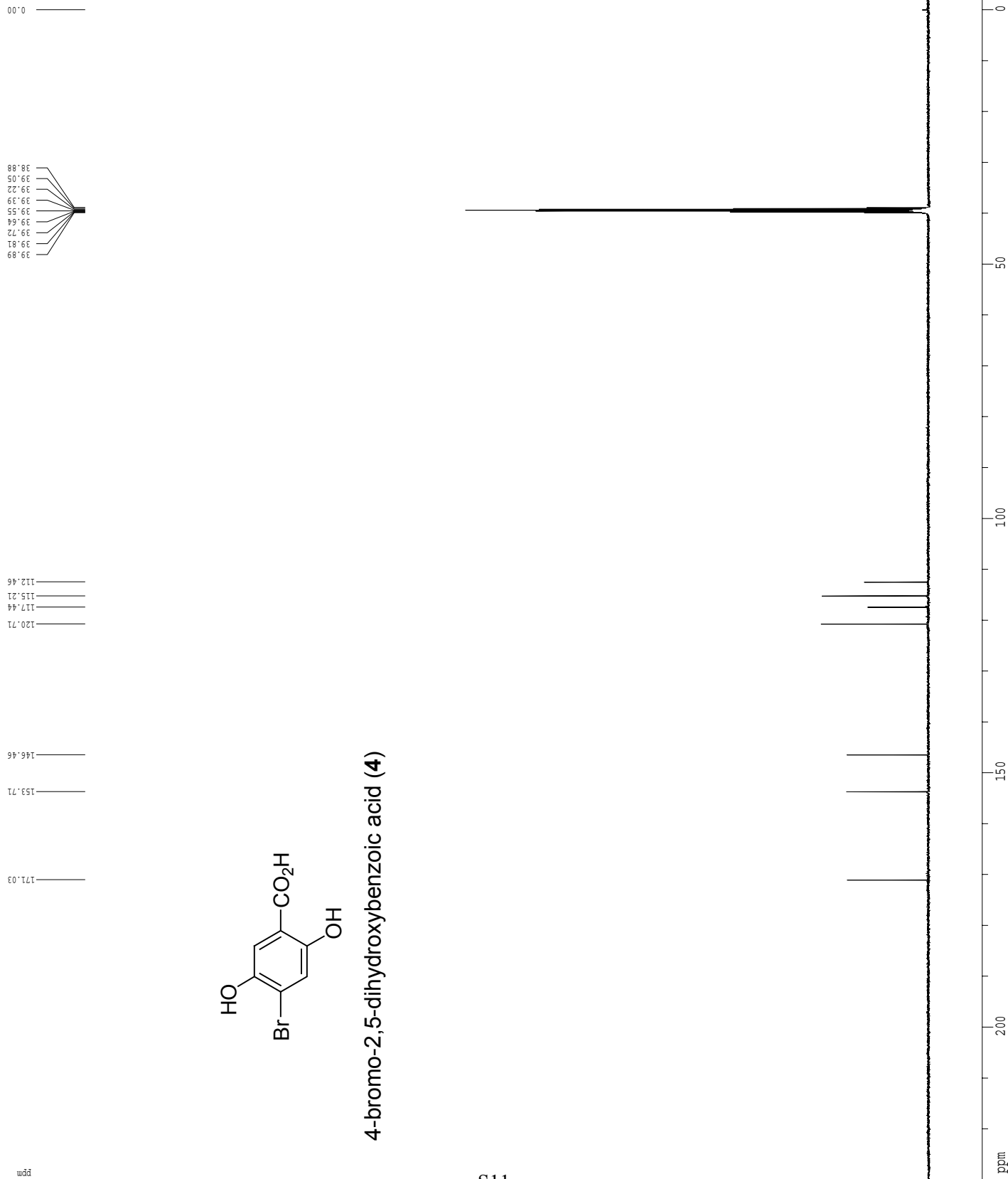
4-bromo-2,5-dimethoxybenzoic acid (3)



4-Bromo-2,5-dihydroxybenzoic acid (4). A solution of 4-bromo-2,5-dihydroxybenzoic acid (**3**) (6.75 g, 25.9 mmol), 48% aq HBr (130 mL) and acetic acid (30 mL) was heated at reflux for 4 h. The mixture was then concentrated by rotary evaporation to remove most of the acetic acid and then extracted with ether (3 × 200 mL). The organic layer was washed with 6 N HCl (200 mL) and then extracted with 2 M NaOH (3 × 50 mL). Acidification with concd HCl and filtration with water gave 4-bromo-2,5-dihydroxybenzoic acid (**4**) as a tan-colored solid (5.55 g, 92%): mp 229-230 °C; IR (KBr) 3700-2000 (br), 1690, 1611 cm^{-1} ; ^1H NMR, (500 MHz, CD_3SOCD_3 , 298 K) δ 10.70 (br. s, 1 H), 9.95 (s, 1 H), 7.33 (s, 1 H), 7.14 (s, 1 H); ^{13}C NMR (125 MHz, CD_3SOCD_3 , 298 K) δ 171.0, 153.7, 146.5, 120.7, 117.4, 115.2, 112.5; HRMS (ESIMS) m/z for $\text{C}_7\text{H}_4\text{BrO}_4$ $[\text{M}-\text{H}]^-$ calcd 230.9293, found 230.9283.

4-bromo-2,5-dihydroxybenzoic acid (**4**)

13C spectrum with 1H decoupling



4-bromo-2,5-dihydroxybenzoic acid (4)

