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A Quantitative Investigation of the Water-Solubilizing Properties of Branched Oligoglycerols

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Water solubility and partition-coefficient measurements have been conducted on already known monobenzoylated octamethylenediamine-containing branched oligoglycerols. A new oligoglycerol, a hexamer bearing eight primary hydroxy groups, has also been prepared and its properties examined. Water solubility was found to increase in an approximately geometric progression with the number of hydroxy groups and the water solubility of the hexamer derivative was at least half a million times greater than that of the propanamide derivative.

Introduction

Water solubility is a frequent requirement of compounds for medicinal use. To administer poorly water-soluble compounds, the usual method is to pretreat the compound with amphiphilic materials[1] to form a solid dispersion,[1a,1b] an inclusion complex,[1c,1d] micelles,[1e,1f] liposomes,[1g,1h] or a nanosuspension,[1i,1j] and much research has been carried out in this area. Most of these publications describe the utilization of weak noncovalent interactions, but there have been few reviews on water solubilization by covalent bond formation with hydrophilic moieties.[2] However, for example, papers on the chemical modification of a famous anticancer agent, paclitaxel,[3] by covalent bond formation with carboxylate,[4] poly(ethylene glycols),[5] or saccharides[6] have recently been published independently. Oligoglycerols[7,8] can be classified among these water-solubilizing agents. We have developed a series of water-solubilizing agents, branched glycerols (BGLs),[9] and demonstrated the synthesis and properties of compounds bearing these moieties.[9–17] As shown in Scheme 1, a lipophilic material **5** undergoing BGL modification can be converted into the water-soluble analogue **1** or **2**.

We have applied the methodology shown in Scheme 1 to a 1,2-dicarbadodecaborane(12) derivative, which is an extremely water-insoluble boron cluster.[9–12] The synthesis[13,14] of water-soluble *p*-boronophenylalanines[14] and studies of their effects on melanoma cells[15,16] have also been carried out and liposomes constructed with modified β-cholestanol using **1** or **2** have been prepared.[17] Throughout these studies, we found that not only was BGL modification helpful in increasing water solubility, but it also changed the pharmacokinetic and/or pharmacodynamic behavior of the original material **5**.

BGLs are designed to have certain characteristic chemical features: (1) BGL derivatives such as **1** or **2** are water-soluble under a wider range of pH conditions than compounds possessing ammonium cations or sulfonate anions because of the number of neutral functionalities (hydroxy groups); (2) BGL derivatives possess polar primary hydroxy groups that cause dissolution in water more effectively than the ether functionality in poly(ethylene glycols); (3) because the BGL moiety has no asymmetric center,[18] a water-soluble derivative such as **1** or **2** cannot be a mixture of diastereomers even if the target molecule **5** contains asymmetric center(s). We have devoted considerable effort to increasing the number of concrete examples of BGL modification. However, until now, a systematic and quantitative review of water solubilization by BGL modification has not been carried out.

Furthermore, the partition coefficients of BGL-modified molecules have not been measured until now. Although water solubilization is useful as a practical technology for many different purposes, we concentrate here on its application in medicinal uses. It is well known that extreme water solubility in certain medicinal compounds can result in a disturbance of the membrane permeation process. For this reason, the regulation of water solubility is important in terms of both administration and permeation.[19] Therefore, it is desirable to know the partition coefficients of BGL-modified compounds.