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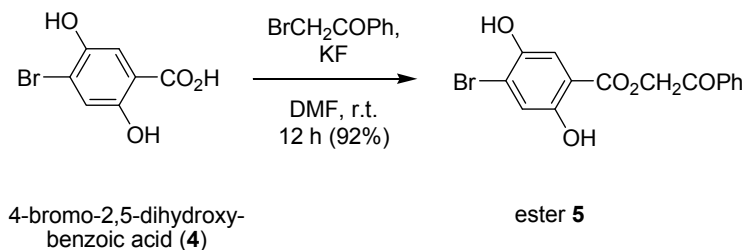
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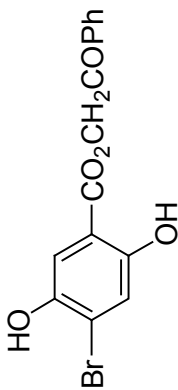
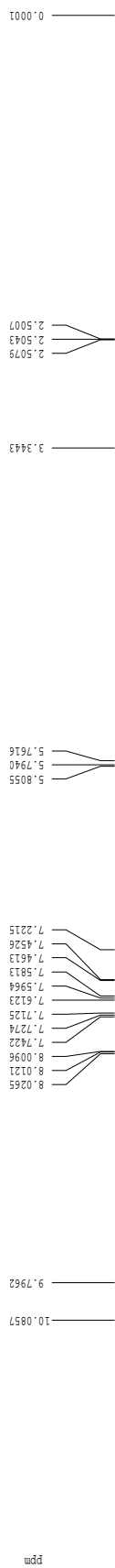
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HZCM         1329.00332 Hz/cm

```



Ester 5. A solution of 4-bromo-2,5-dihydroxybenzoic acid (**4**) (4.21 g, 18.1 mmol), 2-bromoacetophenone (3.60 g, 18.1 mmol), potassium fluoride (2.31 g, 39.8 mmol), and DMF (100 mL) was stirred under an atmosphere of nitrogen for ca. 12 h at 25 °C. The reaction mixture was then partitioned between water (100 mL) and CH₂Cl₂ (100 mL) and the organic layer was extracted with CH₂Cl₂ (2 × 50 mL). The combined organic layers were washed with saturated aq sodium chloride (250 mL), dried (Na₂SO₄, 2 h), filtered, and concentrated by rotary evaporation to provide a yellow solid. The yellow solid was dissolved in CH₂Cl₂ (20 mL) and ethyl acetate (20 mL), and precipitated with hexanes (100 mL) to provide ester **5** as an off-white solid (5.86 g, 92%): mp 184-186 °C; IR (KBr) 3408, 3061, 2920, 1721, 1692, 1616, 1592 cm⁻¹; ¹H NMR, (500 MHz, CD₃SOCD₃, 298 K) δ 10.09 (s, 1 H), 9.80 (s, 1 H), 8.02 (d, *J* = 7.2 Hz, 2 H), 7.71 (t, *J* = 7.4 Hz, 1 H), 7.59 (t, *J* = 7.8 Hz, 2 H) 7.46 (s, 1 H), 7.22 (s, 1 H), 5.79 (s, 2 H); ¹³C NMR (125 MHz, CD₃SOCD₃, 298 K) δ 192.3, 166.7, 152.3, 146.7, 134.1, 133.6, 128.9, 127.8, 121.3, 117.7, 115.3, 112.7, 67.3; HRMS (ESIMS) *m/z* for C₁₅H₁₁BrO₅Na [M+Na]⁺ calcd 372.9688, found 372.9675.

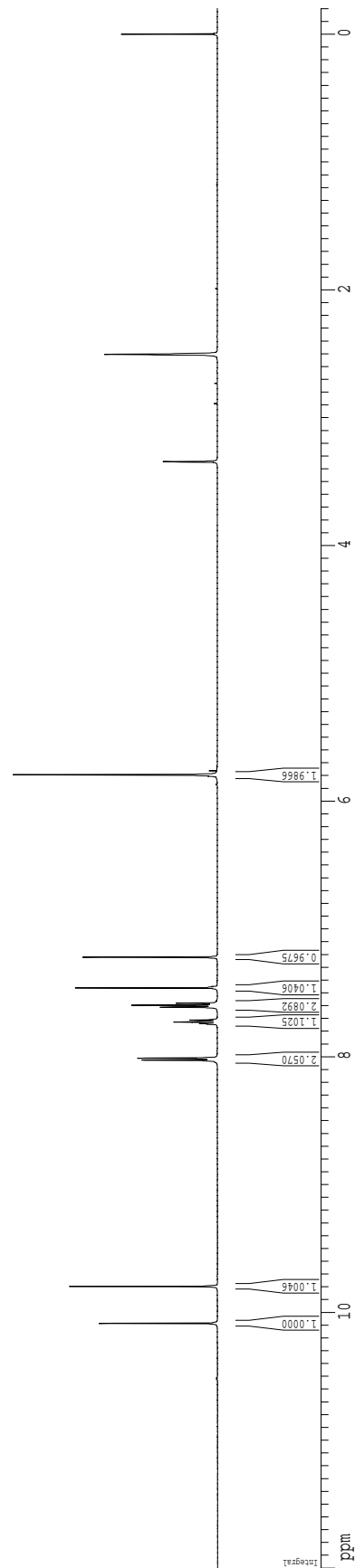
¹H spectrum

ester 5

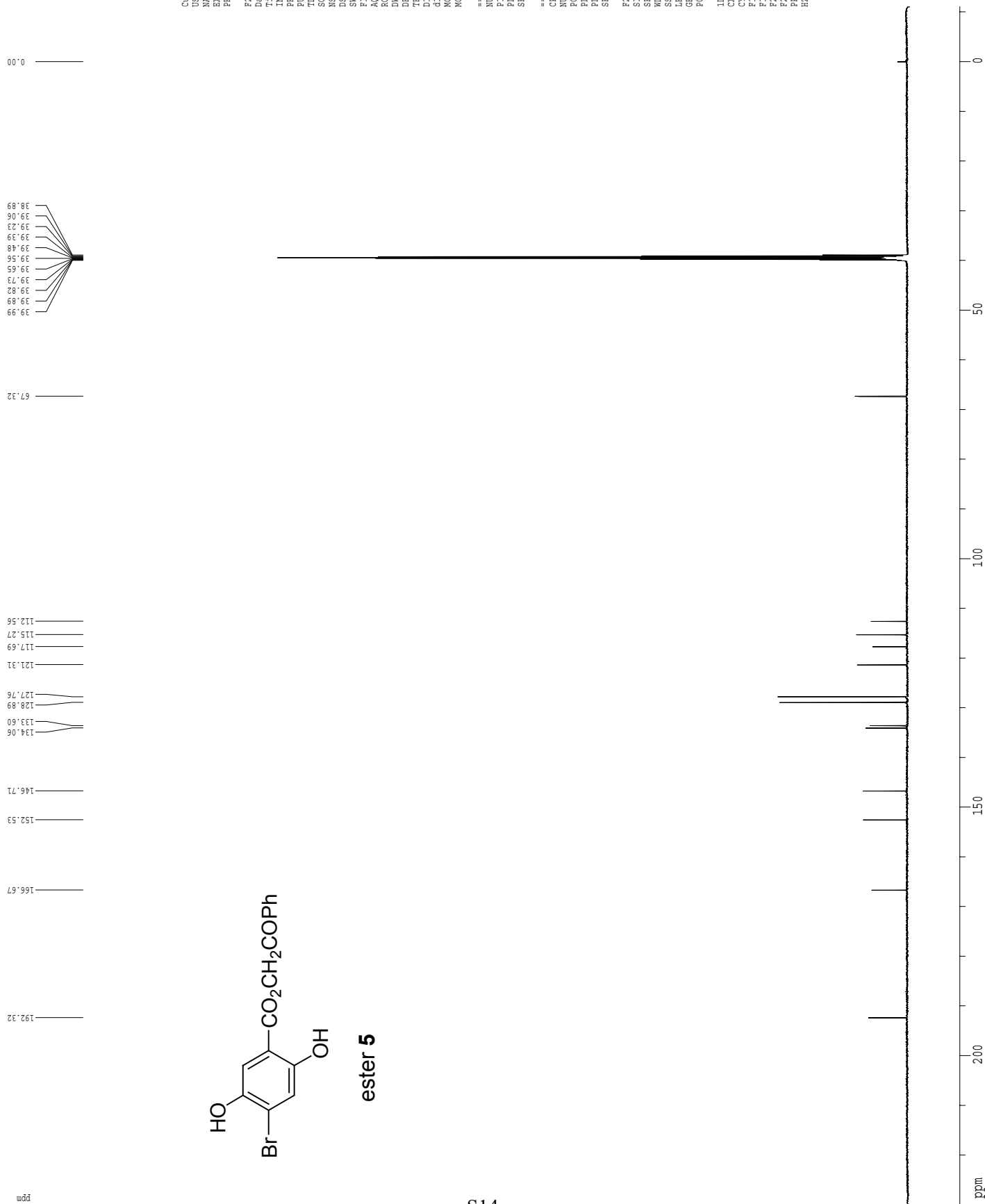
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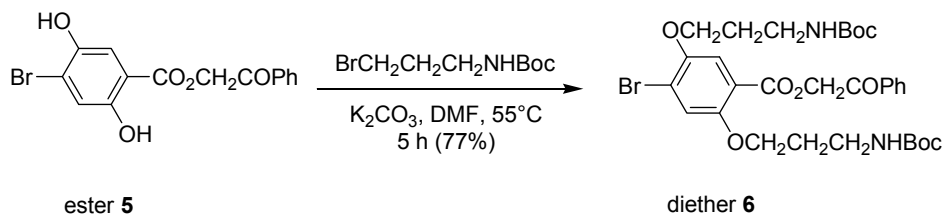
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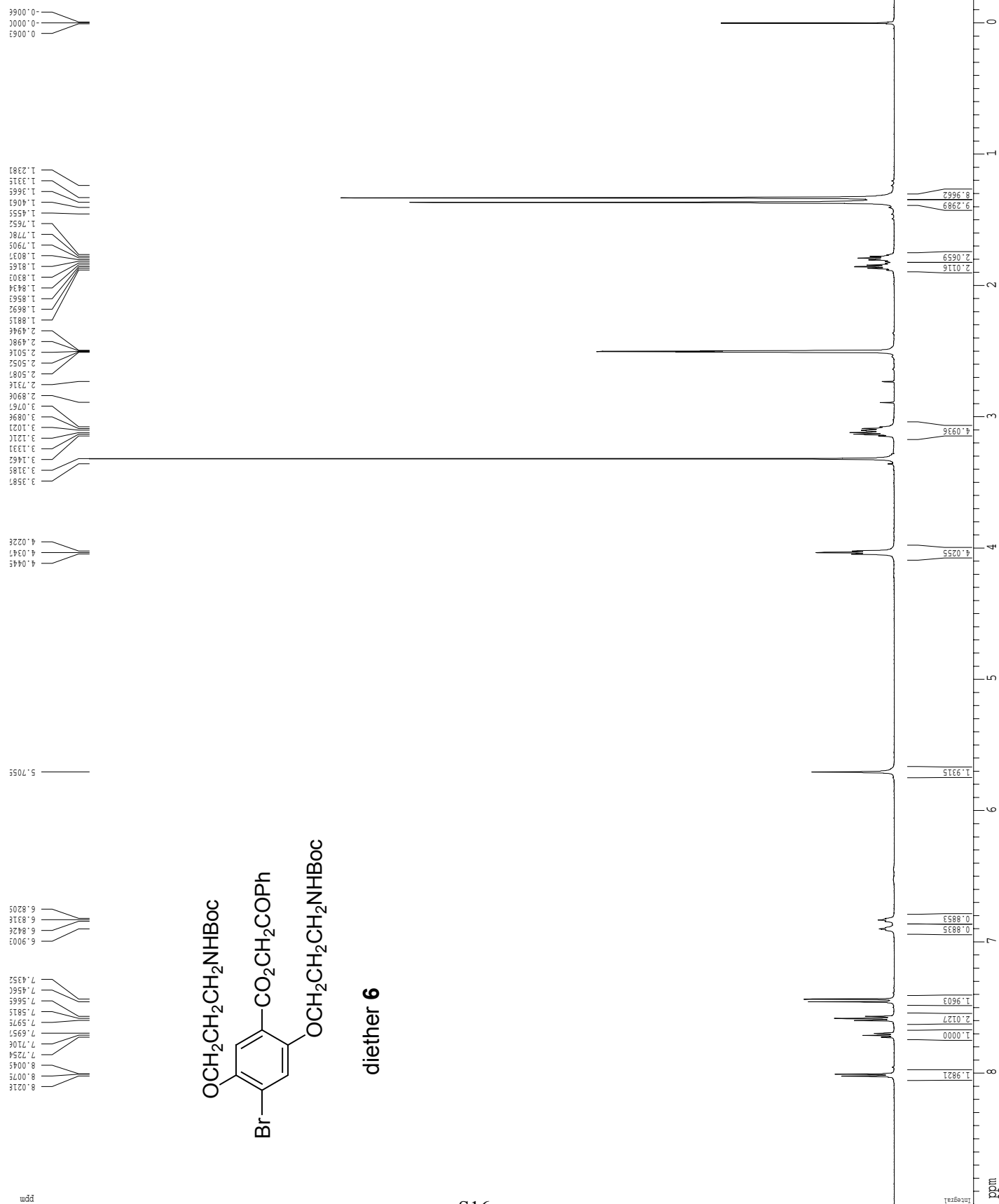
13C spectrum with 1H decoupling

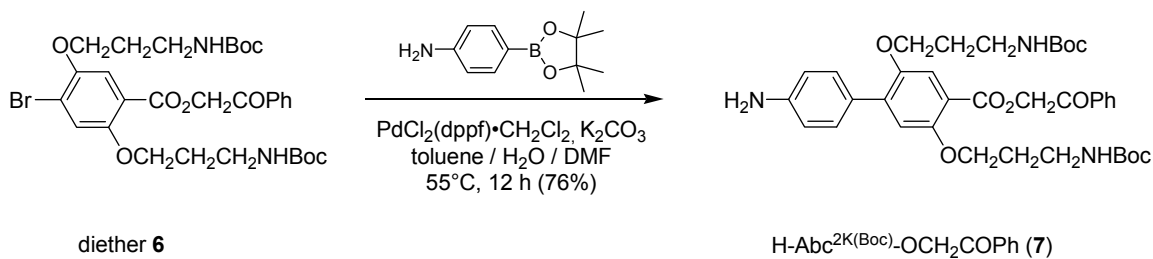




Diether 6. A solution of ester **5** (2.21 g, 6.29 mmol), *t*-butyl-3-bromopropylcarbamate² (5.24 g, 22.0 mmol), dry K₂CO₃ (5.22 g, 37.7 mmol), and DMF (100 mL) was stirred at 50 °C for 5 h under an atmosphere of nitrogen. Saturated aq sodium chloride (ca. 100 mL) was then added to the mixture and the solution was extracted with CH₂Cl₂ (3 × 40 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated by rotary evaporation to give a yellow solid. The yellow solid was dissolved in warm ethyl acetate (ca. 50 mL), precipitated with hexanes (ca. 100 mL), and the resultant solid was filtered to provide diether **6** as a white powder (3.22 g, 77%): mp 159-161 °C; IR (KBr) 3356, 2984, 2937, 2877, 1740, 1674, 1524 cm⁻¹; ¹H NMR, (500 MHz, CD₃SOCD₃, 298 K) δ 8.02 (d, *J* = 7.2 Hz, 2 H), 7.72 (t, *J* = 7.4 Hz, 1 H), 7.59 (t, *J* = 7.8 Hz, 2 H), 7.45 (d, *J* = 10.4 Hz, 2 H), 6.90 (t, *J* = 5.3 Hz, 1 H), 6.83 (t, *J* = 5.4 Hz, 1 H), 5.71 (s, 2 H), 4.04 (appar. t, *J* = 5.4 Hz, 4 H), 3.15-3.08 (m, 4 H), 1.87 (quintet, *J* = 6.5 Hz, 2 H), 1.79 (quintet, *J* = 6.4 Hz, 2 H), 1.37 (s, 9 H), 1.33 (s, 9 H); ¹³C NMR (125 MHz, CD₃SOCD₃, 298 K) δ 192.6, 164.0, 155.5, 152.6, 148.6, 133.87, 133.86, 128.8, 127.7, 119.5, 119.0, 117.1, 115.3, 77.4, 77.3, 67.6, 67.3, 67.0, 36.9, 36.8, 29.1, 28.2, 28.1; HRMS (ESIMS) *m/z* for C₃₁H₄₁BrN₂O₉Na [M+Na]⁺ calcd 687.1893, found 687.1873.

² Zych, A. J.; Iverson, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 8898-8909.

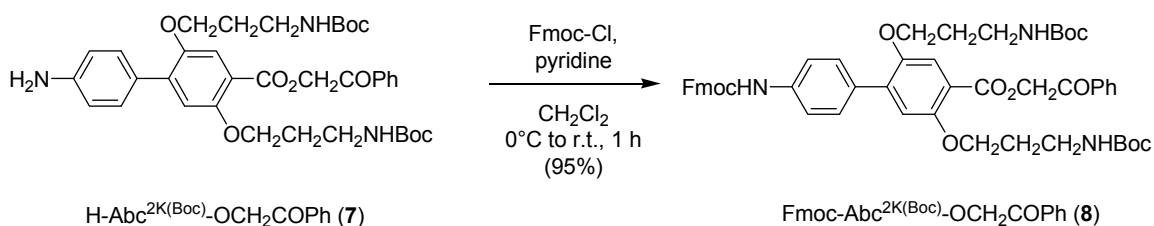




H-Abc^{2K(Boc)}-OCH₂COPh (7). Diether **6** (7.55 g, 11.5 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.52 g, 11.5 mmol), PdCl₂(dppf)•CH₂Cl₂³ (0.38 g, 0.46 mmol), K₂CO₃ (7.95 g, 57.6 mmol) were dissolved in a mixture of toluene (245 mL), water (70 mL), and DMF (35 mL) and was stirred at 55 °C for ca. 12 h under an atmosphere of nitrogen. The suspension was then concentrated by rotary evaporation to remove most of the toluene and then diluted with CH₂Cl₂ (250 mL). The organic layer was washed with water (ca. 250 mL), saturated aq sodium chloride (ca. 250 mL), and dried (Na₂SO₄). After filtration and concentration by rotary evaporation, a brown oil was obtained and was purified using column chromatography (silica gel, ethyl acetate–hexanes, 2/1, v/v) to provide H-Abc^{2K(Boc)}-OCH₂COPh (**7**) as an off-white solid (6.55 g, 84%): mp 149-151 °C; IR (KBr) 3477, 3366, 2974, 2930, 2874, 1736, 1681 cm⁻¹; ¹H NMR, (500 MHz, CD₃SOCD₃, 298 K) δ 8.03 (d, *J* = 7.0 Hz, 2 H), 7.71 (t, *J* = 7.3 Hz, 1 H), 7.59 (t, *J* = 7.8 Hz, 2 H), 7.43 (s, 1 H), 7.35 (d, *J* = 8.5 Hz, 2 H), 7.02 (s, 1 H), 6.88 (t, *J* = 5.3 Hz, 1 H), 6.83 (t, *J* = 5.5 Hz, 1 H), 6.63 (d, *J* = 8.5 Hz, 2 H), 5.69 (s, 2 H), 5.30 (s, 2 H), 4.06 (t, *J* = 6.0 Hz, 2 H), 3.92 (t, *J* = 6 Hz, 2 H), 3.12 (q, *J* = 6.3 Hz, 2 H), 3.07 (q, *J* = 6.2 Hz, 2 H), 1.83-1.77 (m, 4 H), 1.37 (s, 9 H), 1.33 (s, 9 H); ¹³C NMR (125 MHz, CD₃SOCD₃, 298 K) δ 192.9, 164.3, 155.5, 153.0, 148.8, 148.5, 136.6, 134.0,

³ Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158-163.

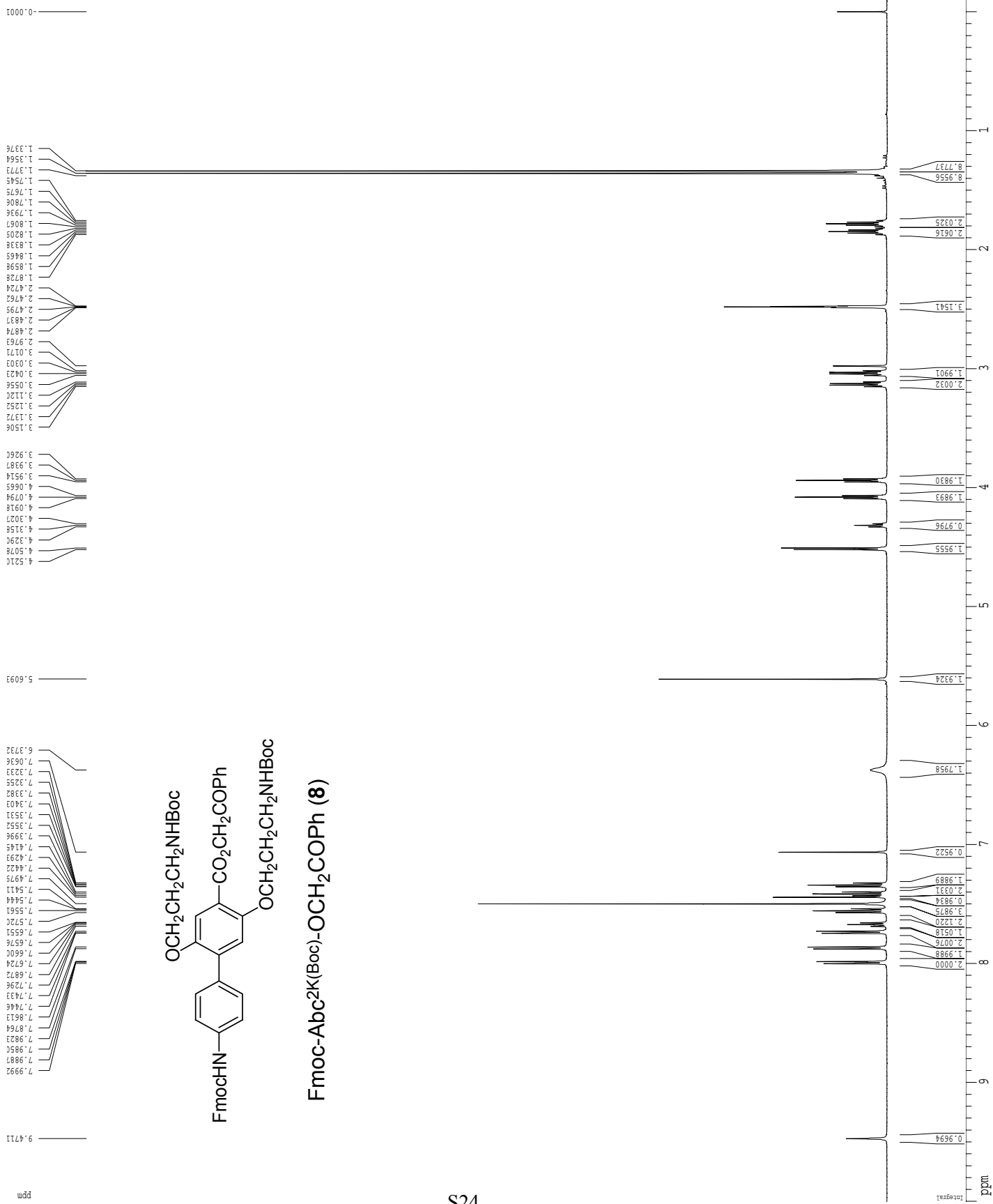
133.8, 130.0, 128.8, 127.7, 123.8, 116.4, 115.9, 115.3, 113.2, 77.4, 77.3, 67.2, 66.7, 66.2, 37.1, 36.8, 29.3, 29.2, 28.2, 28.1; HRMS (ESIMS) m/z for $C_{37}H_{47}N_3O_9Na$ $[M+Na]^+$ calcd 700.3210, found 700.3205.



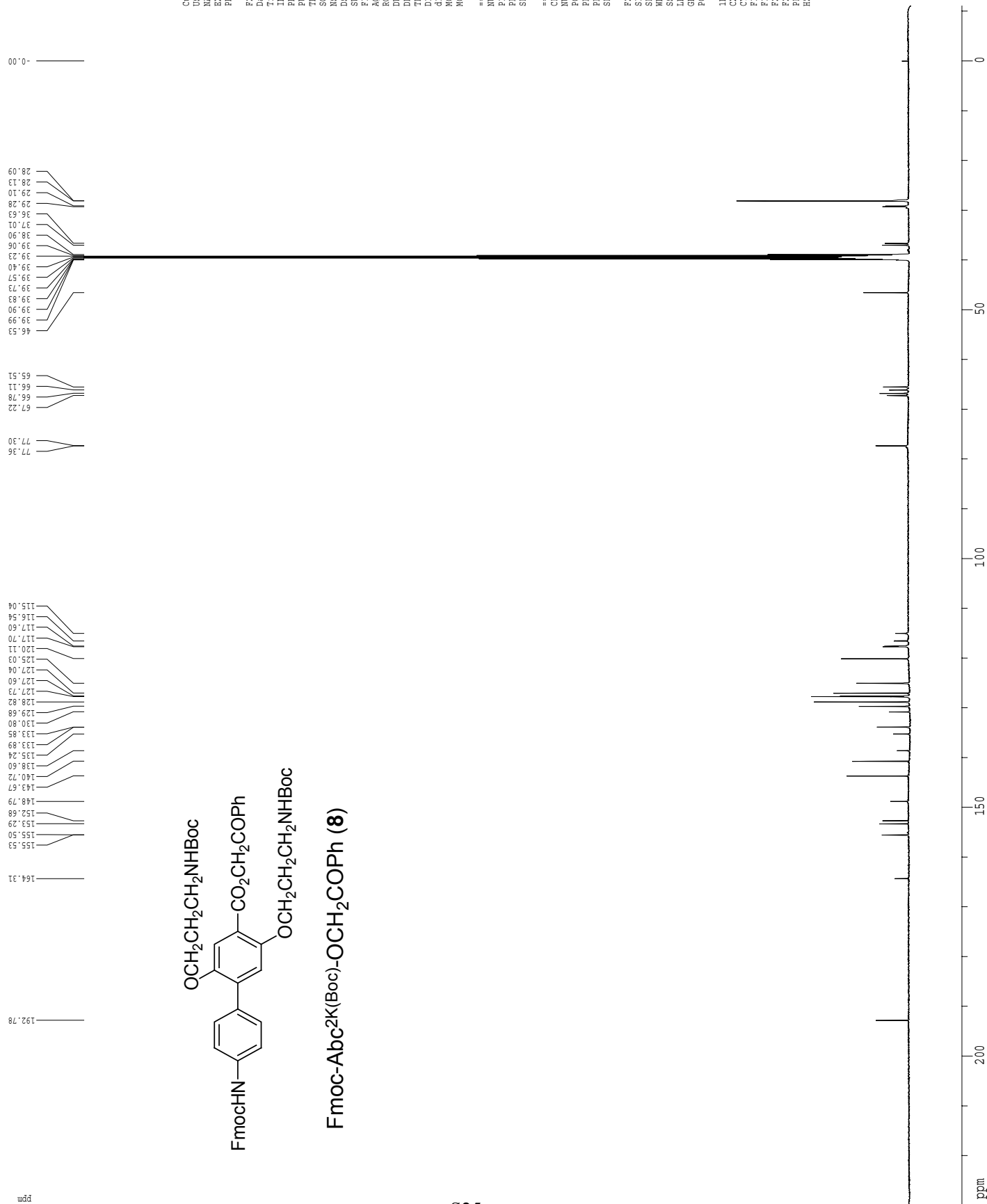
Fmoc-Abc^{2K(Boc)}-OCH₂COPh (8). A solution of H-Abc^{2K(Boc)}-OCH₂COPh (7) (6.55 g, 9.66 mmol), pyridine (0.95 mL, 11.6 mmol), and CH₂Cl₂ (200 mL) was cooled to 0 °C in an ice-bath. Fmoc-Cl (2.75 g, 10.6 mmol) in CH₂Cl₂ (50 mL) was added in drops over 5 min. After 30 min, the solution was allowed to warm to 25 °C and stirred for an additional 30 min. The mixture was then washed with water (100 mL), dried (Na₂SO₄), filtered, and the filtrate was concentrated by rotary evaporation to give a yellow oil. The yellow oil was dissolved in CH₂Cl₂ (ca. 15 mL), precipitated using ethyl acetate (ca. 50 mL) and hexanes (ca. 100 mL), and filtered to provide Fmoc-Abc^{2K(Boc)}-OCH₂COPh (8) as a white solid (8.82 g, 95%): mp 108-110 °C; IR (KBr) 3349, 2980, 2935, 2873, 1732, 1698, 1596 cm⁻¹; ¹H NMR, (500 MHz, CD₃SOCD₃, 358 K) δ 9.47 (s, 1 H), 7.99 (d, *J* = 8.5 Hz, 2 H), 7.87 (d, *J* = 7.5 Hz, 2 H), 7.74 (d, *J* = 7.5 Hz, 2 H), 7.67 (t, *J* = 7.4 Hz, 1 H), 7.56 (t, *J* = 7.7 Hz, 2 H), 7.50 (s, 4 H), 7.44 (s, 1 H), 7.42 (t, *J* = 7.4 Hz, 2 H), 7.34 (td, *J* = 7.4, 1.1 Hz, 2 H), 7.06 (s, 1 H), 6.37 (br. s, 2 H), 5.61 (s, 2 H), 4.51 (d, *J* = 6.6 Hz, 2 H), 4.32 (t, *J* = 6.6 Hz, 1 H), 4.08 (t, *J* = 6.2 Hz, 2 H), 3.94 (t, *J* = 6.3 Hz, 2 H), 3.13 (q, *J* = 6.4 Hz, 2 H), 3.04 (q, *J* = 6.4 Hz, 2 H), 1.85 (quintet, *J* = 6.5 Hz, 2 H), 1.78 (quintet, *J* = 6.5 Hz, 2 H), 1.36 (s, 9 H), 1.34 (s, 9 H); ¹³C NMR (125 MHz, CD₃SOCD₃, 298 K) δ 192.8, 164.3, 155.53, 155.51, 153.3, 152.7, 148.8, 143.7, 140.7, 138.6, 135.2, 133.90, 133.85, 130.8, 129.7, 128.8, 127.7, 127.6, 127.0, 125.0, 120.1, 117.7, 117.6,

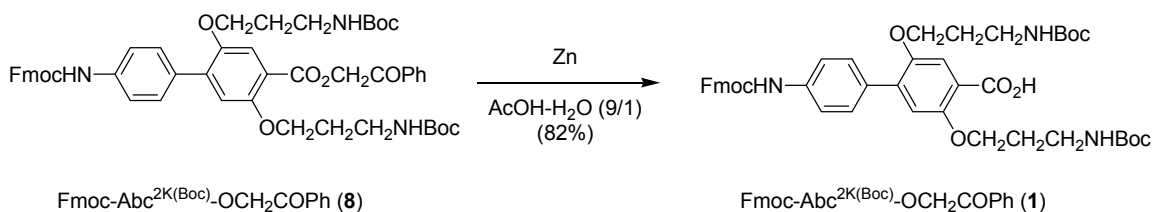
116.5, 115.0, 77.4, 77.3, 67.2, 66.8, 66.1, 65.5, 46.5, 37.0, 36.6, 29.2, 29.1, 28.1, 28.0;

HRMS (ESIMS) m/z for $C_{52}H_{57}N_3O_{11}Na$ $[M+Na]^+$ calcd 922.3891, found 922.3874.

$T = 358 \text{ K}$ 

13C spectrum with 1H decoupling

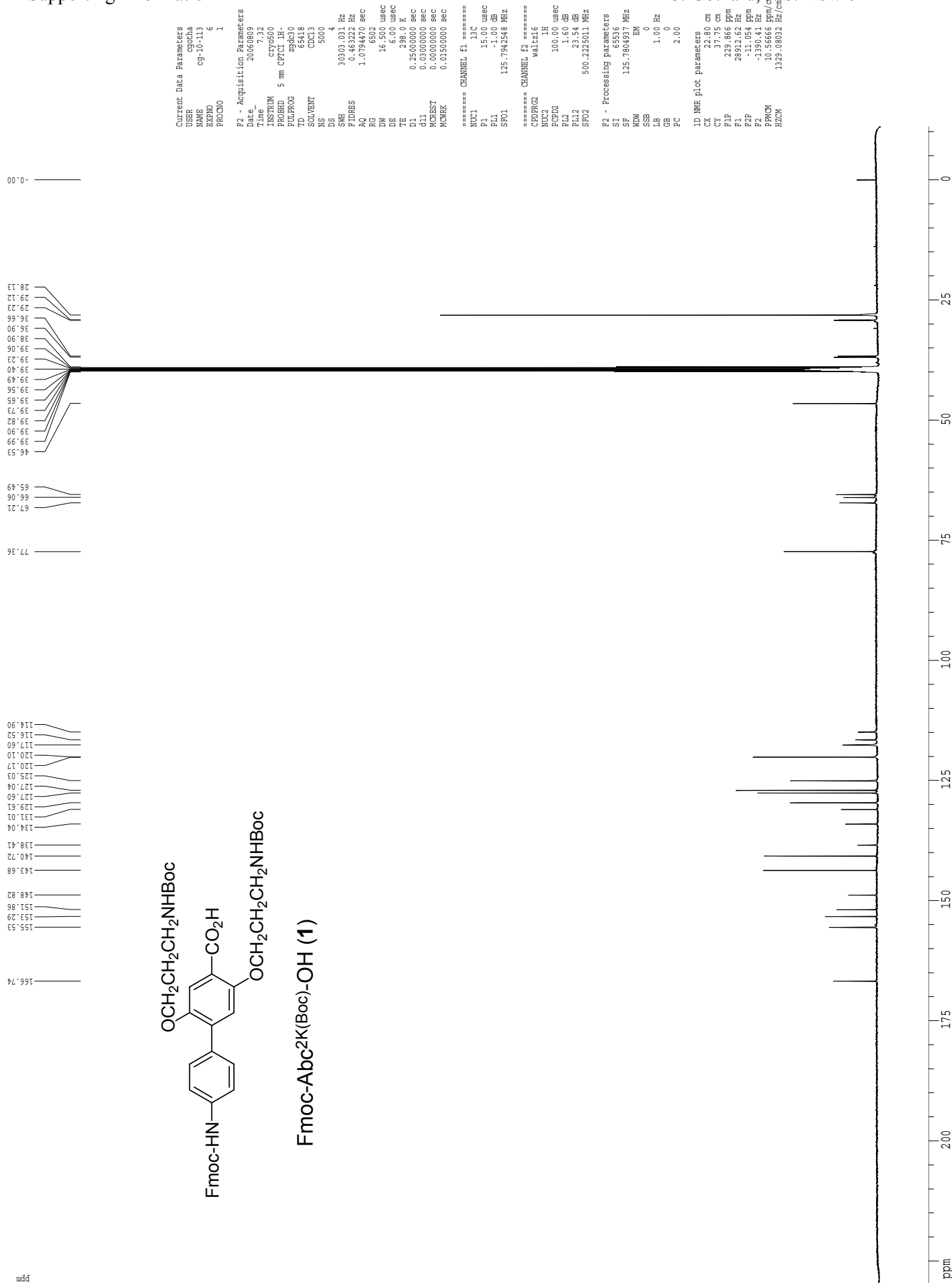




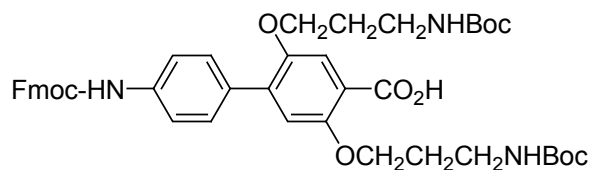
Fmoc-Abc^{2K(Boc)}-OH (1). Zn dust (31.1 g, 460 mmol) was added to a solution of Fmoc-Abc^{2K(Boc)}-OCH₂COPh (**8**) (8.28 g, 9.20 mmol), AcOH (100 mL), and H₂O (10 mL) and was stirred at 25 °C for 18 h.⁴ The suspension was then diluted with CH₂Cl₂ (ca. 100 mL) and stirred for an additional 30 min before the solids were removed by filtering the mixture through a bed of Celite[®]. The filtrate was concentrated by rotary evaporation and the resultant yellow oil was dissolved in CH₂Cl₂ (300 mL), washed with 0.2 N HCl (250 mL), H₂O (250 mL), and saturated aq sodium chloride (250 mL). The organic layer was dried over Na₂SO₄ and concentrated by rotary evaporation to give a yellow oil. Purification was performed by dissolving the yellow oil in ether (ca. 50 mL) and precipitating with hexanes (ca. 200 mL) to provide Fmoc-Abc^{2K(Boc)}-OH (**1**) as a white solid (5.9 g, 82 %): mp 108-110 °C; IR (KBr) 3366, 2978, 2874, 1712, 1689, 1608, 1590, 1533 cm⁻¹; ¹H NMR, (500 MHz, CD₃SOCD₃, 328 K) δ 12.32 (s, 1 H), 9.63 (s, 1 H), 7.89 (d, *J* = 7.5 Hz, 2 H), 7.75 (d, *J* = 7.5 Hz, 2 H), 7.48 (s, 4 H), 7.42 (t, *J* = 7.4 Hz, 2 H), 7.35 (td, *J* = 7.4, 1.1 Hz, 2 H), 7.33 (s, 1 H), 7.01 (s, 1 H), 6.63 (br. s, 2 H), 4.51 (d, *J* = 6.6 Hz, 2 H), 4.32 (t, *J* = 6.7 Hz, 1 H), 4.05 (t, *J* = 6.3 Hz, 2 H), 3.92 (t, *J* = 6.3 Hz, 2 H), 3.11 (q, *J* = 6.6 Hz, 2 H), 3.02 (q, *J* = 6.5 Hz, 2 H), 1.83 (quintet, *J* = 6.5 Hz, 2 H), 1.75 (quintet, *J* = 6.5 Hz, 2 H), 1.36 (s, 18 H); ¹³C NMR (125 MHz, CD₃SOCD₃, 298 K) δ 166.7, 155.5, 153.3, 151.9, 148.8, 143.7, 140.7, 138.4, 134.0, 131.0, 129.6, 127.6, 127.0,

⁴ Hendrickson, J. B.; Kandall, C. *Tetrahedron Lett.* **1970**, *5*, 343-344.

125.0, 120.2, 120.1, 117.6, 116.5, 114.9, 77.4, 67.2, 66.1, 65.5, 46.5, 36.9, 36.7, 29.2, 29.1, 28.1; HRMS (ESIMS) m/z for $C_{44}H_{51}N_3O_{10}Na$ $[M+Na]^+$ calcd 804.3472, found 804.3456.

^{13}C spectrum with ^1H decoupling

Fmoc-Abc^{2K(Boc)}-OH (1) Analytical RP-HPLC chromatograph



Analytical RP-HPLC (5-90% acetonitrile with 0.1% TFA over 20 min, $\lambda = 214$)

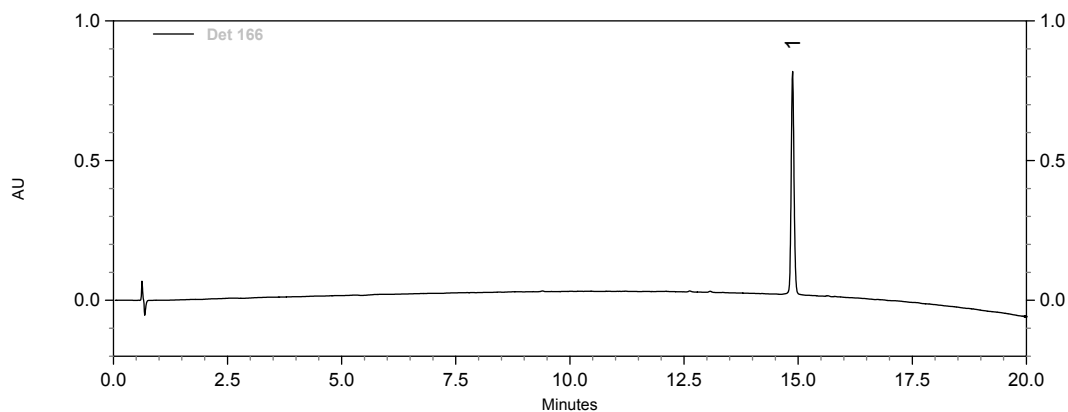
Sample ID: Fmoc-Abc2KBoc-OH 2nd recryst

Filename : D:\32Karat\Projects\Default\Data\Chris\cg-10-216 fmoc-Abc2K(Boc)-OH

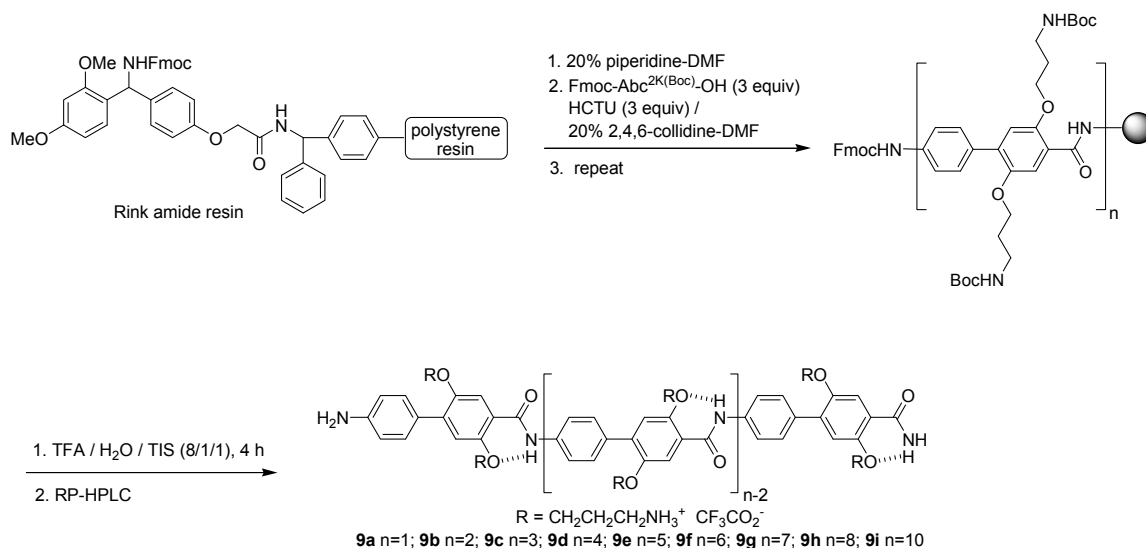
Synthesis\Fmoc-Abc2KBoc-OH 2nd recryst

Method : Rocket Platinum Column 5-90% B in 20 min (214 nm)

Date Inj. : 10/15/2006 6:37:54 PM



Det 166 Results					
Time	Area	Area %	Height	Height %	Pk #
14.878	3403014	100.00	793697	100.00	1
Totals	3403014	100.00	793697	100.00	



Synthesis of Abc^{2K} Oligomers 9a-9i. A Bio-Rad Poly-Prep chromatography column containing 47 mg of Rink amide resin (0.64 mmol/g., Novabiochem, Rink Amide resin co. 100-200 mesh, 1% DVB) was soaked with DMF (3 × ca. 5 mL, 1 min each) and then drained under nitrogen pressure. The Fmoc group was removed by adding a solution of 20% piperidine-DMF (1 × ca. 5 mL for 1 min, 1 × ca. 5 mL for 20 min) to the resin, capping the column on both ends, and gently agitating the resin. The piperidine solution was drained, and the resin was washed with DMF (6 × ca. 5 mL, 1 min each) and CH₂Cl₂ (6 × ca. 5 mL, 1 min each). Coupling of Fmoc-Abc^{2K}(Boc)-OH (**1**) to the resin was accomplished by pre-activating Fmoc-Abc^{2K}(Boc)-OH (70 mg, 0.09 mmol) with diisopropylcarbodiimide (13 μL, 0.085 mmol) and HOAt (12 mg, 0.09 mmol) in DMF-CH₂Cl₂ (ca. 0.5 mL / ca. 0.2 mL). After 2-3 min, the coupling solution was added to the resin and the resin was gently agitated for ca. 12 h. (Fmoc-Abc^{2K}(Boc)-OH (**1**) (3 equiv) was also coupled using HCTU⁵ (3 equiv) in a solution of 20% 2,4,6-collidine-DMF and became the preferred method of coupling.) The reaction vessel was then drained and the

⁵ Marder, O.; Shvo, Y.; Albericio, F. *Chim. Oggi* **2002**, *20*, 37-41.

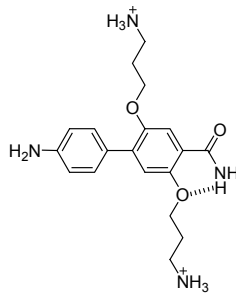
resin was washed with DMF ($6 \times$ ca. 5 mL, 1 min each) and then with CH_2Cl_2 ($3 \times$ ca. 5 mL, 1 min each).

To monitor the completeness of the couplings, a small amount of resin was cleaved in a new Bio-Rad column using a ca. 1-mL solution of CF_3COOH /water/triisopropylsilane, 8/1/1, v/v/v) and was vigorously agitated for ca. 2 h. The solution was then drained, concentrated by rotary evaporation, and the residue was dissolved in a mixture of water and CH_3CN and injected into an analytical RP-HPLC instrument to determine if any remaining aniline was present. (If any uncoupled aniline was observed on the chromatograph, an additional coupling was carried out. Typically, only the longer oligomers ($n = 7-10$) required an additional coupling and were required less often when the HCTU coupling method was used.)

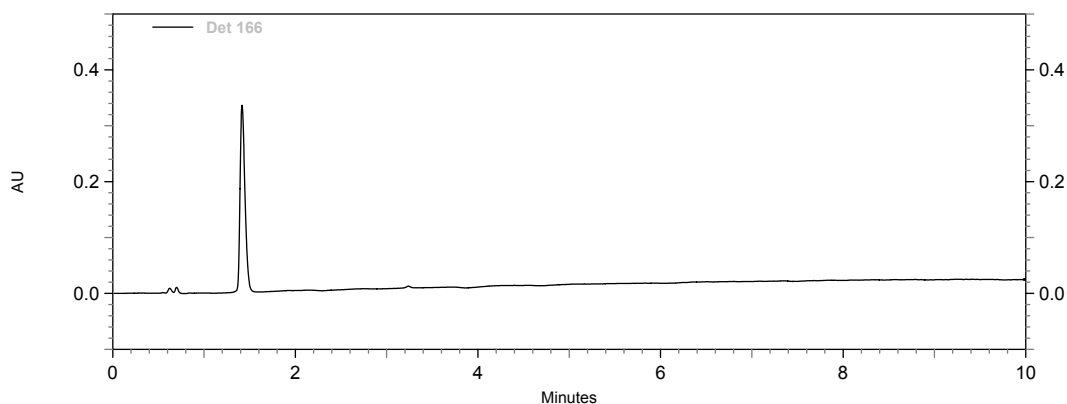
The above procedure was repeated until the desired length of Abc^{2K} oligomer was obtained. After final Fmoc deprotection using 20% piperidine-DMF, washing with DMF ($5\times$) and CH_2Cl_2 ($5\times$), the resin was transferred to a small round bottomed flask equipped with a magnetic stirring bar and treated with ca. 10 mL of CF_3COOH /water/triisopropylsilane (8/1/1, v/v/v) for 2-4 h. The resin was then filtered off using a fritted filter funnel and washed several times with the cleavage cocktail. The solution was concentrated by rotary evaporation. The resultant oil was dissolved in a mixture of water and CH_3CN , and the oligomer was purified by preparative RP-HPLC (water- CH_3CN buffers with 0.1 % TFA). (The oligomers typically eluted between 20 and 30% CH_3CN .) Pure fractions of the product were concentrated by rotary evaporation to remove most of the CH_3CN , frozen, and then lyophilized to afford a white powder (15-

20 mg). The remaining less pure HPLC fractions were also lyophilized into a white powder (ca. 20 mg) and stored for future use.

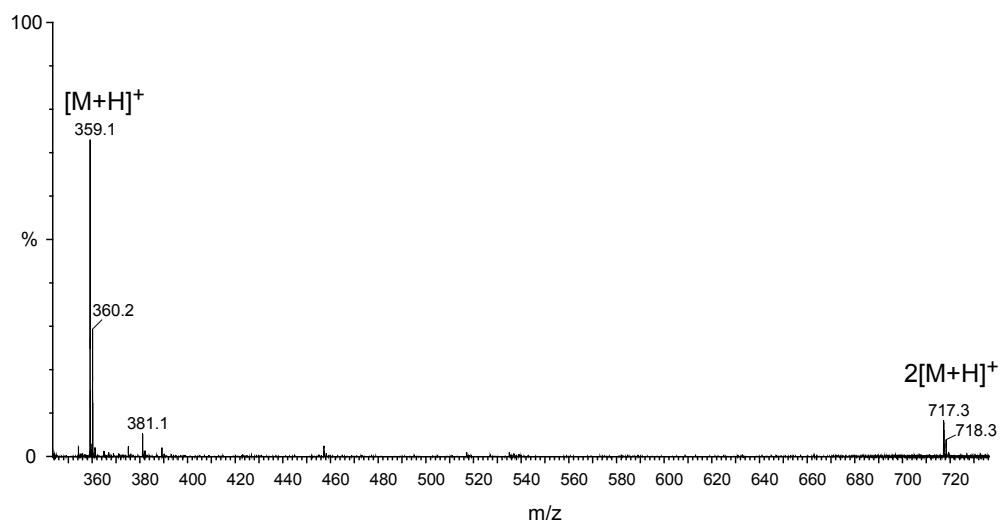
H-(Abc^{2K})₁-NH₂ TFA salt **9a**
Analytical RP-HPLC chromatograph and mass spectrum (ESI-MS)



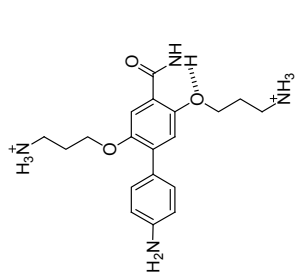
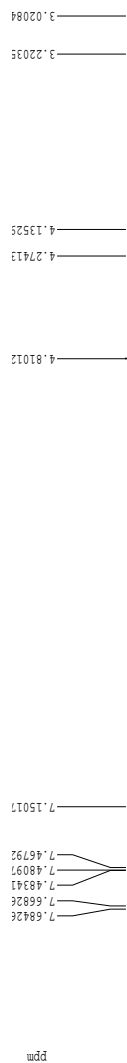
(a) Analytical RP-HPLC (5-50% acetonitrile with 0.1% TFA over 10 min, $\lambda = 214$)



(b) ESI Mass spectrum. (Calcd exact mass for C₁₉H₂₆N₄O₃ [M] = 358.20.)



¹H NMR of Abc2K Monomer H-Abc2K-NH₂ (500 MHz, 298 K, D₂O)



H-(Abc²K)₁-NH₂ (9a)

HDO

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PROCNO_    1

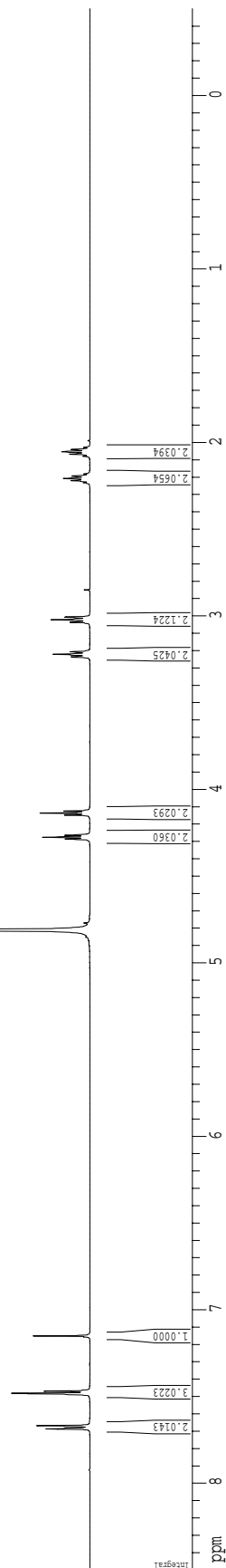
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DS_        2
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FIDRES_     0.098043 Hz
AQ_         5.0989774 sec
RG_         9
DM_         62.400 usec
DE_         6.00 usec
TE_         298.0 K
D1_         0.1000000 sec
MCREST_    0.0000000 sec
MORBK_     0.01500000 sec

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PL1_        1.60 dB
SFO1_       500.225015 MHz

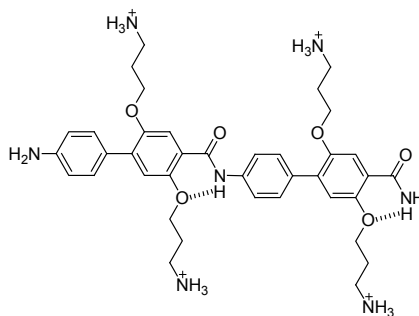
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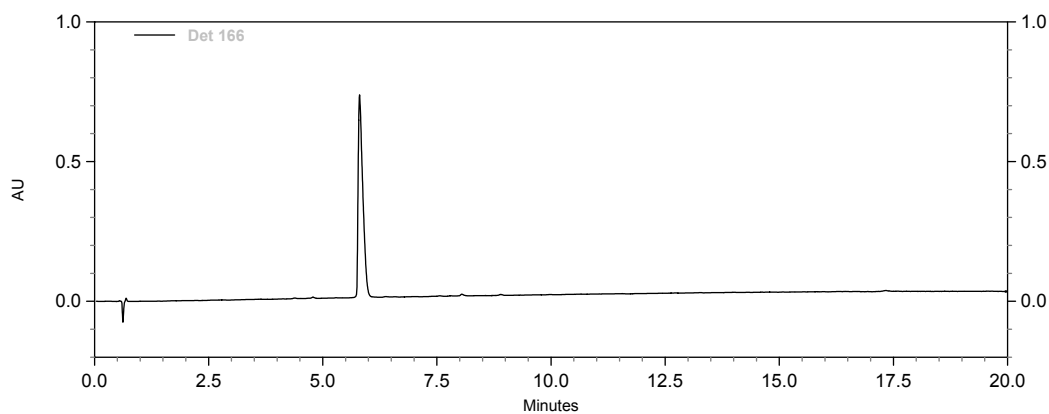
Gothard, J. S. Nowick



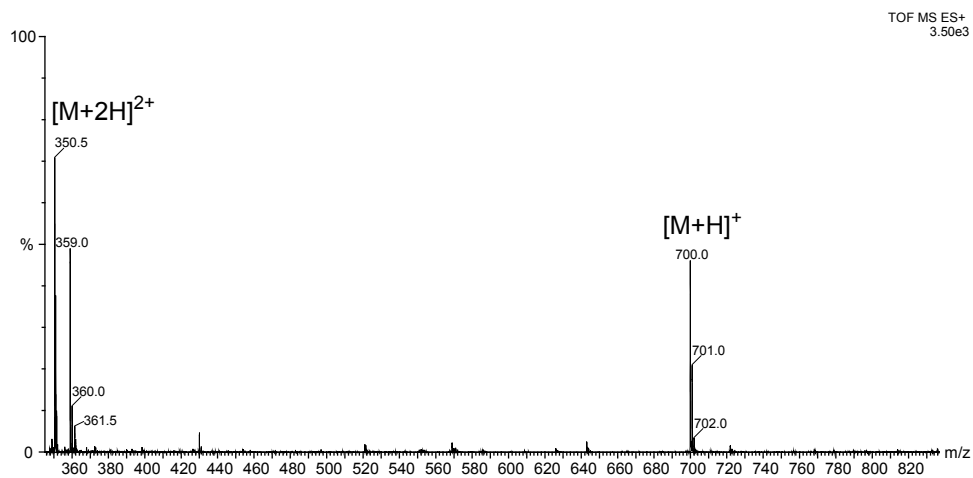
H-(Abc^{2K})₂-NH₂ TFA salt **9b**
Analytical RP-HPLC chromatograph and mass spectrum (ESI-MS)



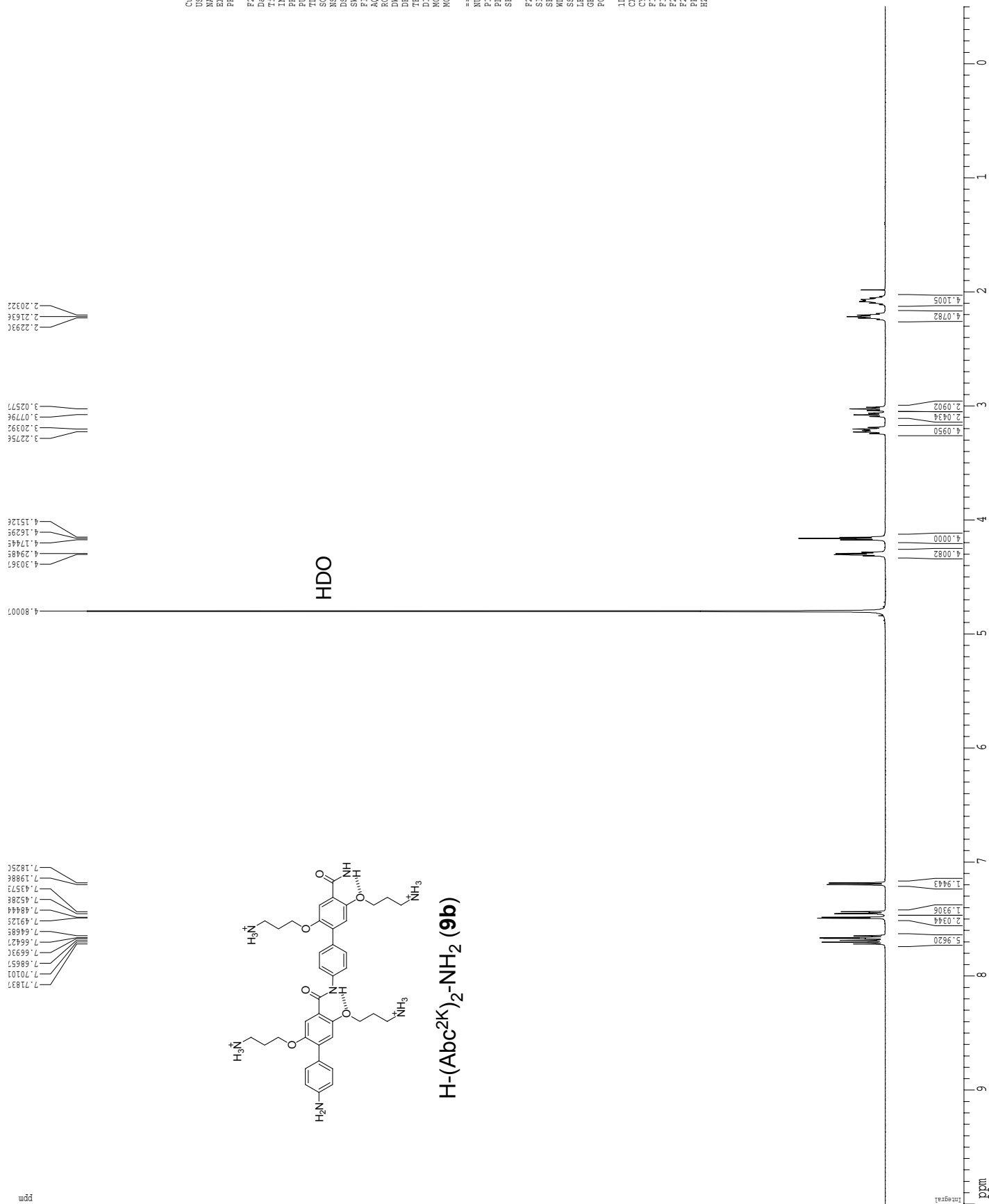
(a) Analytical RP-HPLC (5-50% acetonitrile with 0.1% TFA over 20 min, $\lambda = 214$)



(b) ESI Mass spectrum. (Calcd exact mass for C₃₈H₄₉N₇O₆ [M] = 699.37)



¹H NMR of Abc2K Dimer H-(Abc2K)₂-NH₂ (500 MHz, 298 K, D₂O)



Supporting Information

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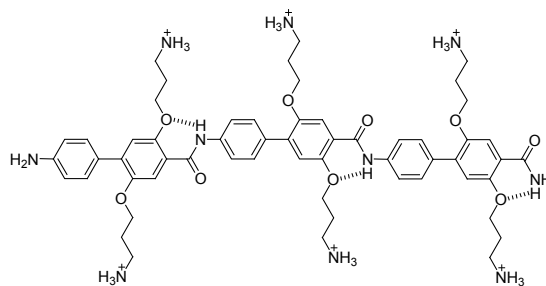
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P1           8.00 usec
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F2 - Processing parameters
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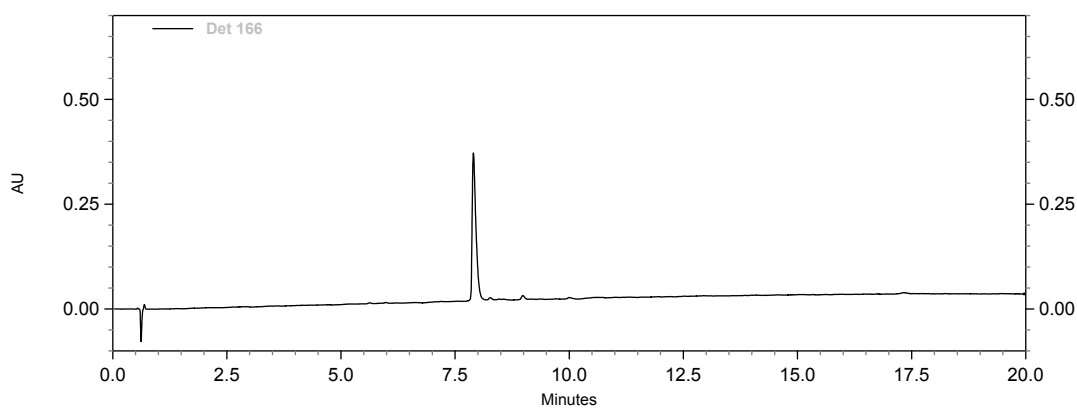
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F2           -0.500 ppm
F3           -250.11 Hz
PQMCN       0.46053 ppm/cm
HZCN        230.36449 Hz/cm
    
```

C. Gothard, J. S. Nowick

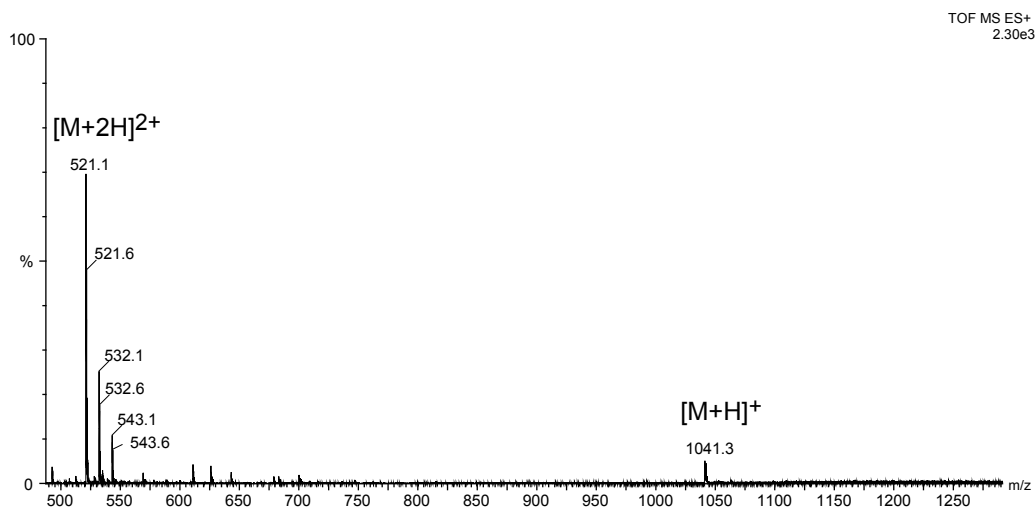
H-(Abc^{2K})₃-NH₂ TFA salt **9c**
Analytical RP-HPLC chromatograph and mass spectrum (ESI-MS)



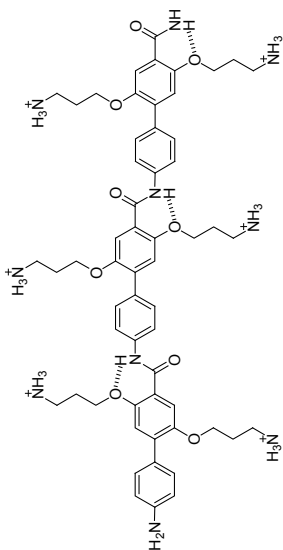
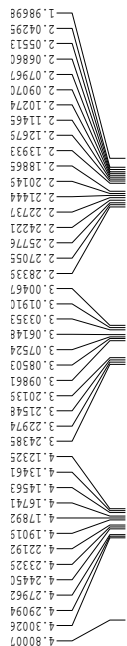
(a) Analytical RP-HPLC (5-50% acetonitrile with 0.1% TFA over 20 min, $\lambda = 214$)



(b) ESI Mass spectrum. (Calcd exact mass for C₅₇H₇₂N₁₀O₉ [M] = 1040.55)



¹H NMR of Abc2K Trimer H-(Abc2K)₃-NH₂ (500 MHz, 298 K, D₂O)



H-(Abc2K)₃-NH₂ (9c)

H₂O

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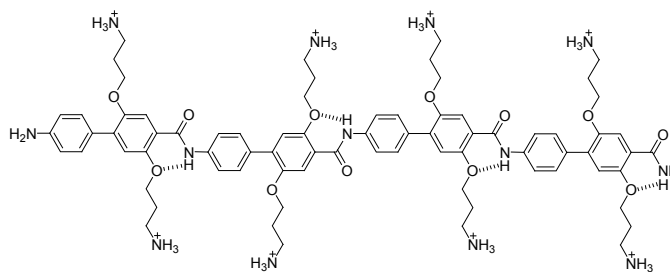
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FIDRES 0.098043 Hz
AQ 5.0998774 sec
RG 203.2
WDW 62.400 usec
SS 8.00 usec
LB 0.30 Hz
GB 0
PC 4.00

===== CHANNEL f1 =====
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PL1 1.60 dB
SFO1 500.2135015 MHz

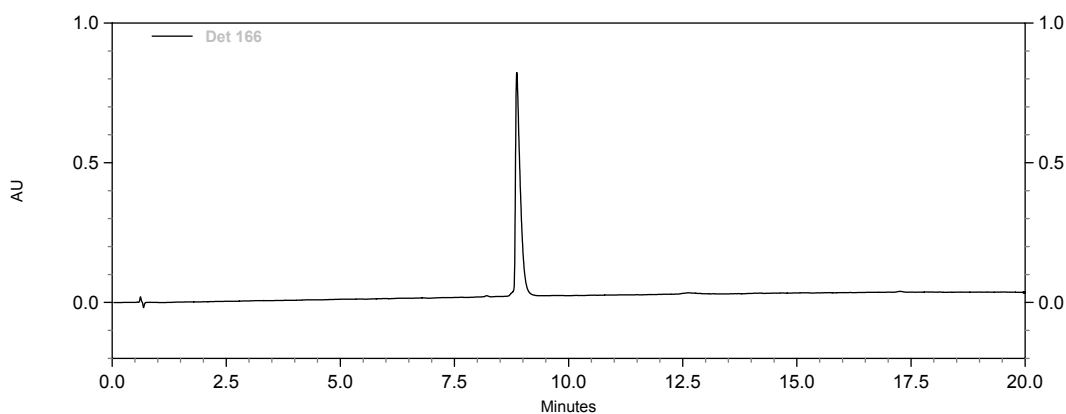
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LB 0.30 Hz
GB 0
PC 4.00