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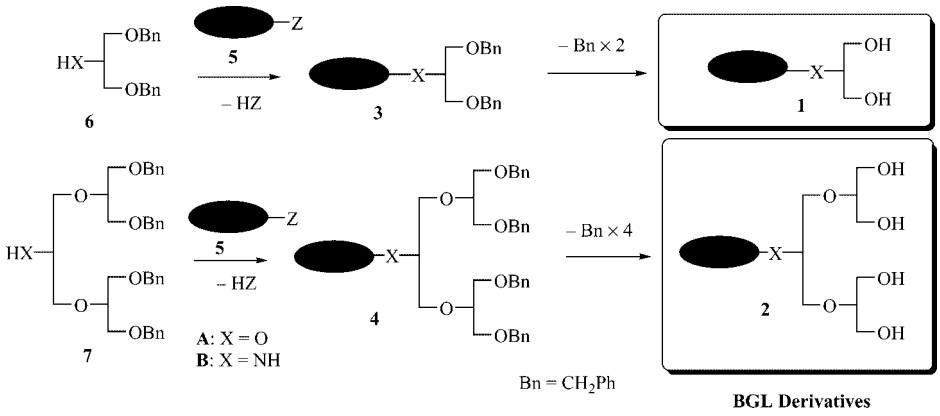


Scheme 1. General scheme of BGL modification.

Results and Discussion

In this paper we report the quantitative values of the water solubility and the partition coefficients of BGL derivatives and related compounds. Monobenzoylated octamethylenediamine (**8**) was chosen[20,21] as a representative example (Scheme 2). The derivatives **16**–**19**, prepared with the purpose of measuring water-solubilizing properties, are shown in a rectangular frame in Scheme 2. In addition, propanamide **10**, a non-hydroxylated derivative, and the hydrochloride salt **9** were examined for comparison.