1D NMR plot parameters
CX 22.80 cm
CY 75.00 cm
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F1 5002.10 Hz
F2 -0.500 ppm
F3 0.000 Hz
F4 0.000 Hz
F5 0.000 Hz
F6 0.000 Hz
F7 0.000 Hz
F8 0.000 Hz
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F10 0.000 Hz
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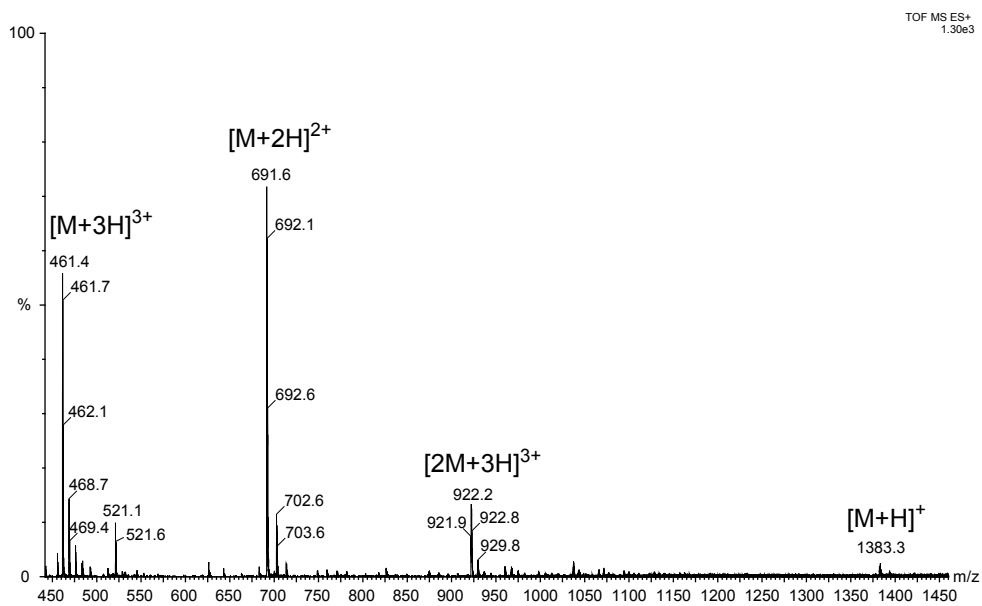
H-(Abc^{2K})₄-NH₂ TFA salt **9d**
Analytical RP-HPLC chromatograph and mass spectrum (ESI-MS)

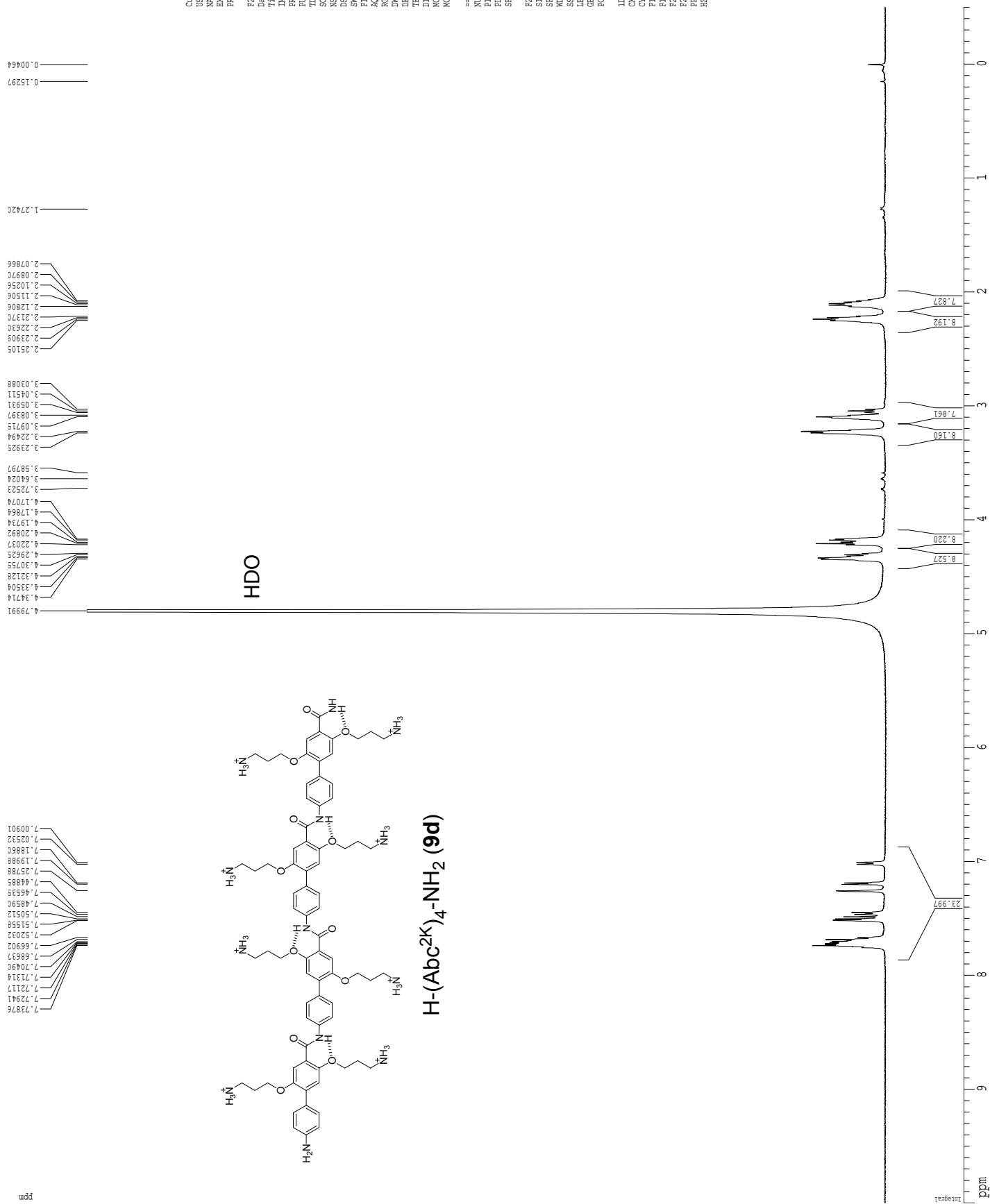


(a) Analytical RP-HPLC (5-50% acetonitrile with 0.1% TFA over 20 min, $\lambda = 214$)

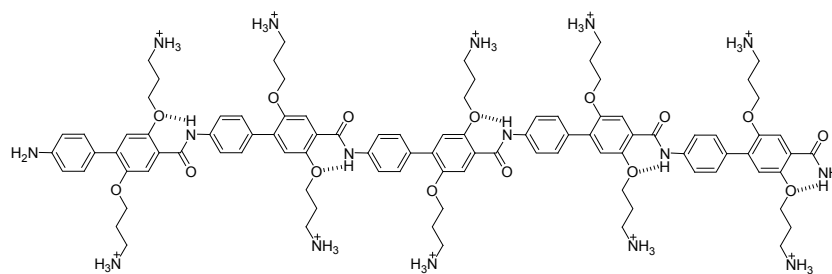


(b) ESI Mass spectrum. (Calcd exact mass for C₇₆H₉₅N₁₃O₁₂ [M] = 1381.72)

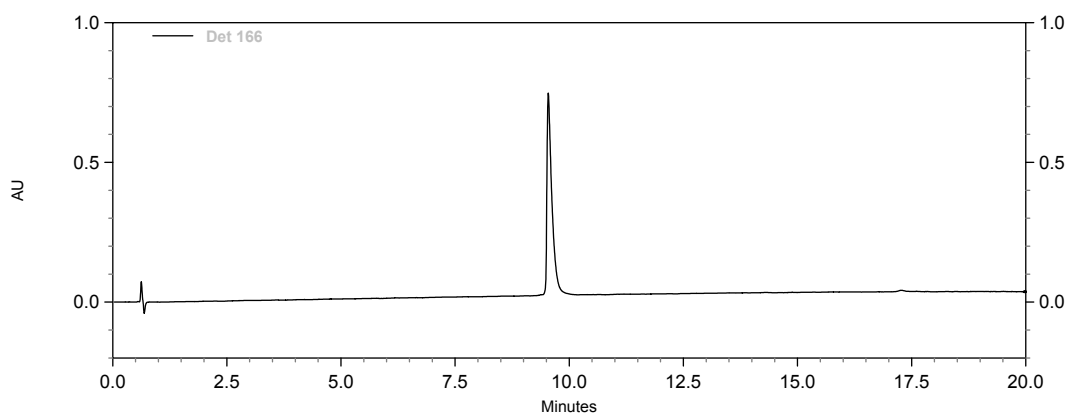


¹H NMR of Abc2k Tetramer H-(Abc2k)₄-NH₂ (500 MHz, 298 K, D₂O)

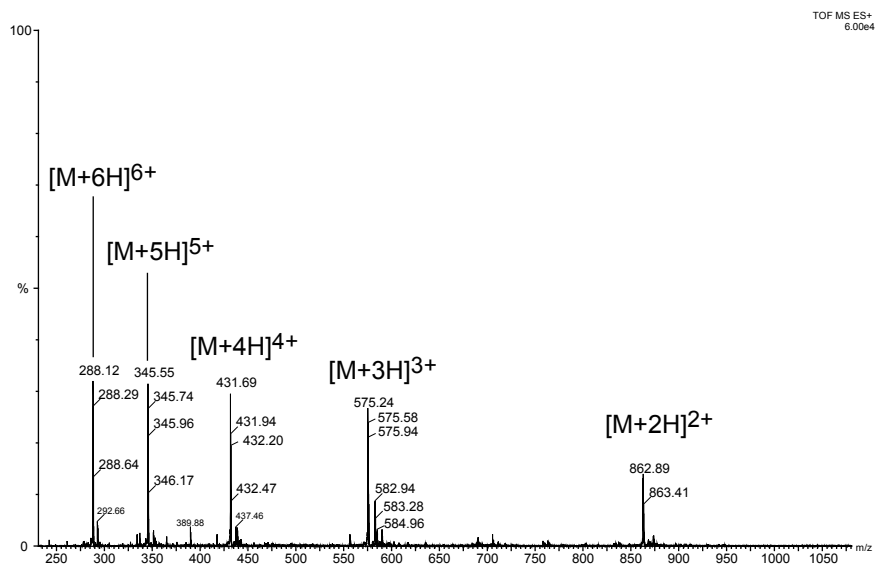
H-(Abc^{2K})₅-NH₂ TFA salt **9e**
Analytical RP-HPLC chromatograph and mass spectrum (ESI-MS)

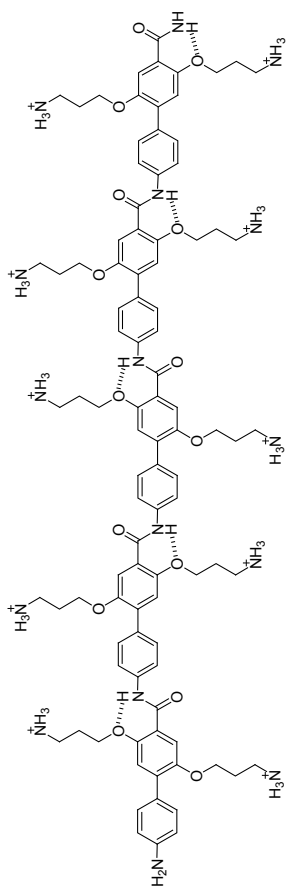


(a) Analytical RP-HPLC (5-50% acetonitrile with 0.1% TFA over 20 min, $\lambda = 214$)



(b) ESI Mass spectrum. (Calcd exact mass for C₉₅H₁₁₈N₁₆O₁₅ [M] = 1722.90)



¹H NMR of Abc2K Pentamer H-(Abc2K)₅-NH₂ (500 MHz, 298 K, D₂O)**H-(Abc2K)₅-NH₂ (9e)**

HDO

S43

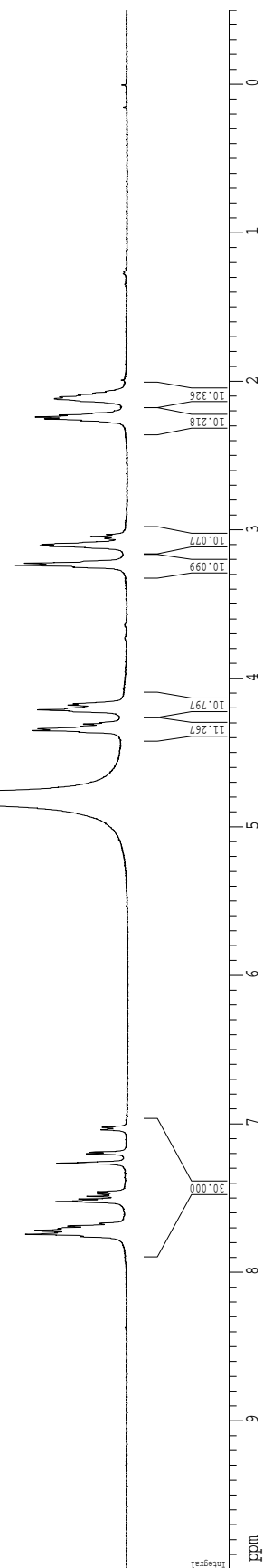
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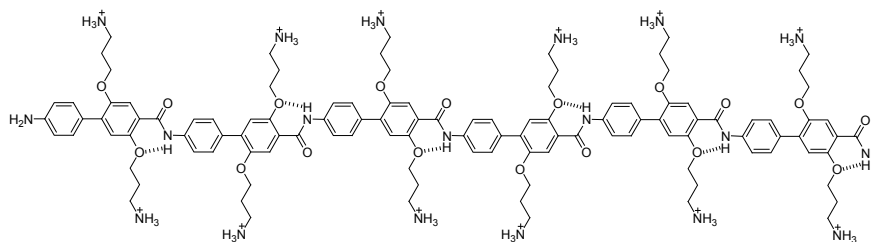
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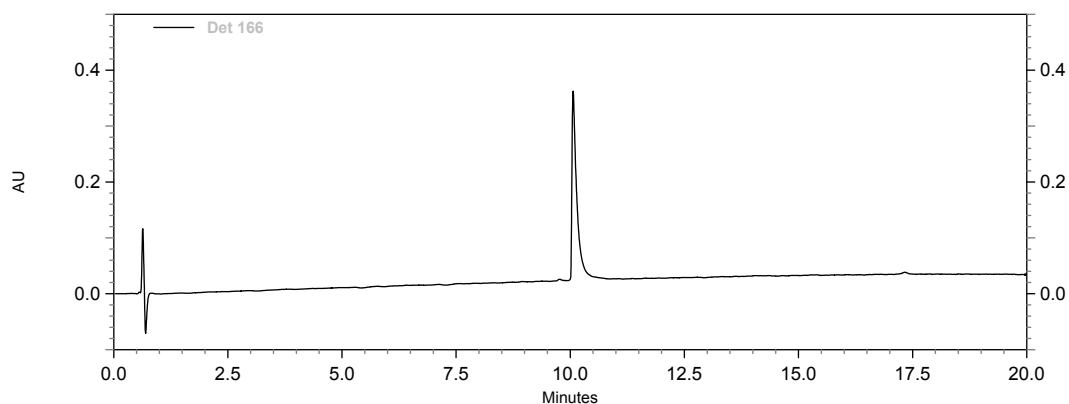
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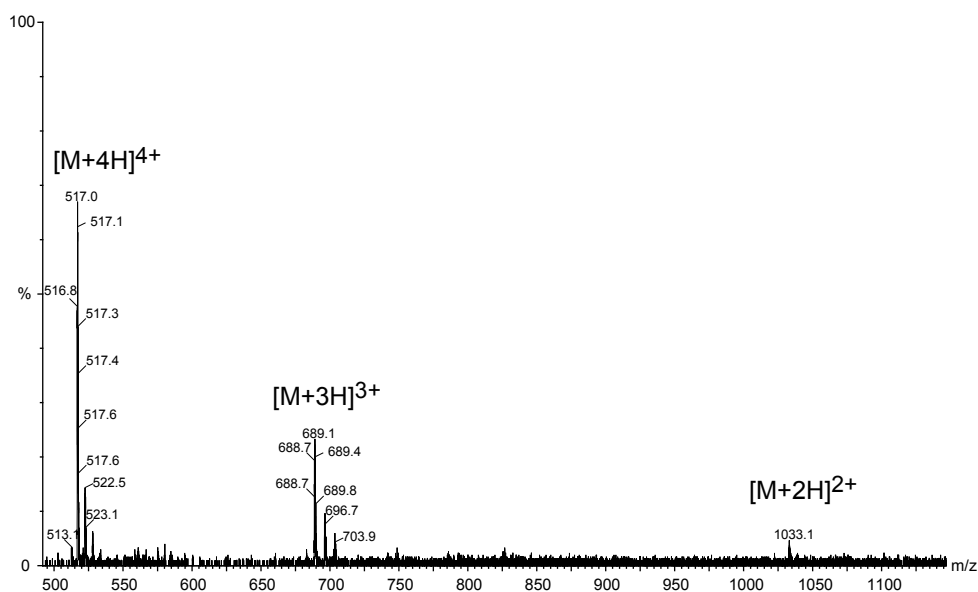
H-(Abc^{2K})₆-NH₂ TFA salt **9f**
Analytical RP-HPLC chromatograph and mass spectrum (ESI-MS)



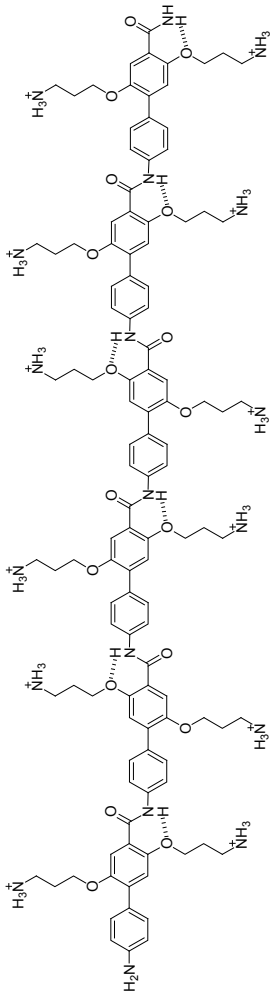
(a) Analytical RP-HPLC (5-50% acetonitrile with 0.1% TFA over 20 min, $\lambda = 214$)



(b) ESI Mass spectrum. (Calcd exact mass for C₁₁₄H₁₄₁N₁₉O₁₈ [M] = 2064.07)

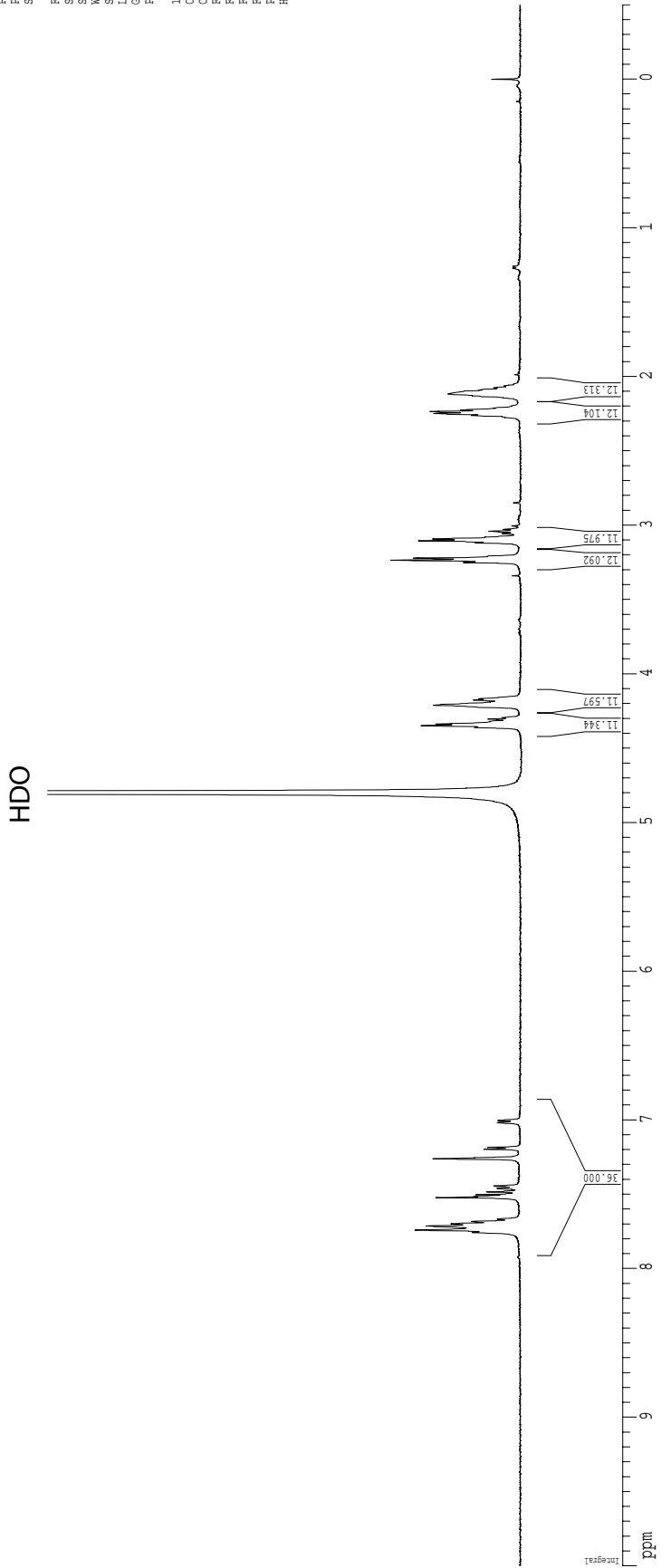


¹H NMR of Abc2K Hexamer H-(Abc2K)₆-NH₂ (500 MHz, 298 K, D₂O)



H-(Abc2K)₆-NH₂ (9f)

H₂O



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PROCNO 1

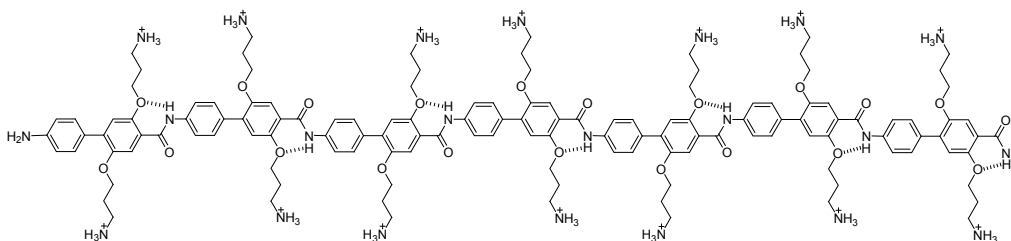
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PULPROG zgpg30
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FIDRES 0.098043 Hz
AQ 5.098774 sec
RG 228.1
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DE 0.0 usec
TE 298.0
D1 0.10000000 sec
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***** CHANNEL f1 *****
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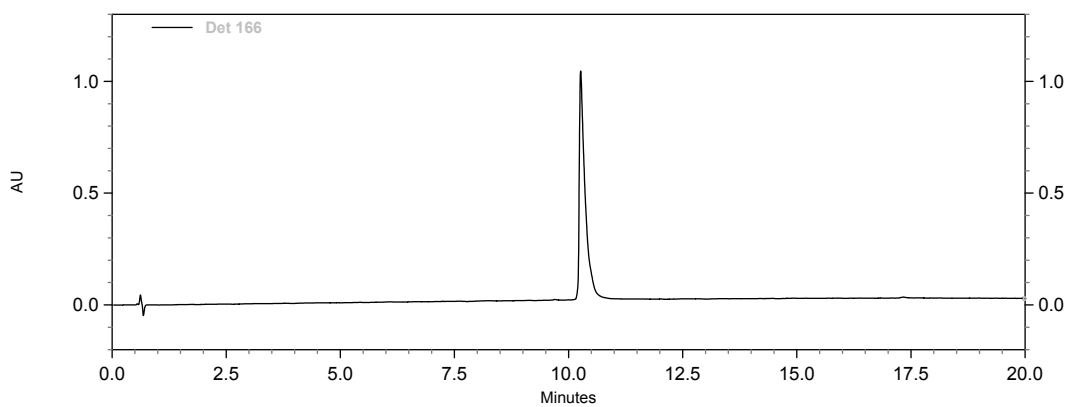
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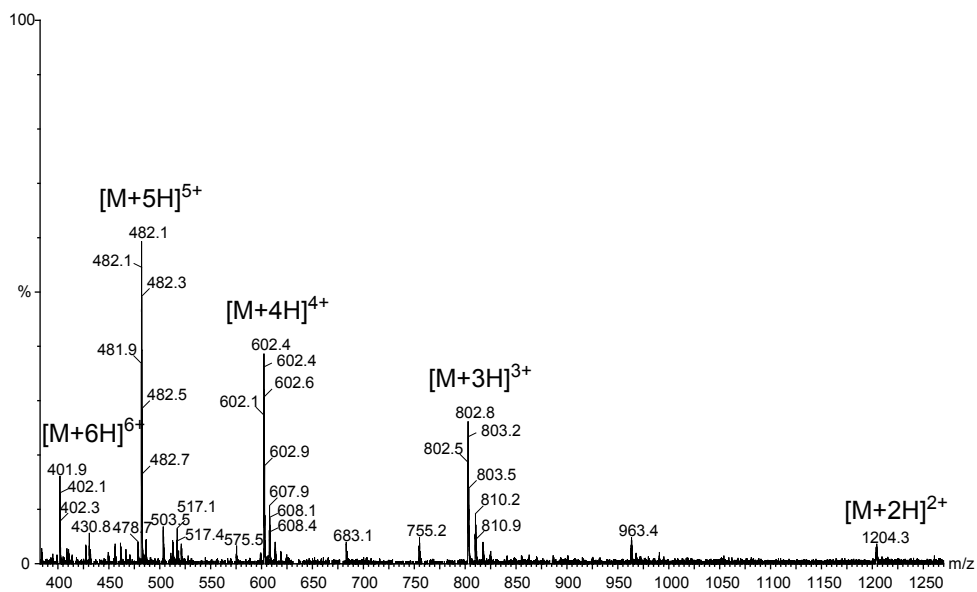
H-(Abc^{2K})₇-NH₂ TFA salt **9g**
Analytical RP-HPLC chromatograph and mass spectrum (ESI-MS)



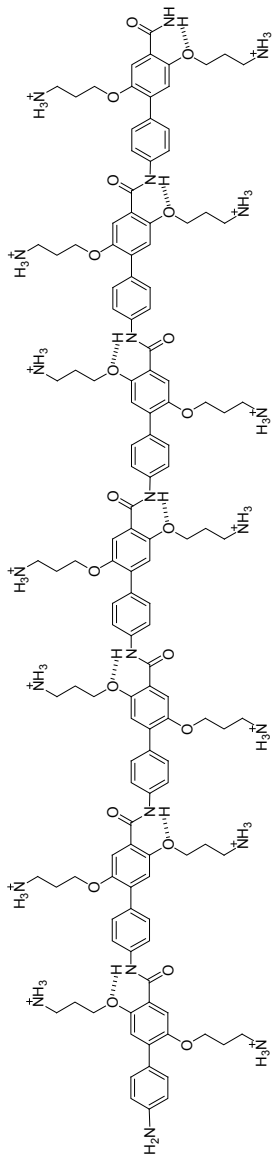
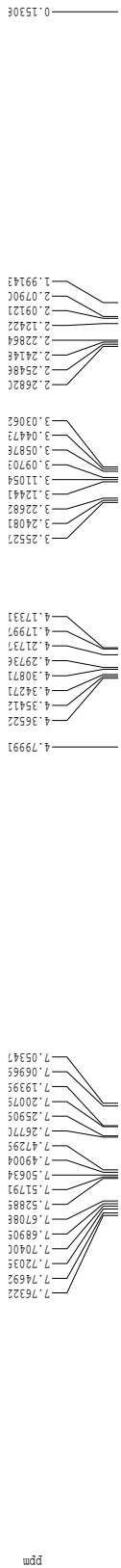
(a) Analytical RP-HPLC (5-50% acetonitrile with 0.1% TFA over 20 min, $\lambda = 214$)



(b) ESI Mass spectrum. (Calcd exact mass for C₁₃₃H₁₆₄N₂₂O₂₁ [M] = 2405.24)

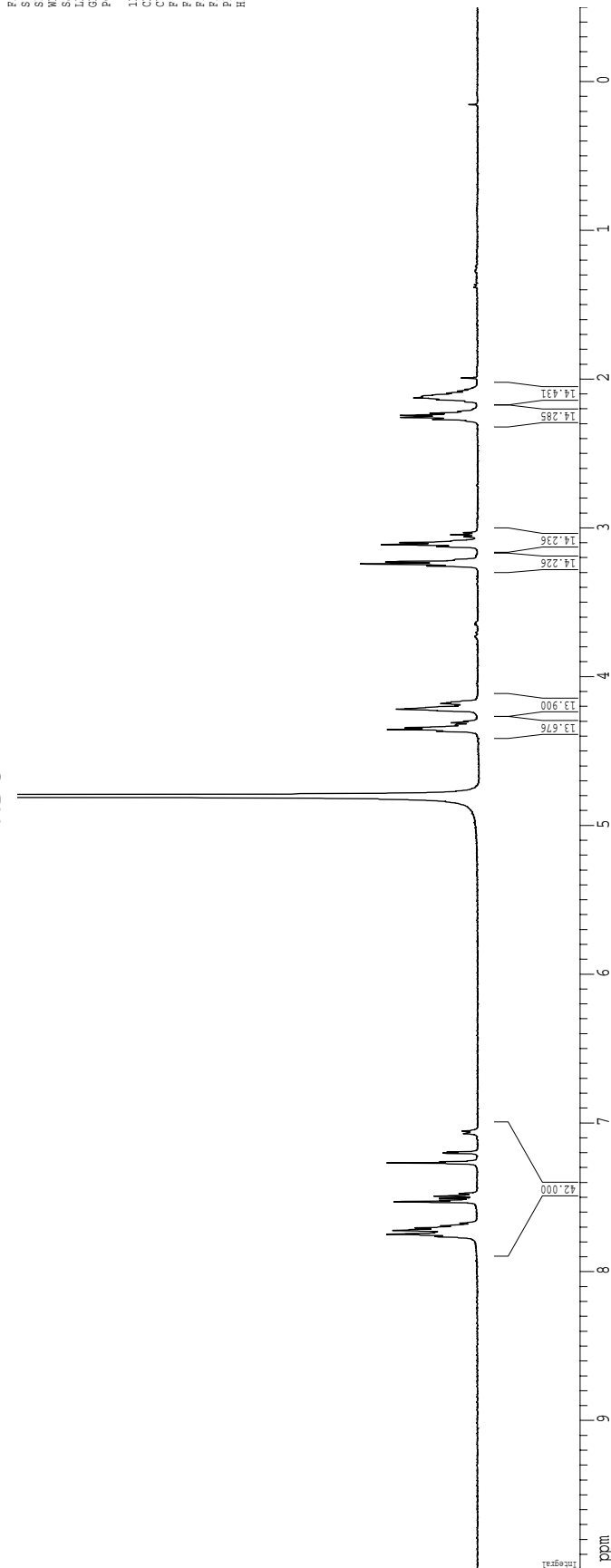


¹H NMR of Abc2K Heptamer H-(Abc2K)₇-NH₂ (500 MHz, 298 K, D₂O)



H-(Abc2K)₇-NH₂ (9g)

HDO



Supporting Information

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 PROCNO 1

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 SWH 8012.820 Hz
 FIDRES 0.098043 Hz
 AQ 5.0989774 sec
 RG 362
 DW 62.400 usec
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 D1 0.10000000 sec
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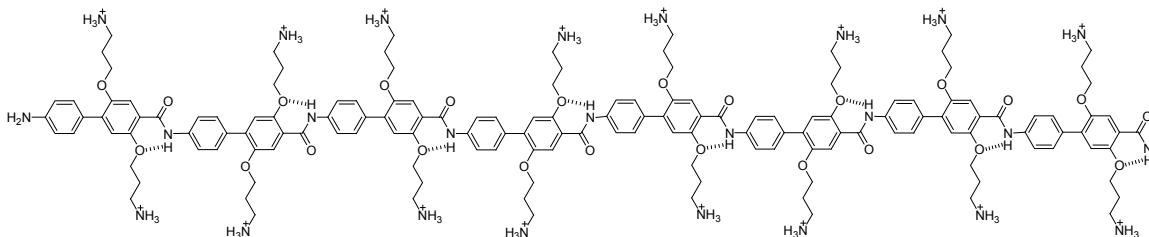
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 PL1 1.60 dB
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 IQ 0
 SSB 0
 LB 0.30 Hz
 GB 0
 PC 4.00

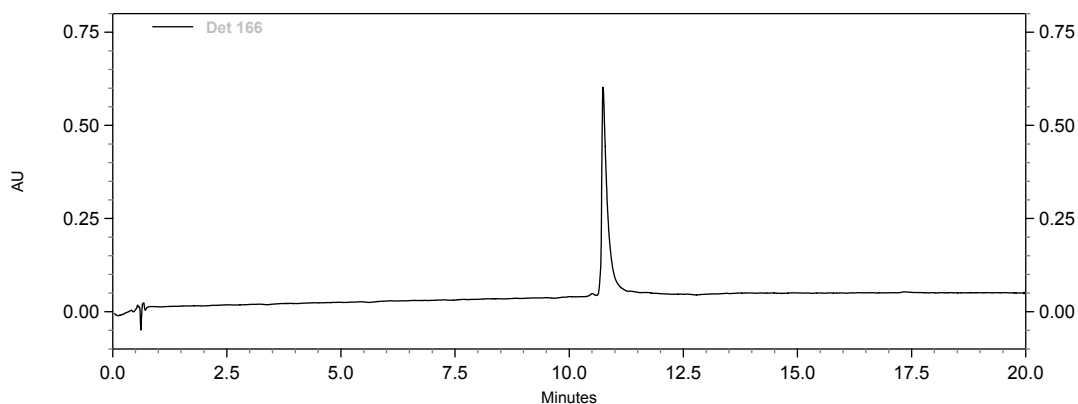
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 CX 22.80 cm
 CY 575.93 cm
 F1P 10.000 ppm
 F1 5002.10 Hz
 F2P -0.500 ppm
 F2 -250.10 Hz
 FFRONT 0.46053 ppm/cm
 HZCM 230.35988 Hz/cm

C. Gothard, J. S. Nowick

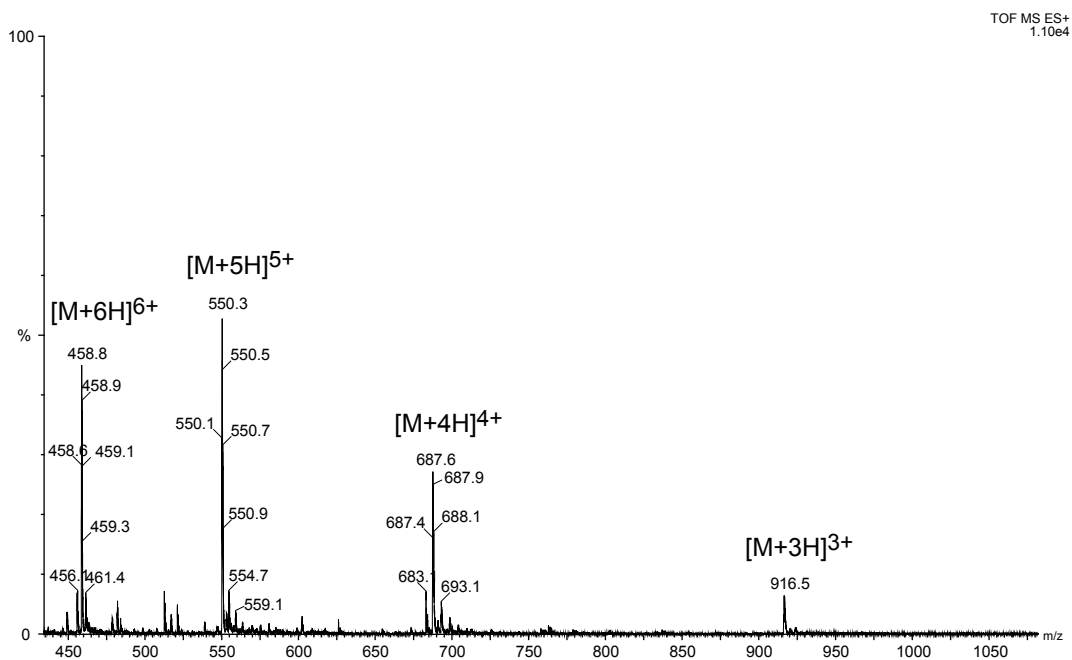
H-(Abc^{2K})₈-NH₂ TFA salt **9h**
Analytical RP-HPLC chromatograph and mass spectrum (ESI-MS)

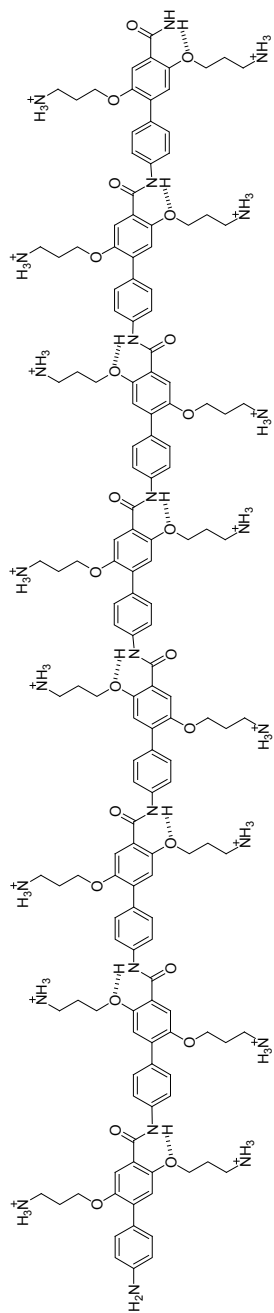
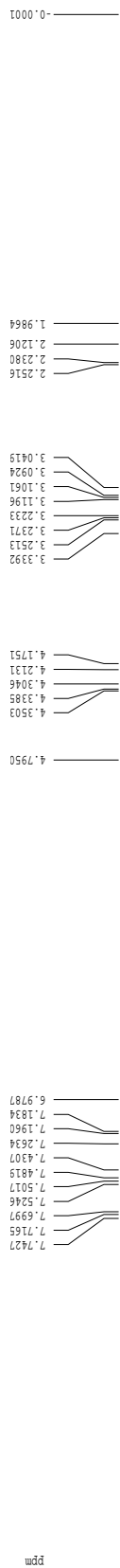
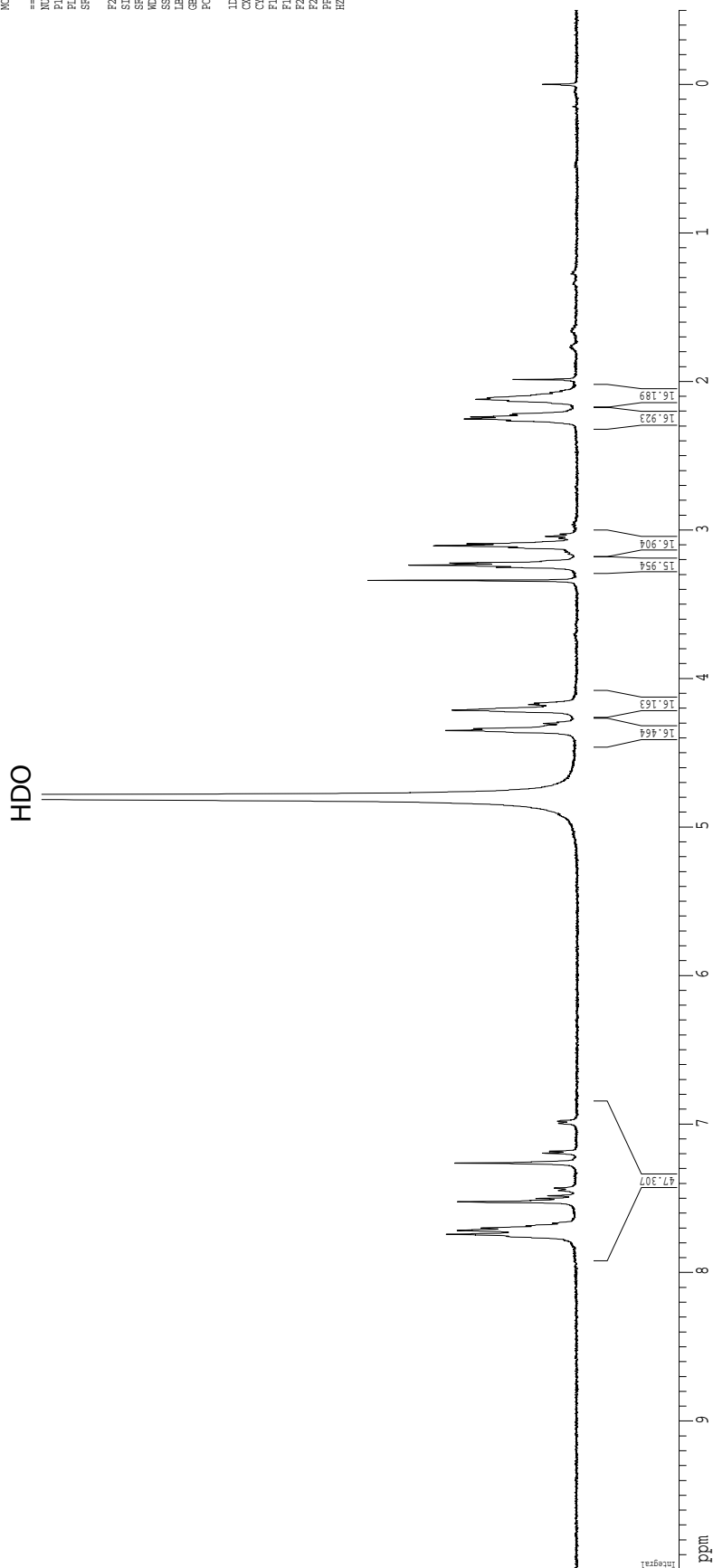


(a) Analytical RP-HPLC (5-50% acetonitrile with 0.1% TFA over 20 min, $\lambda = 214$)



(b) ESI Mass spectrum. (Calcd mass for C₁₅₂H₁₈₇N₂₅O₂₄ [M] = 2746.42)



^1H NMR of Abc^{2k} Octamer H-(Abc^{2k})₈-NH₂ (500 MHz, 298 K, D₂O)**H-(Abc^{2k})₈-NH₂ (9h)**

Current Data Parameters
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 EXFO 2
 PROCNO 1

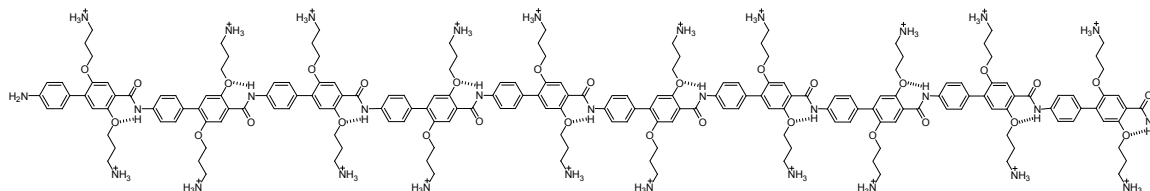
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 SOLVENT D2O
 NS 64
 DS 2
 SWH 8012.820 Hz
 FIDRES 0.098643 Hz
 AQ 5.0998774 sec
 RG 228.1
 DW 62.400 usec
 DE 6.00
 TE 298.0 K
 DL 0.1000000 sec
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 MCWK 0.0150000 sec

===== CHANNEL f1 =====
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 PL1 1.60 dB
 SFO1 500.21135015 MHz

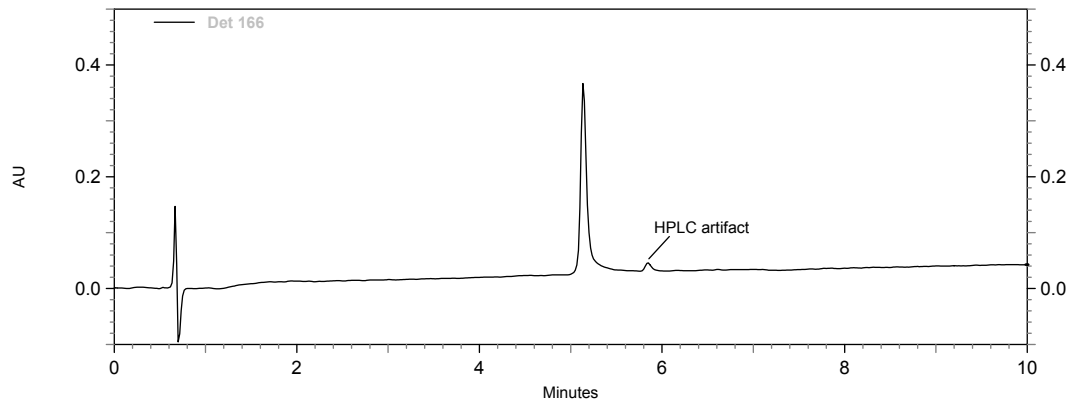
F2 - Processing parameters
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 SF 500.210083 MHz
 EN
 DS 0
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 LB 0
 GB 0
 CB 0
 PC 4.00

ID NMR plot parameters
 CX 22.80 cm
 CY 528.20 cm
 F1P 10.400 ppm
 F1 5002.10 Hz
 F2P -0.500 ppm
 F2 -250.11 Hz
 PPMCM 0.46053 ppm/cm
 HZCM 230.35989 Hz/cm

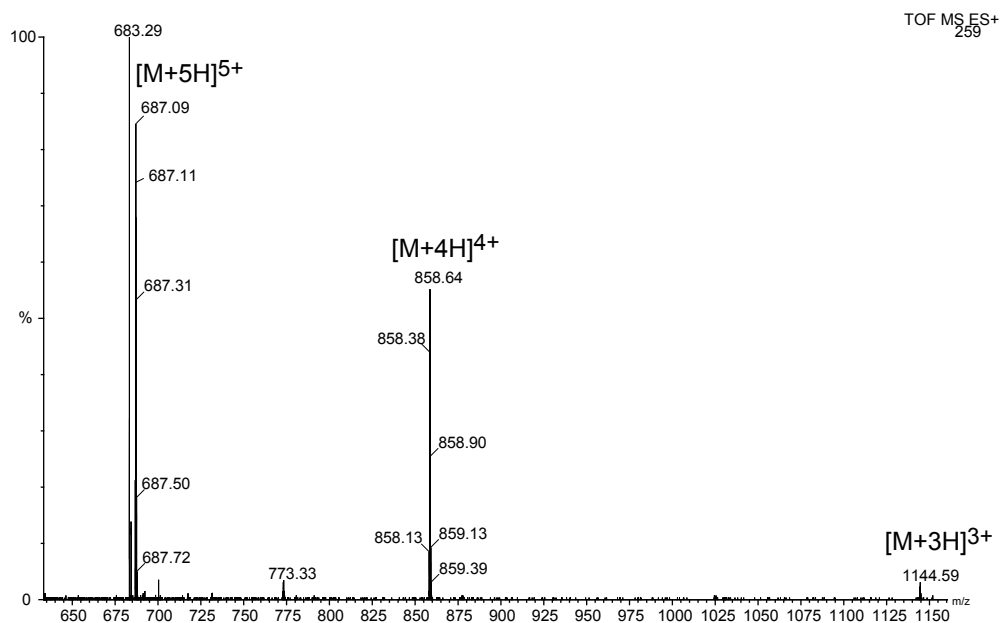
H-(Abc^{2K})₁₀-NH₂ TFA salt **9i**
Analytical RP-HPLC chromatograph and mass spectrum (ESI-MS)