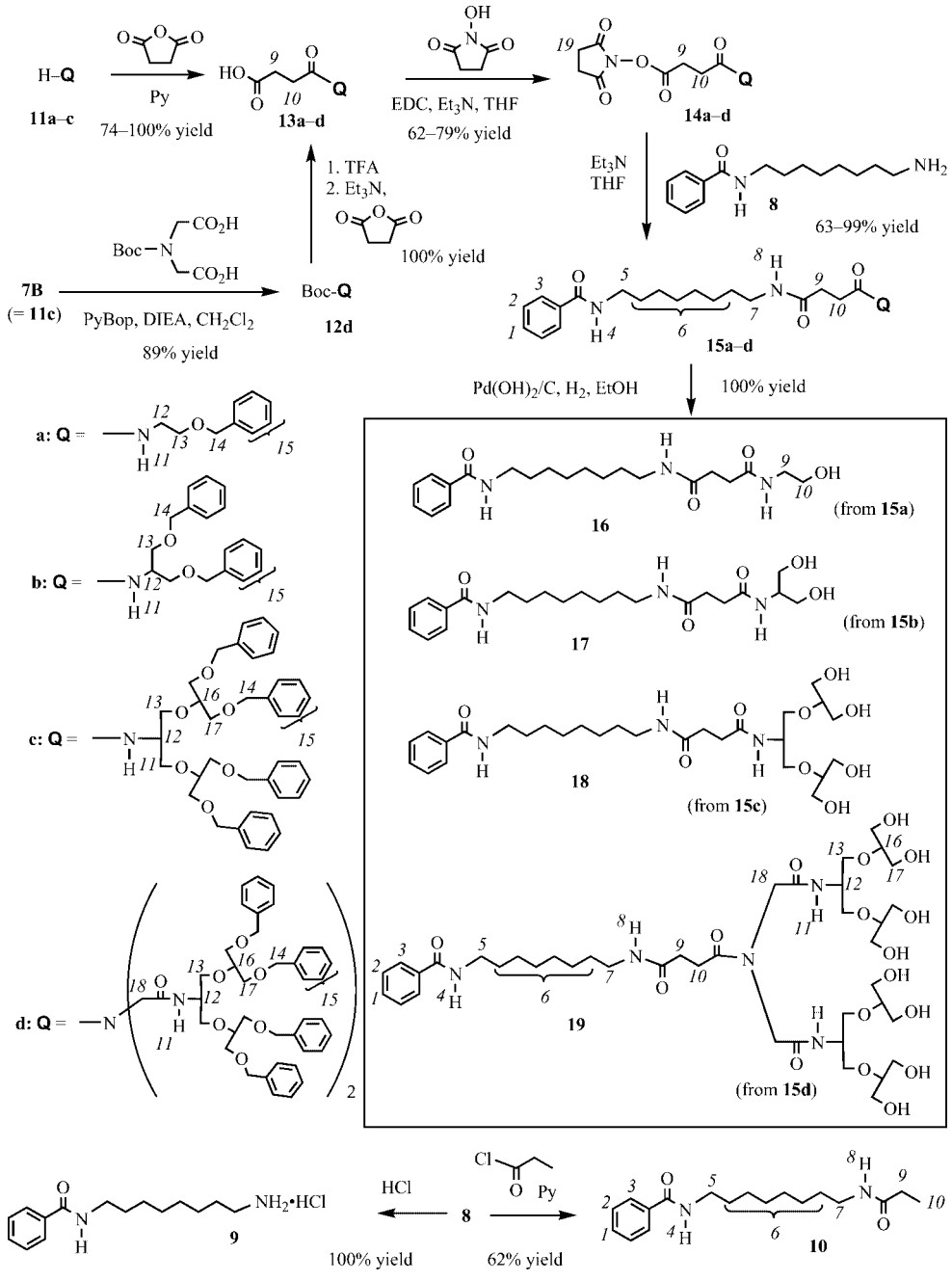
Synthesis

Benzamide **8** was prepared according to the previously reported method.[21] Propanamide **10** was prepared from **8** and propionyl chloride with pyridine (Py). *O*-Benzylethanolamine (**11a**) was converted into **13a** by reaction with succinic anhydride in pyridine. Carboxylic acid **13a** was converted into **14a** by using *N*-hydroxysuccinimide (HOSu), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC), and triethylamine (Et_3N) in THF (reaction C). Amide **15a** was obtained from the condensation reaction between **14a** and **8** in THF. Reductive debenzylation of benzyl ether **15a** in the presence of a catalytic amount of palladium hydroxide (10% on carbon) [$Pd(OH)_2$/C] in methanol under hydrogen afforded **16**. Diol **17** and **18** were obtained starting from **11b** (= **6B**)[13] and **11c** (= **7B**),[9] respectively, in the same manner. A condensation reaction between *N*-*tert*-butyloxycarbonylated iminodiacetic acid [Boc-$N(CH_2CO_2H)_2$][8c] and **7B** (= **11c**)[9] was carried out with (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) and *N*,*N*-diisopropylethylamine (DIEA) to afford octabenzyl ether[22] **12d**. Deprotection of Boc in **12d** was carried out with trifluoroacetic acid (TFA) in dichloromethane (CH_2Cl_2) followed by the removal of TFA by the usual extraction procedure to afford the crude amine, which was converted into **13d** using succinic anhydride and pyridine. Octaol **19** was obtained from **13d** in the same manner as **16** from **13a**.