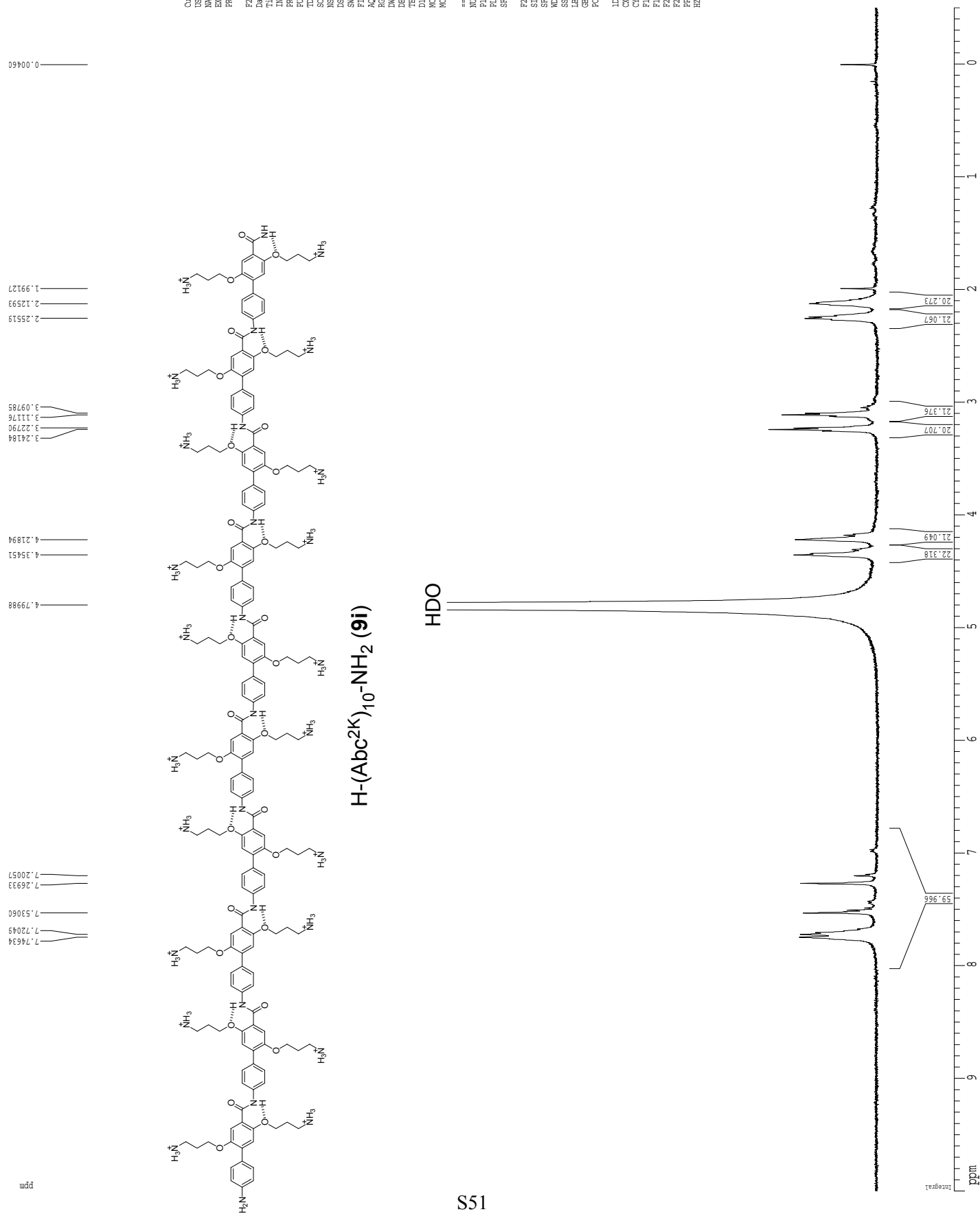
(a) Analytical RP-HPLC (5-50% acetonitrile with 0.1% TFA over 10 min, $\lambda = 214$)

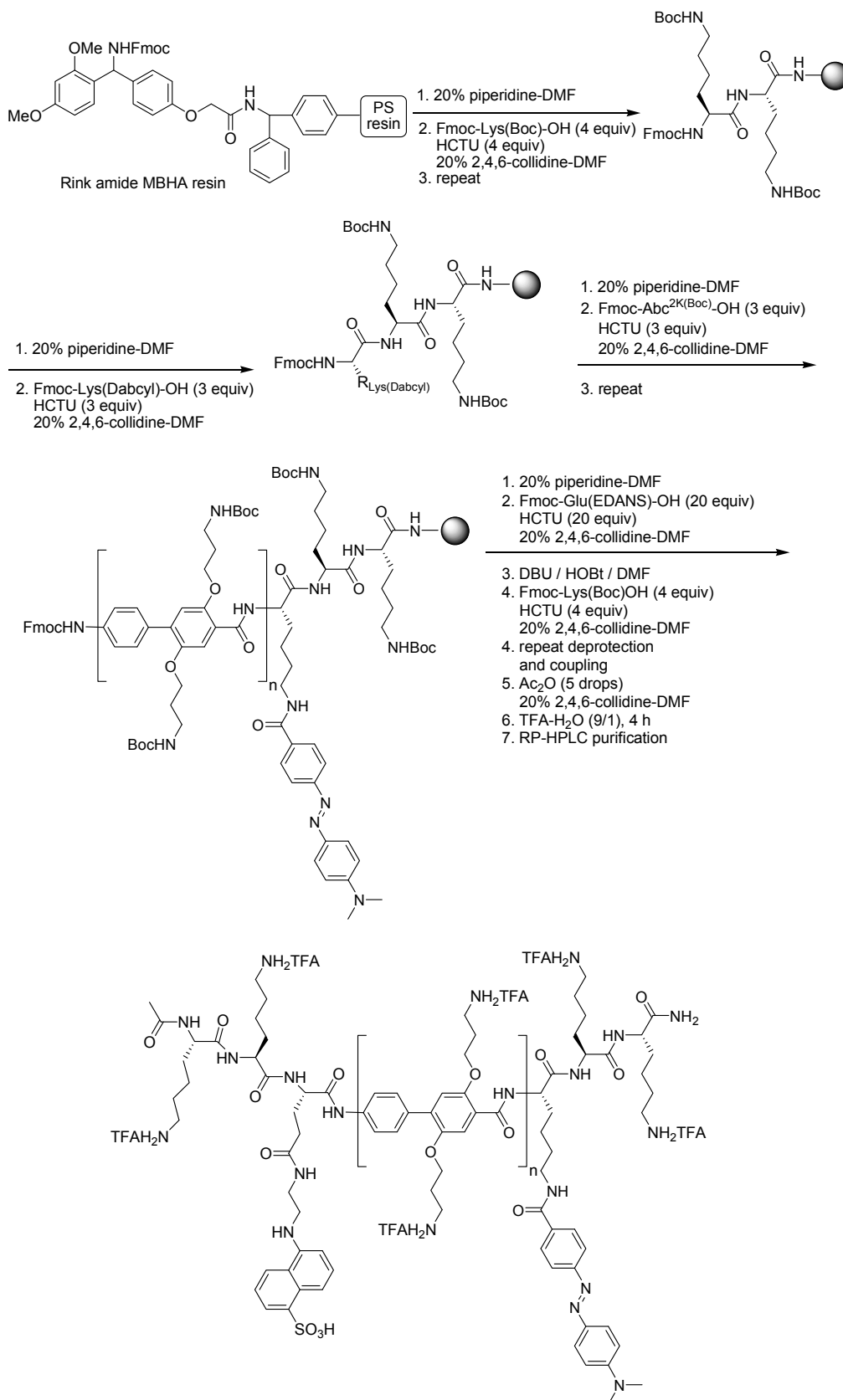


(b) ESI Mass spectrum. (Calcd exact mass for C₁₉₀H₂₃₃N₃₁O₃₀ [M] = 3428.77)



¹H NMR of Abc2K Decamer H-(Abc2K)₁₀-NH₂ (500 MHz, 298 K, D₂O)





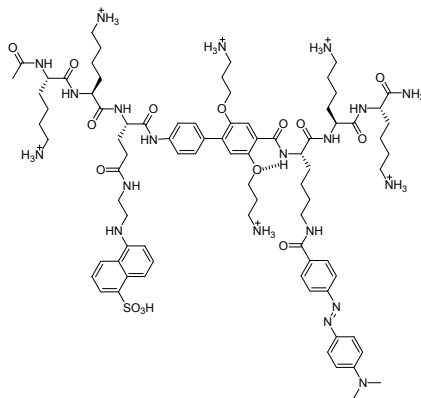
Synthesis of $\text{Abc}^{2\text{K}}$ Oligomers 10a-10j: $\text{Ac-(Lys)}_2\text{-Glu(EDANS)-(Abc}^{2\text{K}})_n\text{-Lys(DabcyI)-(Lys)}_2\text{-NH}_2$ ($n=1-10$). Rink amide MBHA resin (74 mg, 0.34 mmol/g, Novabiochem) contained in Bio-Rad Poly-Prep chromatography column was soaked in CH_2Cl_2 for 15 min and then washed with DMF ($3 \times$ ca. 5 mL, 1 min each). Fmoc deprotection was carried out using a solution of 20% piperidine–DMF ($1 \times$ ca. 5 mL for 1 min, $1 \times$ ca. 5 mL for 20 min). Solutions were mixed with the resin by capping the column on both ends, and slowly agitating the column. Solutions were drained from the column using nitrogen pressure. After Fmoc deprotections, the resin was washed with DMF ($6 \times$ ca. 5 mL, 1 min each) and then CH_2Cl_2 $6 \times$ ca. 5 mL, 1 min each). Lysine residues were coupled to the resin by pre-activating Fmoc-Lys(Boc)-OH (47 mg, 0.10 mmol) with HCTU (41 mg, 0.10 mmol) in ca. 0.5 mL of 20% 2,4,6-collidine for 1 min and then adding the resultant solution to the resin and gently agitating the resin for ca. 2 h. Lysine couplings were determined to be complete by use of the ninhydrin test. Lys(DabcyI) residues were coupled to the resin by dissolving Fmoc-Lys(DabcyI)-OH (31 mg, 0.050 mmol) and HCTU (21 mg, 0.05 mmol) in ca. 0.5 mL of 20% 2,4,6-collidine–DMF, adding the resultant solution to the resin, and then gently agitating the resin for 6–12 h. $\text{Abc}^{2\text{K}}$ residues were coupled to the resin by pre-activating Fmoc- $\text{Abc}^{2\text{K(Boc)}}$ -OH (59 mg, 0.075 mmol) with HCTU (31 mg, 0.075 mmol) in ca. 0.5 mL of 20% 2,4,6-collidine–DMF. The coupling solution was then added to the resin and gently agitated for ca. 12 h. To determine if $\text{Abc}^{2\text{K}}$ couplings were complete, a small amount of resin was treated in a new Bio-Rad column with a solution of CF_3COOH /water (9/1, v/v) and the column was rigorously agitated for ca. 2 h. The solution was then drained, concentrated by rotary evaporation, and the residue was dissolved in a mixture of water and CH_3CN

and then injected into an analytical RP-HPLC instrument to determine if any remaining aniline was present. (If the uncoupled Abc^{2K} aniline was observed on the chromatograph, an additional coupling was carried out.) The Glu(EDANS) residue was coupled to the resin by pre-activating Fmoc-Glu(EDANS)-OH (220 mg, 0.35 mmol) with HCTU (145 mg, 0.35 mmol) in ca. 1 mL of 20% 2,4,6-collidine–DMF. The coupling solution was added to the resin and the resin was gently agitated for ca. 48 h. To avoid degradation of the EDANS group, Fmoc deprotections that followed the couplings of Fmoc-Glu(EDANS)-OH were accomplished by soaking the resin with a solution of DBU (1.2 mL) and HOBT (0.99 g) in DMF (88 mL) (4 × ca. 2 mL for 1 min each).⁶ The resin was then washed with DMF (6 × ca. 5 mL, 1 min each) and then CH₂Cl₂ 6 × ca. 5 mL, 1 min each). After the coupling of the final two lysine residues and removal of last Fmoc group using the above DBU procedure, the aniline was acetylated by the addition of acetic anhydride (7-10 drops) in ca. 2 mL of 20% 2,4,6-collidine–DMF and the resin was gently agitated for 10 min. After the resin was soaked with DMF (4 × ca. 5 mL, for 1 min) and CH₂CH₂ (6 × ca. 5 mL, for 1 min), the resin was then transferred to a small round bottomed flask equipped with a magnetic stirring bar, and mixed with 10-20 mL of CF₃COOH/water (9/1, v/v) for 4 h while being protected from light sources. The resin was then filtered off using a fritted funnel, washed with additional cleavage cocktail, concentrated by rotary evaporation, and the resultant oil was dissolved in a mixture of water and CH₃CN. The oligomer was purified by preparative RP-HPLC (water–CH₃CN buffers with 0.1 % TFA). (The oligomers typically eluted between 20 and 30% CH₃CN). Pure fractions of the product were concentrated by rotary evaporation to remove most of

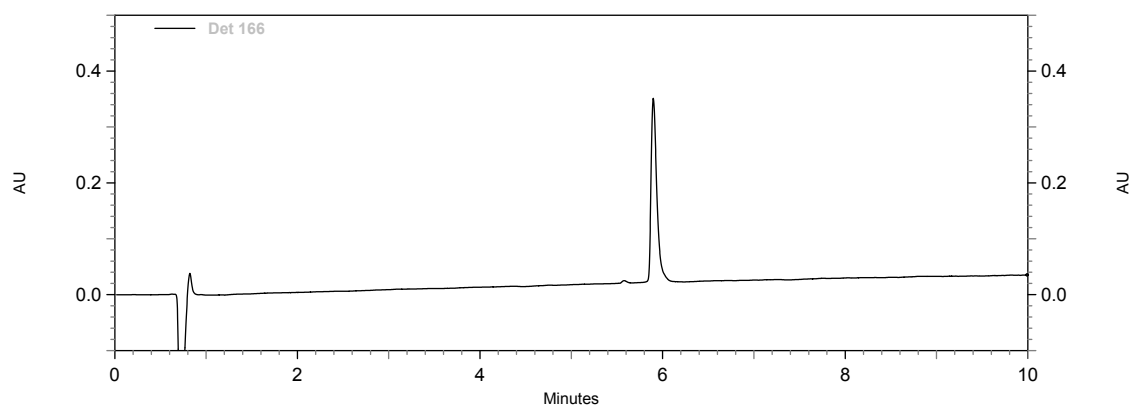
⁶ Tickler, A. K.; Barrow, C. J.; Wade, J. D. *J. Pept. Sci.* **2001**, 7, 488.

the CH₃CN, frozen, and then lyophilized to afford a red powder (5–10 mg). The remaining less pure HPLC fractions were also lyophilized into a red powder (5–10 mg) and stored for future use.

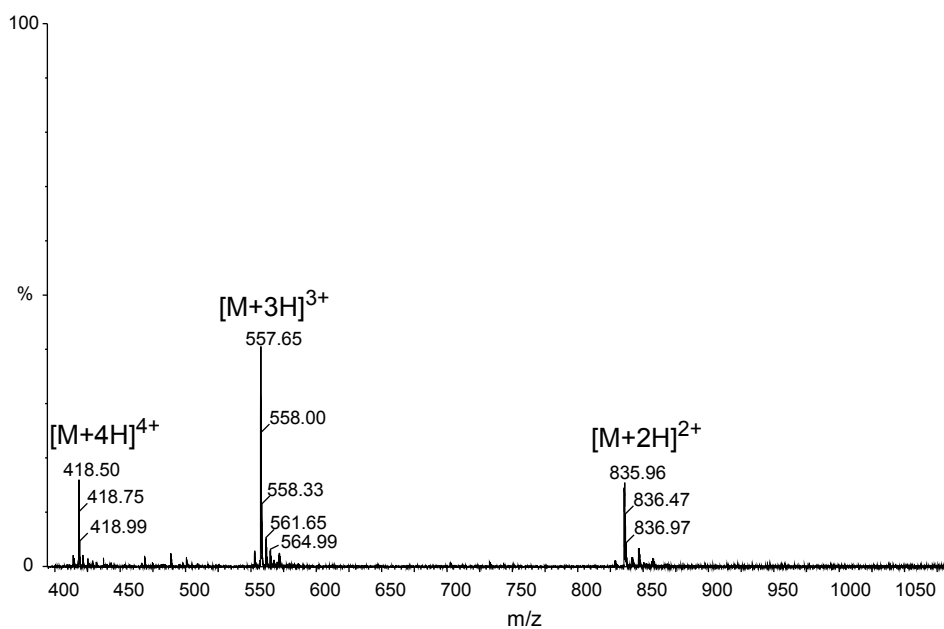
Ac-Lys-Lys-Glu(EDANS)-(Abc^{2K})₁-Lys(DabcyI)-Lys-Lys-NH₂ TFA salt **10a**
Analytical RP-HPLC chromatograph and mass spectrum (ESI-MS)



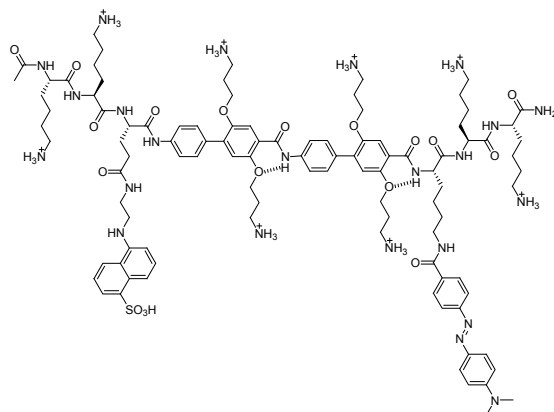
(a) Analytical RP-HPLC (5-50% acetonitrile with 0.1% TFA over 10 min, $\lambda = 214$)



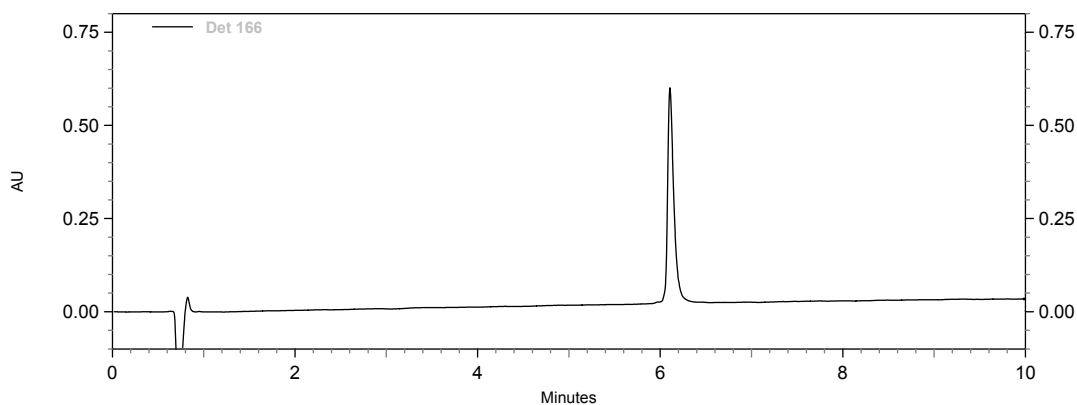
(b) ESI Mass spectrum. (Calcd exact mass for C₈₃H₁₂₀N₂₀O₁₅S [M] = 1668.90)



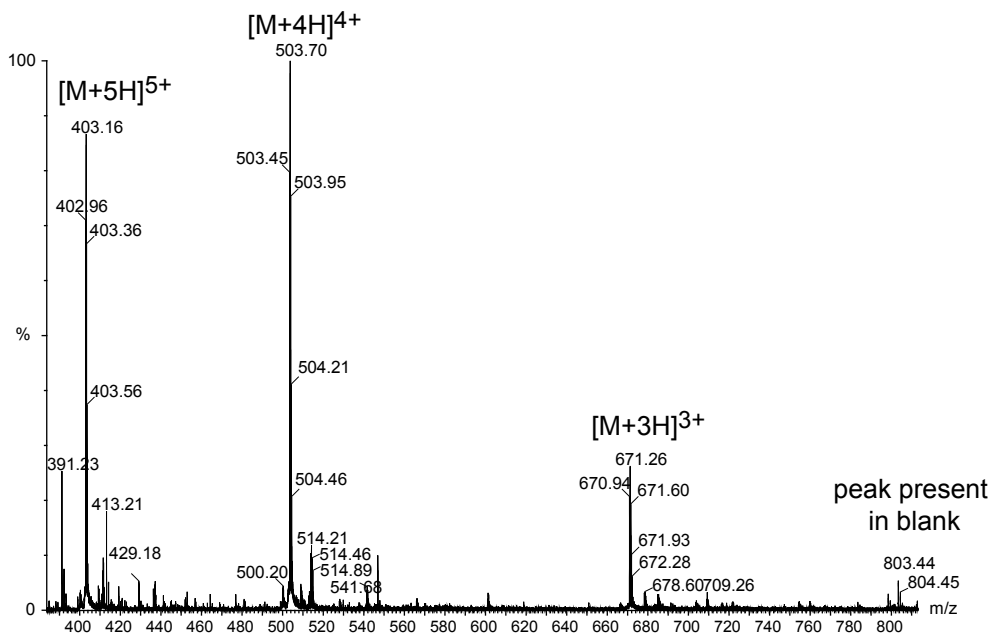
Ac-Lys-Lys-Glu(EDANS)-(Abc^{2K})₂-Lys(DabcyI)-Lys-Lys-NH₂ TFA salt **10b**
 Analytical RP-HPLC chromatograph and mass spectrum (ESI-MS)



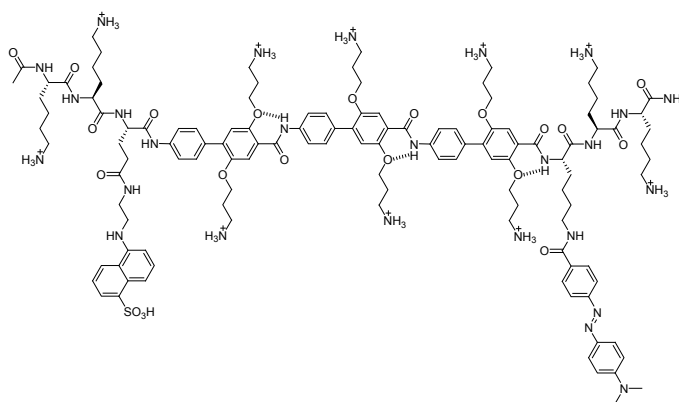
(a) Analytical RP-HPLC (5-50% acetonitrile with 0.1% TFA over 10 min, $\lambda = 214$)



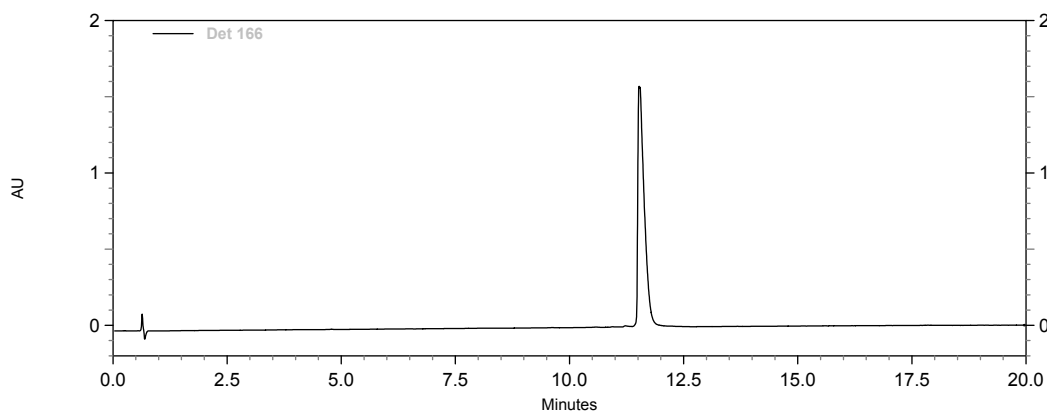
(b) ESI Mass spectrum. (Calcd exact mass for C₁₀₂H₁₄₃N₂₃O₁₈S [M] = 2011.44)



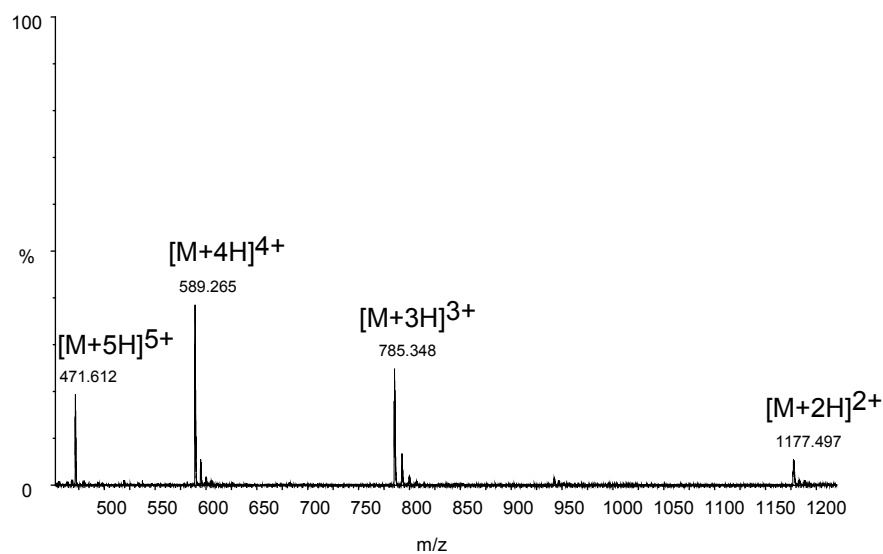
Ac-Lys-Lys-Glu(EDANS)-(Abc^{2K})₃-Lys(Dabcyl)-Lys-Lys-NH₂ TFA salt **10c**
Analytical RP-HPLC chromatograph and mass spectrum (ESI-MS)



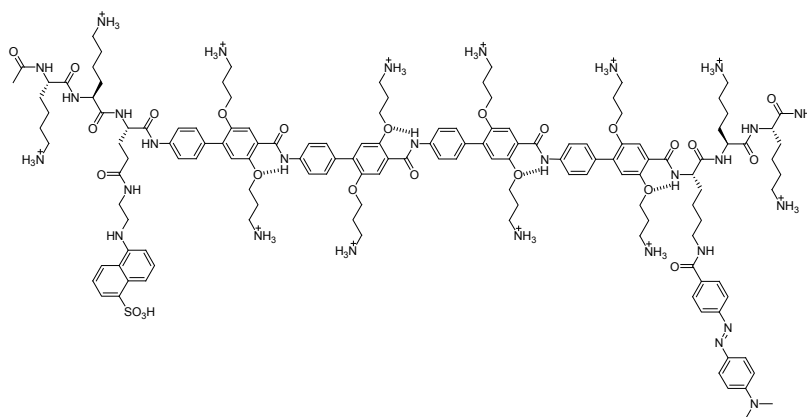
(a) Analytical RP-HPLC (5-50% acetonitrile with 0.1% TFA over 20 min, $\lambda = 214$)



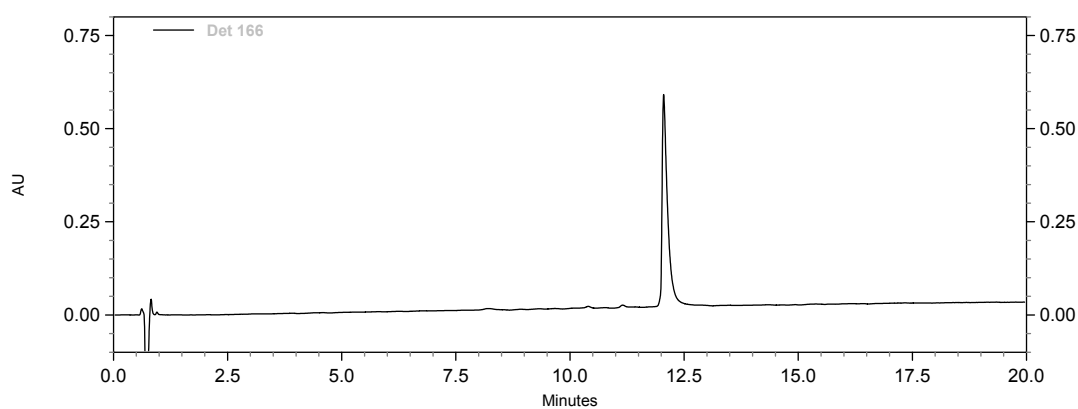
(b) ESI Mass spectrum. (Calcd mass exact for C₁₂₁H₁₆₆N₂₆O₂₁S [M] = 2351.24)



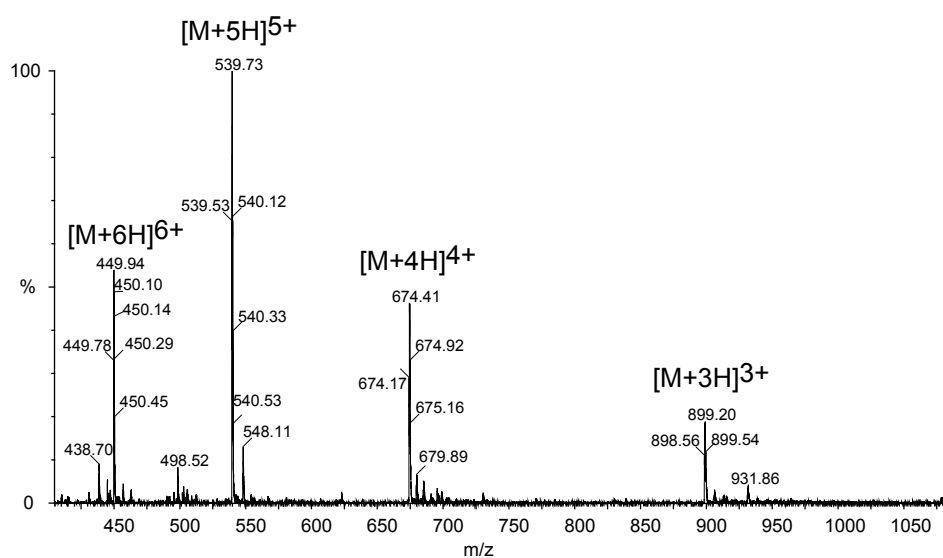
Ac-Lys-Lys-Glu(EDANS)-(Abc^{2K})₄-Lys(DabcyI)-Lys-Lys-NH₂ TFA salt **10d**
Analytical RP-HPLC chromatograph and mass spectrum (ESI-MS)



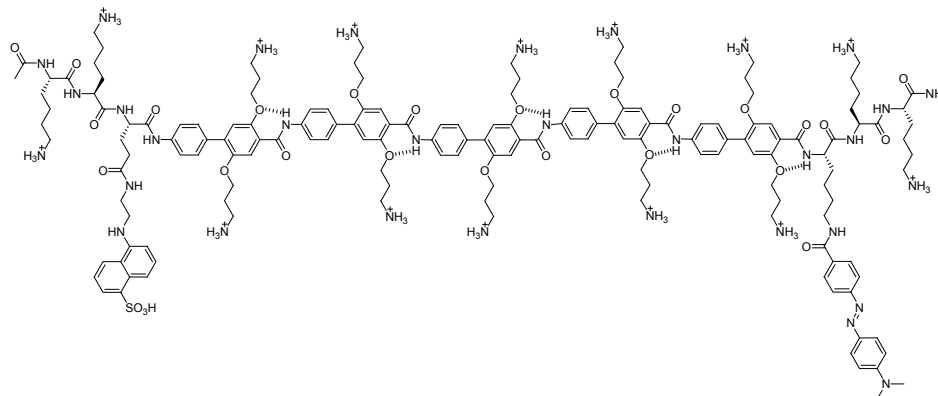
(a) Analytical RP-HPLC (5-50% acetonitrile with 0.1% TFA over 20 min, $\lambda = 214$)



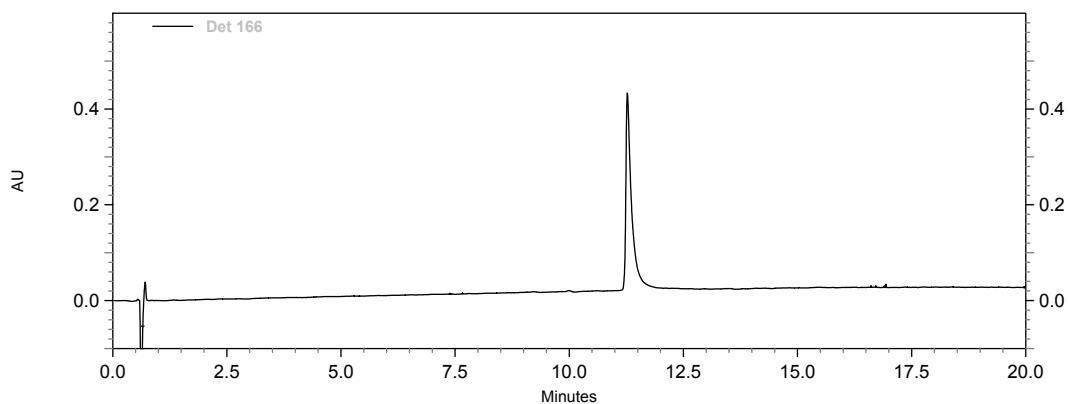
(b) ESI Mass spectrum. (Calcd exact mass for C₁₄₀H₁₈₉N₂₉O₂₄S [M] = 2692.42)



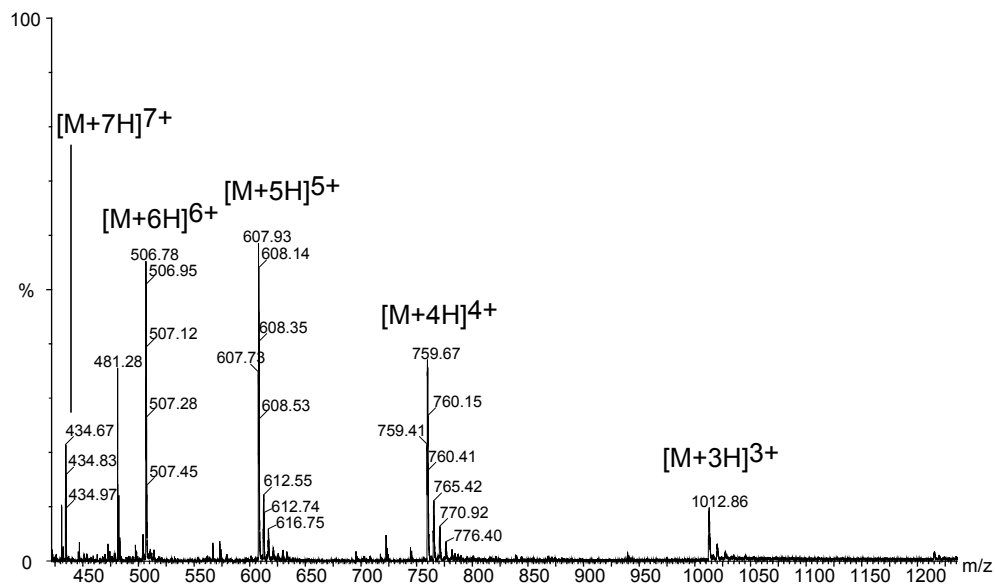
Ac-Lys-Lys-Glu(EDANS)-(Abc^{2K})₅-Lys(DabcyI)-Lys-Lys-NH₂ TFA salt **10e**
 Analytical RP-HPLC chromatograph and mass spectrum (ESI-MS)



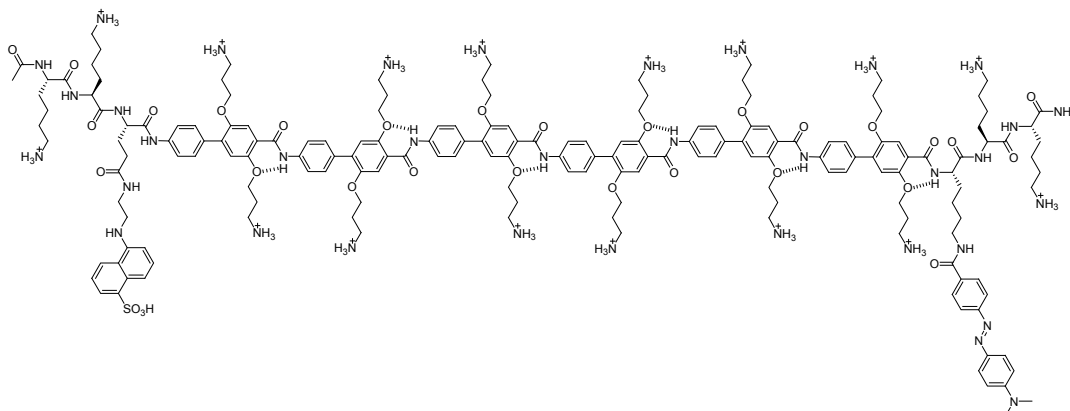
(a) Analytical RP-HPLC (5-50% acetonitrile with 0.1% TFA over 20 min, $\lambda = 214$)



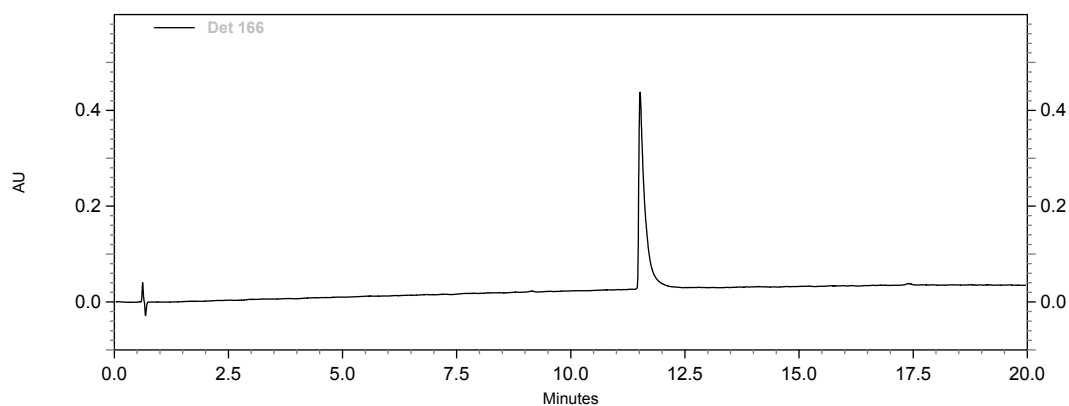
(b) ESI Mass spectrum. (Calcd exact mass for C₁₅₉H₂₁₂N₃₂O₂₇S [M] = 3033.59)



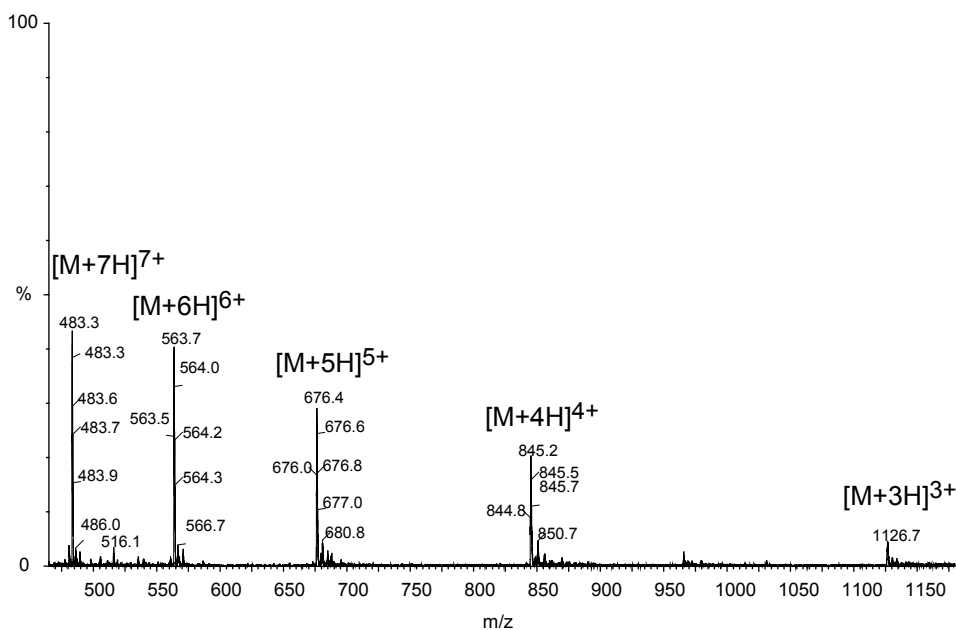
Ac-Lys-Lys-Glu(EDANS)-(Abc^{2K})₆-Lys(DabcyI)-Lys-Lys-NH₂ TFA salt **10f**
Analytical RP-HPLC chromatograph and mass spectrum (ESI-MS)



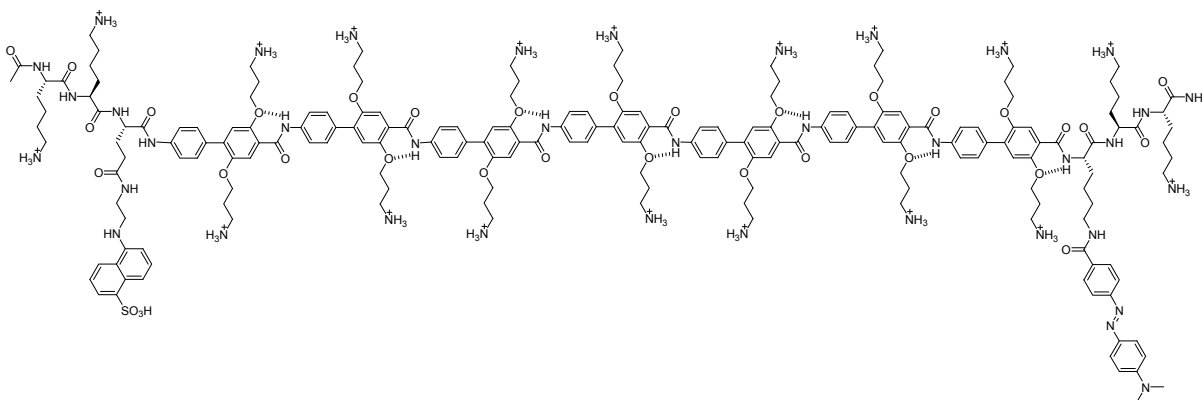
(a) Analytical RP-HPLC (5-50% acetonitrile with 0.1% TFA over 20 min, $\lambda = 214$)



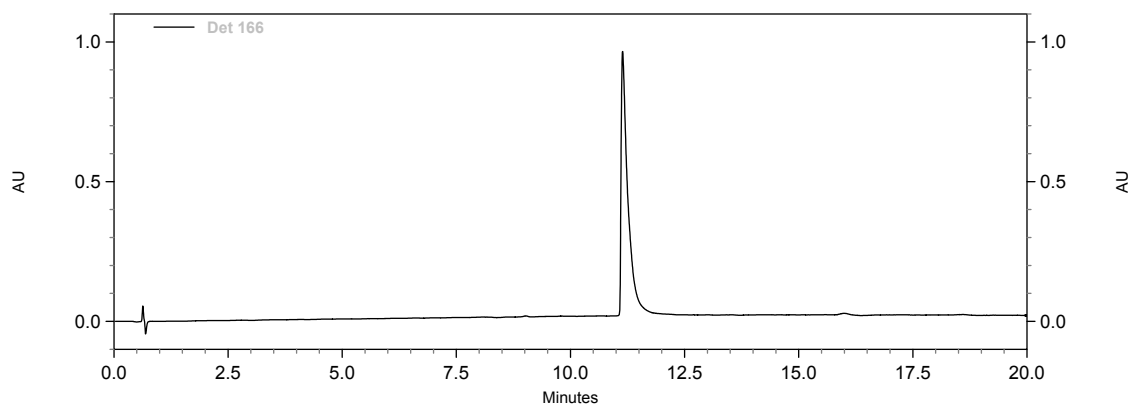
(b) ESI Mass spectrum. (Calcd exact mass for C₁₇₈H₂₃₅N₃₅O₃₀S [M] = 3374.77)



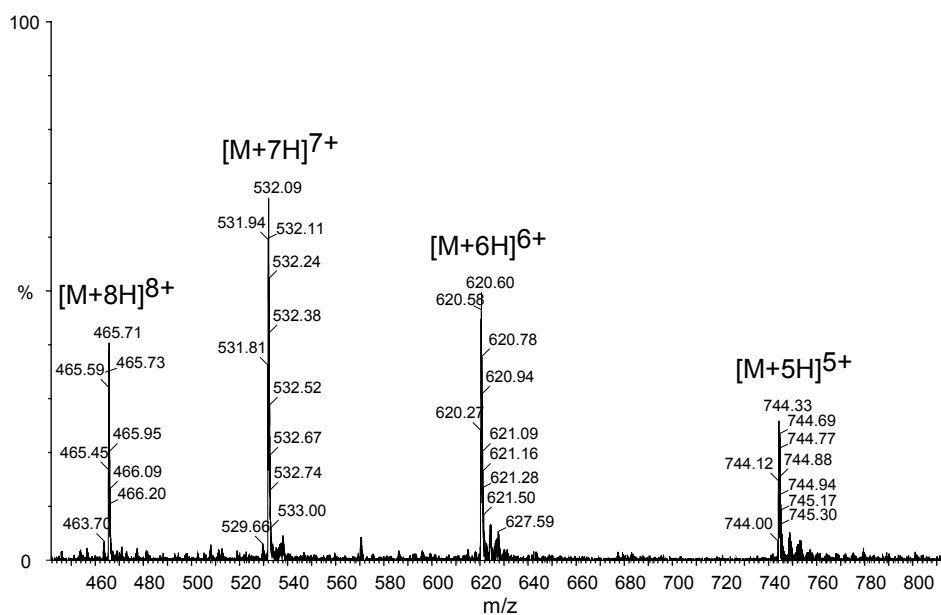
Ac-Lys-Lys-Glu(EDANS)-(Abc^{2K})₇-Lys(DabcyI)-Lys-Lys-NH₂ TFA salt (**10g**)
Analytical RP-HPLC chromatograph and mass spectrum (ESI-MS)



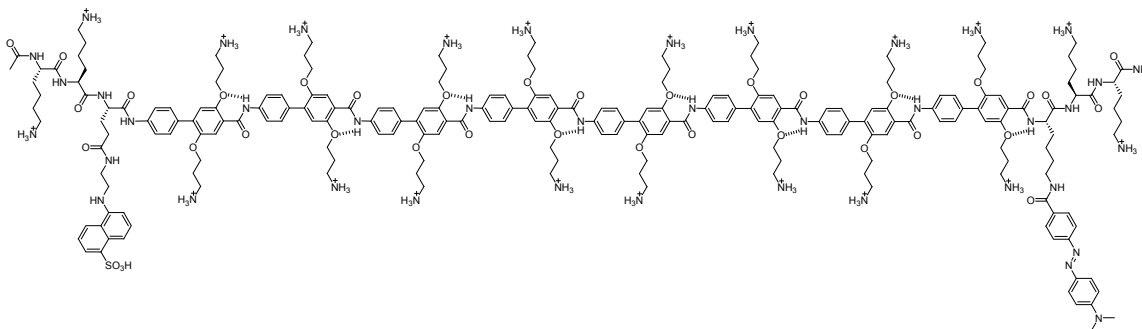
(a) Analytical RP-HPLC (5-50% acetonitrile with 0.1% TFA over 20 min, $\lambda = 214$)



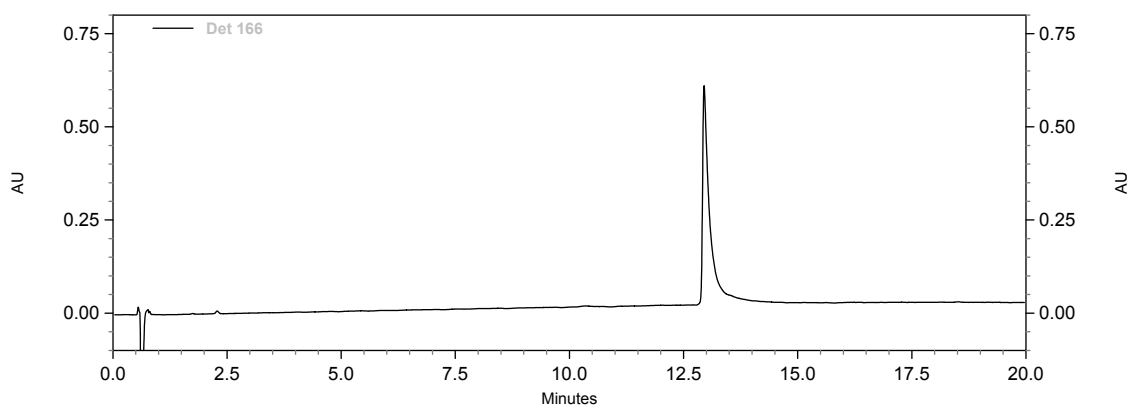
(b) ESI Mass spectrum. (Calcd exact mass for C₁₉₇H₂₅₈N₃₈O₃₃S [M] = 3715.94)