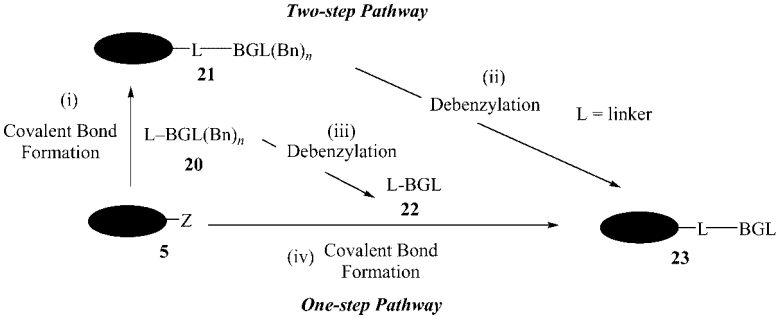
An Alternative BGL Modification Pathway

The procedure in Scheme 2 was outlined from the viewpoint of the BGL moiety. From the viewpoint of the compound undergoing BGL modification, however, **8** was converted into **16**–**19** in two steps: (i) covalent bond formation (condensation of $–NH_2$ and $–CO_2Su$) and (ii) deprotection of the resulting benzyl ethers **15a**–**15d**. This two-step pathway, (i) + (ii), is conceptualized in the upper part of Scheme 3. We employed this pathway, starting from **8** (corresponding to **5**) and yielding **15a**–**15d** (corresponding to **20**) as **8** fortunately contains no functionalities that are sensitive to debenzylation conditions. Furthermore, complete purification of **15a**–**15d** (corresponding to **21**) was easily carried out just prior to the formation of the final product **23**. However, if **5** contains sensitive functional groups such as a benzylic ether, a benzylic amine, an unsaturated bond, or an S–S bond, an alternative method for the synthesis of **23** from **5** must be developed. Although replacement of the benzyl protecting group with a different type of protecting group is a practical way of solving this problem, a judicious choice of protecting group may often be made to suit each occasion.

Hence, we also examined the one-step pathway (iv) from **5** to **23**, as shown in the lower part of Scheme 3. Once **22** has been independently prepared in advance by step (iii), the final target **23** can be obtained from **5** in one step. As a representative example, we demonstrated the synthesis of **19** (corresponding to **23**) starting from **14d** (corresponding to **22**) (Scheme 4): the four benzyl groups of **14d** were deprotected in the presence of a catalytic amount of $Pd(OH)_2$/C in ethanol under hydrogen at room temperature to afford **24** in quantitative yield. Note that the N–O bond of the OSu moiety was not affected at all. A condensation

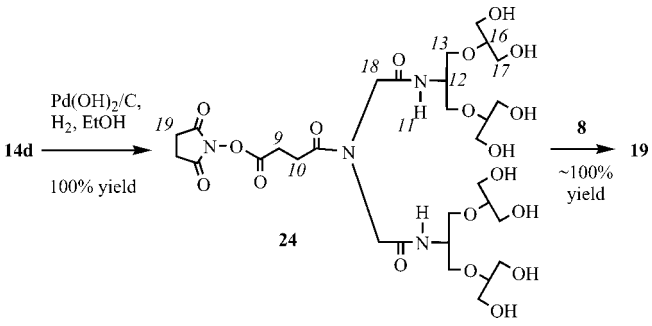


Scheme 2.



Scheme 3. Two pathways for the BGL modification of **5**.

reaction between **8** and **24** afforded **19** in excellent yield. Accordingly, either one- or two-step BGL modification can be chosen depending on the situation.



Scheme 4.

Measurement of Water-Solubilizing Properties and Partition Coefficients

Each compound (**9**, **10**, and **16**–**19**) was placed in an appropriate amount of water and the mixture was shaken well for half an hour. The resulting suspension was allowed to stand for half an hour and then filtered using a membrane filter (pore size 0.45 μM) to remove excess solute, including invisible tiny grains and any micelles that may have formed. Each filtrate, which consisted of a saturated solution, was diluted with water to prepare a solution of appropriate concentration for measuring the strength of ultraviolet absorption at 256 nm by the benzamide moiety. In the case of **19**, a saturated solution was not prepared because **19** was found to be too soluble in water. Instead, a solution of **19** that was approximately one hundred times more concentrated than a saturated solution of **18** was prepared. The water solubilities of **9**, **10**, and **16**–**19**, calculated based on the strength of the 256 nm signal obtained with the dilute solutions, are listed in Table 1.

Table 1. Water solubilities and partition coefficients of BGL derivatives and related compounds.

Compound	Number of OH groups	Number of glycerol units	Water solubility [mol L^{-1}]	Partition coefficient (1-octanol/water)
9	salt	0	2.5×10^{-2}	–
10	0	0	7.7×10^{-5}	54.05
16	1	0[a]	3.0×10^{-4}	4.44
17	2	1	6.5×10^{-3}	3.57
18	4	3	2.1×10^{-2}	2.01
19	8	6	$> 3.3\times10^{1}$	$< 10^{-5}$

[a] Compound **16** contains one ethylene glycol unit instead of glycerol.