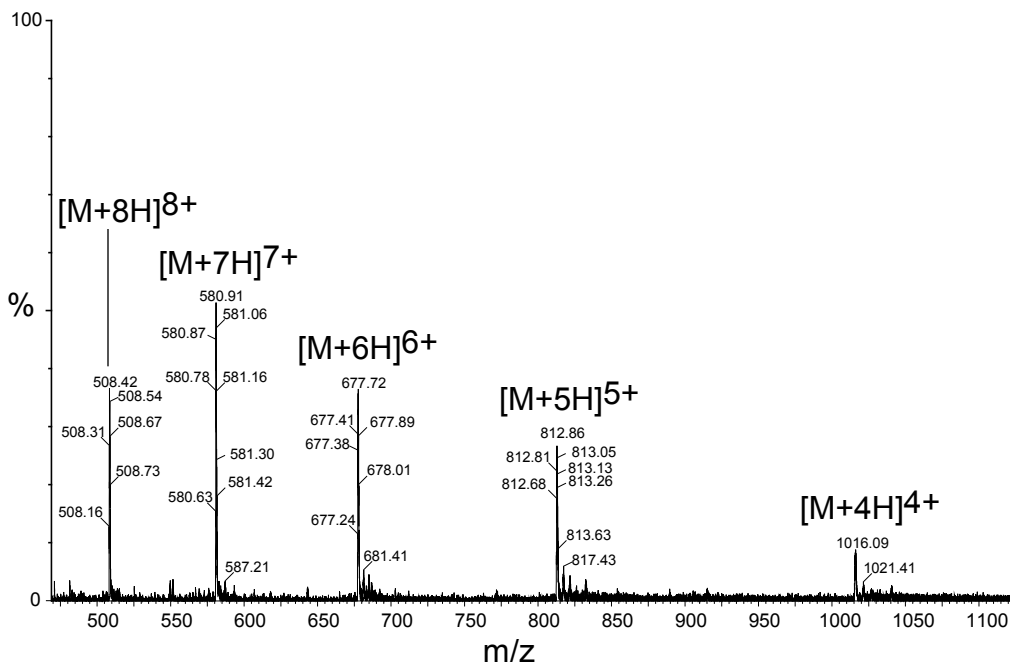
Ac-Lys-Lys-Glu(EDANS)-(Abc^{2K})₈-Lys(DabcyI)-Lys-Lys-NH₂ TFA salt **10h**
Analytical RP-HPLC chromatograph and mass spectrum (ESI-MS)



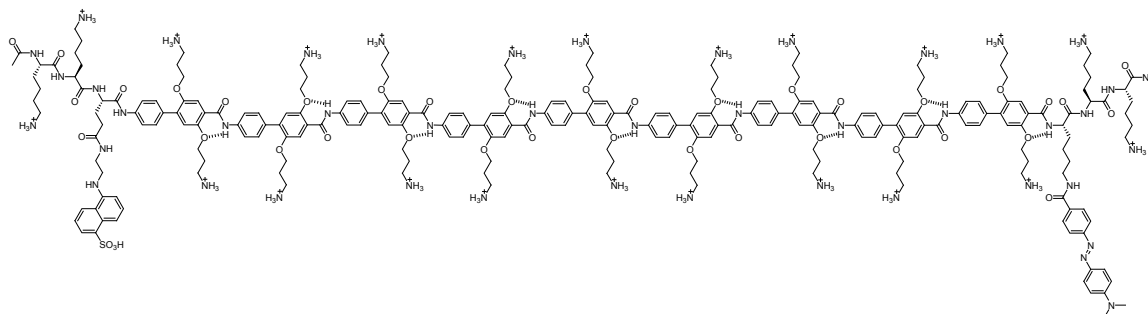
(a) Analytical RP-HPLC (5-50% acetonitrile with 0.1% TFA over 20 min, $\lambda = 214$)



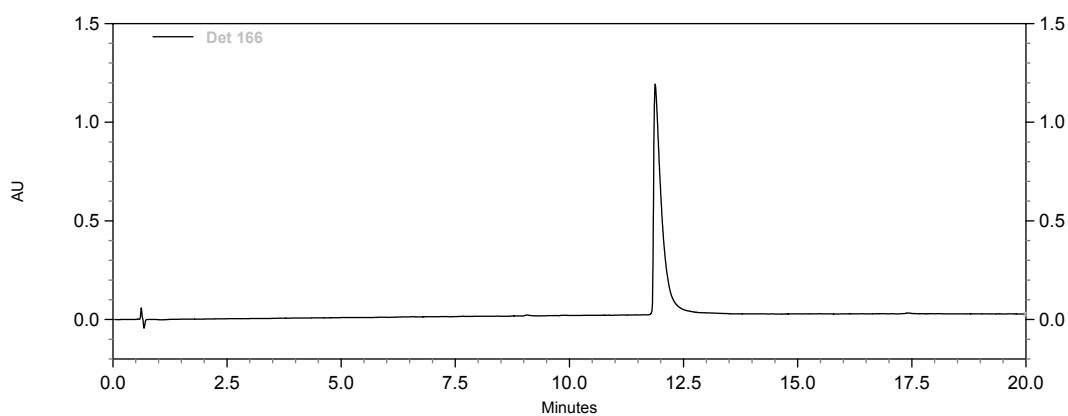
(b) ESI Mass spectrum. (Calcd exact mass for C₂₁₆H₂₈₁N₄₁O₃₆S [M] = 4057.11)



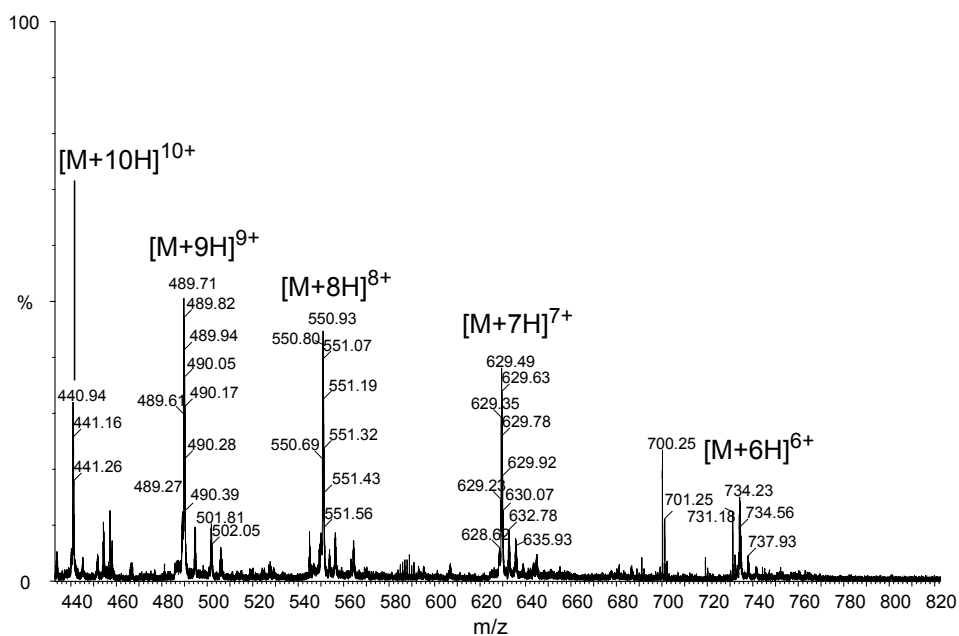
Ac-Lys-Lys-Glu(EDANS)-(Abc^{2K})₉-Lys(Dabcyl)-Lys-Lys-NH₂ TFA salt **10i**
Analytical RP-HPLC chromatograph and mass spectrum (ESI-MS)



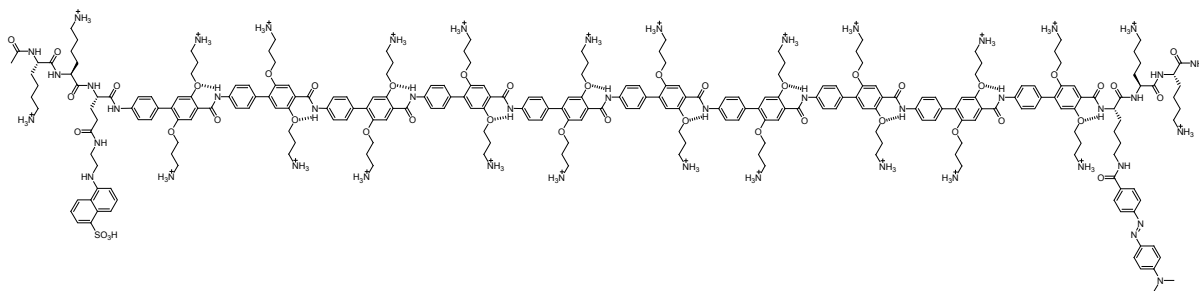
(a) Analytical RP-HPLC (5-50% acetonitrile with 0.1% TFA over 20 min, $\lambda = 214$)



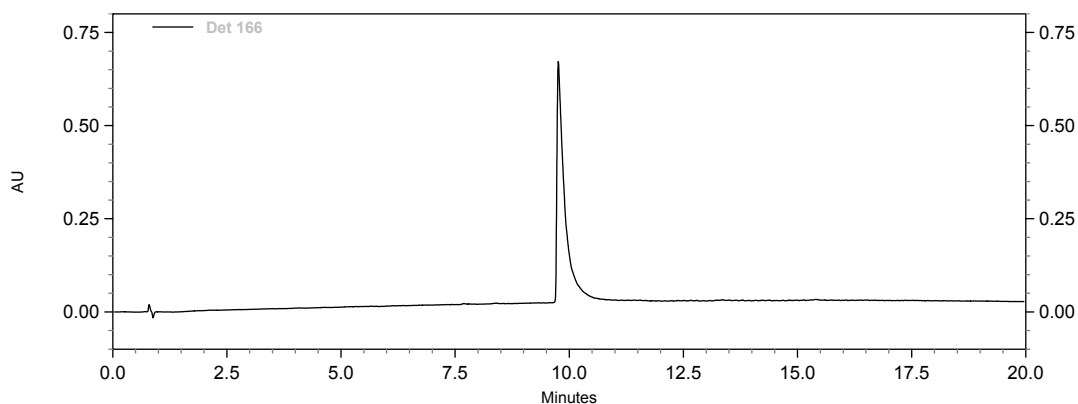
(b) ESI Mass spectrum. (Calcd exact mass for C₂₃₅H₃₀₄N₄₄O₃₉S [M] = 4398.29)



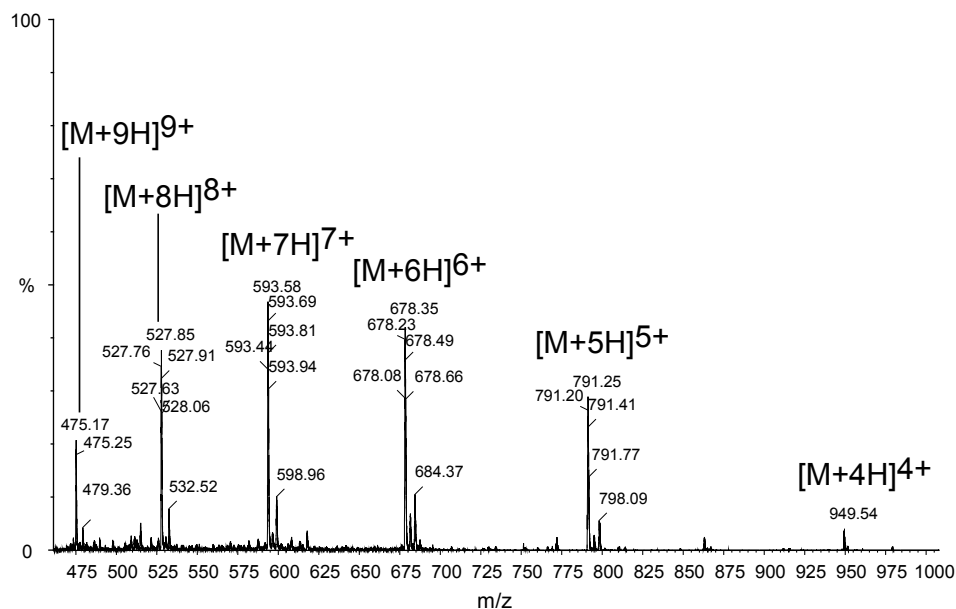
Ac-Lys-Lys-Glu(EDANS)-(Abc^{2K})₁₀-Lys(Dabcyl)-Lys-Lys-NH₂ TFA salt **10j**
Analytical RP-HPLC chromatograph and mass spectrum (ESI-MS)



(a) Analytical RP-HPLC (5-50% acetonitrile with 0.1% TFA over 20 min, $\lambda = 214$)

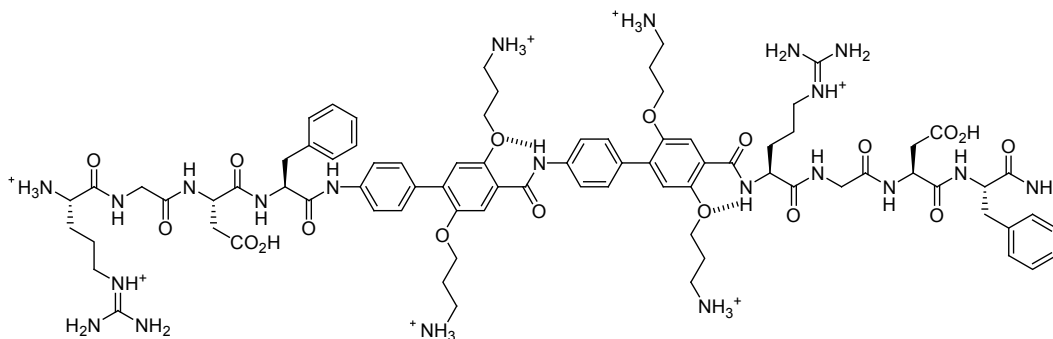


(b) ESI Mass spectrum. (Calcd exact mass for C₂₅₄H₃₂₇N₄₇O₄₂S [M] = 4739.46)

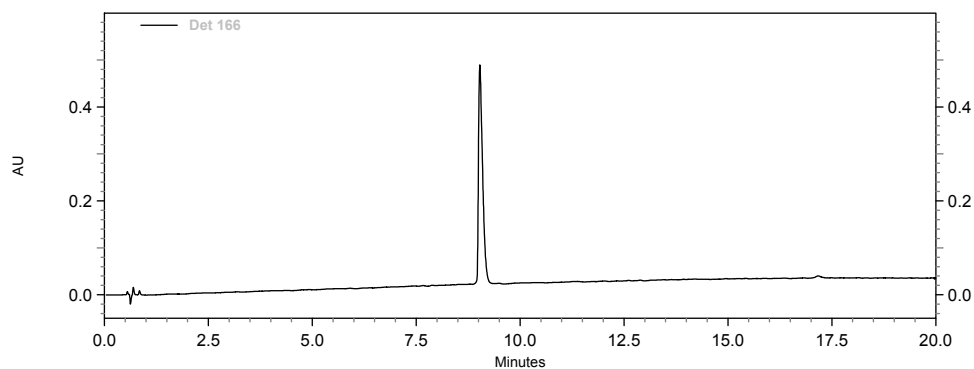


Synthesis of H-Arg-Gly-Asp-Phe-(Abc^{2K})₂-Arg-Gly-Asp-Phe-NH₂ (11). Rink amide MBHA resin (59 mg, 0.34 mmol/g, Novabiochem) contained in Bio-Rad Poly-Prep chromatography column was soaked with DMF (3 × ca. 5 mL, 1 min each) and drained under nitrogen pressure. Fmoc deprotection was carried out by soaking the resin with a solution of 20% piperidine–DMF (1 × ca. 5 mL for 1 min, 1 × ca. 5 mL for 20 min) and gently agitating the resin. After deprotection of the Fmoc group, the resin was soaked with DMF (5 × ca. 3 mL for 1 min) and CH₂Cl₂ (5 × ca. 3 mL for 1 min). Standard amino acids were coupled to the resin using 4 equiv with HCTU (4 equiv) in a ca. 1-mL solution of 20% 2,4,6-collidine–DMF, and the resin was gently agitated for 2–4 h (or in some cases was allowed to couple overnight). Fmoc-Abc^{2K(Boc)}-OH (**1**) was coupled to the resin using 2 equiv with HCTU (2 equiv) in a ca. 1-mL solution of 20% 2,4,6-collidine–DMF. The solution was added to the resin and the resin was gently agitating for 4–12 h. Couplings to the α-amino groups of standard amino acids were monitored by the ninhydrin test to determine coupling completeness. Couplings to the aniline amino groups of Abc^{2K} were not monitored and assumed to be complete. The peptide was cleaved from resin using 10–20 mL of CF₃COOH/water/triisopropylsilane (8/1/1, v/v/v) and mixed for ca. 6 h. Purification was accomplished using preparative RP-HPLC (water–CH₃CN buffers with 0.1 % TFA) and resulted in a yield of 12 mg (29%) of peptide **11**. (The 12 mg of peptide **11** had a purity of >99% and the 29% yield does not include the HPLC fractions that showed a purity level of 95%.)

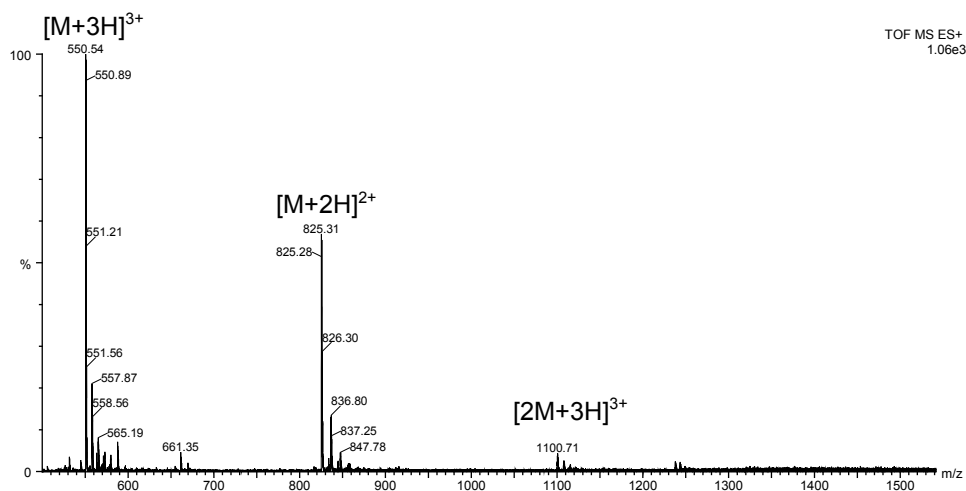
H-Arg-Gly-Asp-Phe-(Abc^{2K})₂-Arg-Gly-Asp-Phe-NH₂ TFA salt (**11**) Analytical RP-HPLC chromatograph and mass spectrum (ESI-MS)



(a) Analytical RP-HPLC (5-50% acetonitrile with 0.1% TFA over 20 min, $\lambda = 214$)



(b) ESI Mass spectrum. (Calcd exact mass for C₈₀H₁₀₇N₂₁O₁₈ [M] = 1649.81)



H-Arg-Gly-Asp-Phe-(Abc^{2k})₂-Arg-Gly-Asp-Phe-NH₂ TFA salt 11

Supporting Information

Current Data Parameters
 USER cgotha
 NAME c3-10-290
 EXPNO 2
 PROCNO 1

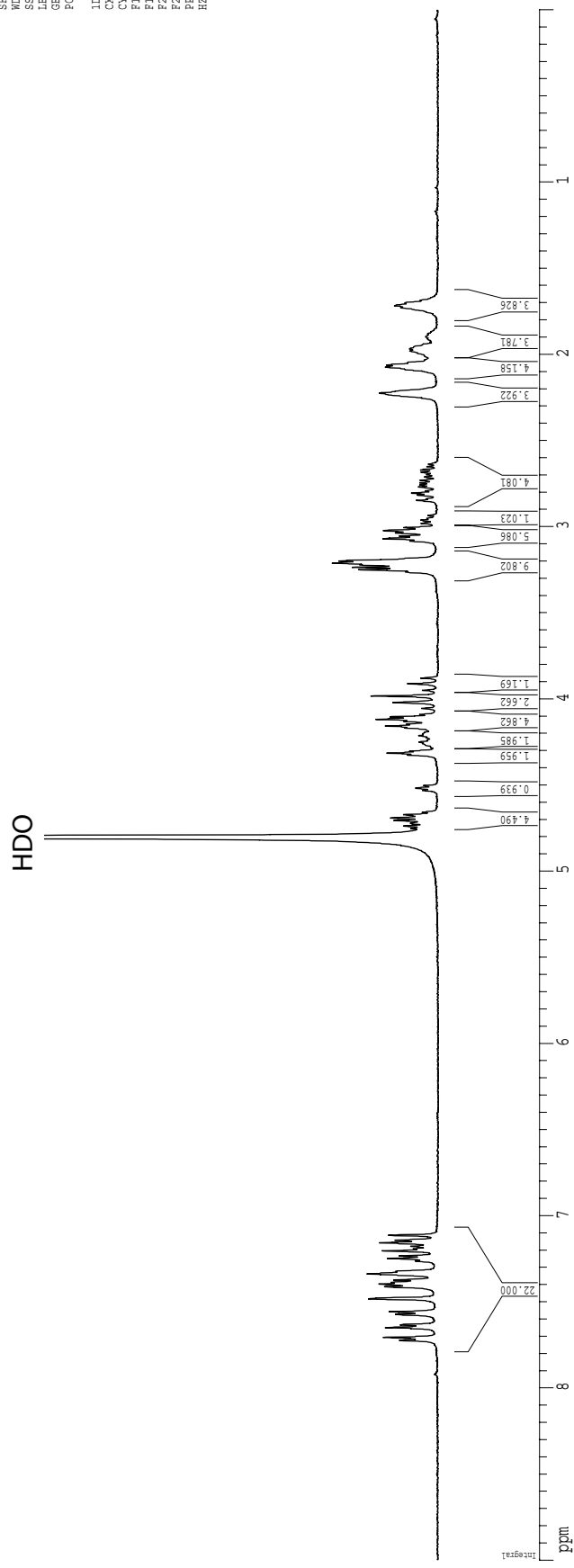
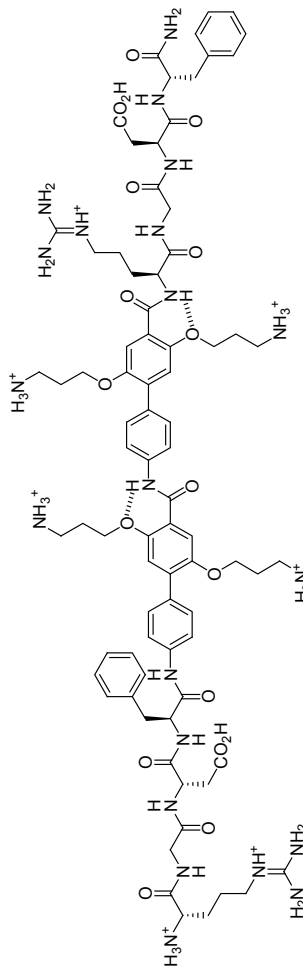
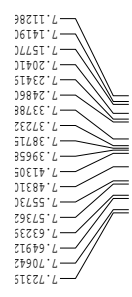
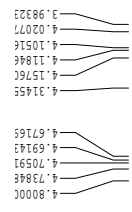
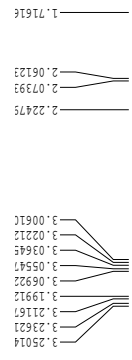
F2 - Acquisition Parameters
 Date_ 20070120
 Time 15:42
 INSTRON cryos00
 PROBHD 5 mm CPCL1 H-
 PULPROG zgpg30
 TD 81738
 SFO1 500.1350000 MHz
 SOLVENT D₂O
 NS 128
 DS 2
 SWH 8012.820 Hz
 FIDRES 0.098043 Hz
 AQ 5.0989774 sec
 RG 6.3
 DM 62.400 usec
 DE 6.00 usec
 TE 298.0 K
 TL 0.1000000 sec
 ACQST 0.0100000 sec
 MCWK 0.01500000 sec

===== CHANNEL f1 =====
 NUC1 ¹H
 P1 8.00 usec
 PL1 1.60 dB
 SFO1 500.2235015 MHz

F2 - Processing parameters
 SI 65536
 SF 500.2200014 MHz
 MDW EN
 USB 0 Hz
 GB 0
 PC 4.00

1D NMR plot parameters
 CX 22.80 cm
 CY 97.22 cm
 F1P 9.000 ppm
 F1 4501.98 Hz
 F2P 0.000 ppm
 F2 0.00 Hz
 PRCN 0.39474 ppm/cm
 HZCN 197.45528 Hz/cm

Gothard, J. S. Nowick



FRET Experiments. Fluorescence resonance energy transfer studies on labeled Abc^{2K} oligomers, Ac-(Lys)₂-Glu(EDANS)-(Abc^{2K})_n-Lys(Dabcyl)-(Lys)₂-NH₂ (n=1–10), were carried out using a Hitachi F-4500 Fluorescence Spectrophotometer. Concentrations for initial stock solutions were determined spectrophotometrically based on the extinction coefficient of Dabcyl ($\epsilon = 32,000$). Serial dilutions were carried out on the stock solutions to make 1.75 μM (water/DMSO 1/1) solutions. Samples were excited at 335 nm and their fluorescence was observed from 400 to 600 nm. Additional instrument parameters were set as follows: excitation slit (nm) = 10, emission slit (nm) = 10, PMT voltage (V) = 700, response (sec.) = auto, shutter control = on, scan speed = 60.

FRET Experiments of Compounds 10a-10j.