The partition coefficients of **10** and **16**–**19** were also measured. Each compound (1.0 mmol) was dissolved in water/octanol (5 mL/5 mL), the mixture was shaken for 30 min, and then allowed to stand for 30 min. The aqueous layers were treated with a centrifugal separator to remove tiny drops of organic solvent and the aqueous solutions were diluted with water to prepare solutions of appropriate concentration for the measurement of ultraviolet spectra. The partition coefficients of **10** and **16**–**19** were calculated based on the strength of the 256 nm signal of the dilute solutions.

Broadly speaking, water solubility was found to increase in a geometric progression according to the number of hydroxy groups. Tetrahydroxylated derivative **18** was approximately 5000 times more water-soluble than the control compound **10** and the water solubility of the octahydroxylated derivative **19** was at least half a million times greater than that of **10**. Note that the water solubility of neutral molecules such as **18** and **19** is greater than that of the ionic compound **9**. Accordingly, it was concluded that the level of water solubility is influenced by the number of primary hydroxy groups in the BGL moiety. Furthermore, the observed partition coefficients indicate that BGL modification never causes complete loss of lipophilicity in these substrates but instead results in amphiphilicity.

Conclusion

Measurement of the water solubility of the representative BGL derivatives indicates that the BGL family exhibits high-performance water solubilization despite having small numbers of glycerol units. Accordingly, BGL modification is shown to be an efficient method for converting water-insoluble compounds into water-soluble ones. In addition, based on the measured partition coefficients, it seems that BGL modification, rather than removing the lipophilicity of the original compound, results in amphiphilicity, so that BGL derivatives may be well suited to membrane permeation. In conclusion, the values reported herein will be useful for regulating the water solubility and partition coefficients of target molecules based on the use of available BGL modification agents.

Experimental Section

General Experimental Methods: Melting points were determined using a Yanagimoto Micro melting point apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer 1720 or Jasco FT-IR/420 spectrometer with data listed in cm^{-1}. ^{1}H and ^{13}C NMR spectra were measured with a JEOL JMN-AL300 spectrometer at 300 and 75 MHz or a JEOL AL-400 spectrometer at 400 and 100 MHz, respectively, in [D]chloroform and chemical shifts are given as the δ value in ppm measured relative to the internal tetramethylsilane standard at 25 °C unless otherwise noted. High-resolution mass spectra (HRMS) were measured with a JEOL JMS-DX303 spectrometer. UV spectra were measured with a Hitachi U-3310 spectrometer. Methanol was distilled from magnesium methoxide. Pyridine (Py), *N*,*N*-diisopropylethylamine (DIEA), and triethylamine (Et_3N) were distilled from potassium hydroxide. Dichloromethane (CH_2Cl_2) was distilled from phosphorus pentaoxide. Anhydrous tetrahydrofuran (THF) was purchased from Kanto Chemicals. *N*,*N*-Dimethylformamide (DMF) was distilled from barium oxide at 20 Torr.

***N*-[8-(Phenylcarbonylamino)octyl]propanamide (10):** Propionyl chloride (0.34 mL, 3.86 mmol) and Py (0.57 mL, 7.02 mmol) were added to a solution of **8** (1.0 g, 3.51 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The mixture was stirred at room temperature for 4 h, poured into HCl (aq) (1 N, 50 mL), and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate [$NaHCO_3$ (aq)] and then brine, dried with anhydrous magnesium sulfate ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluted with ethyl acetate) to afford **10** as a colorless solid (662.3 mg, 2.18 mmol, 62% yield); m.p. 95–96 °C (recrystallized from hexane/ethyl acetate). FTIR (KBr): $\tilde{\nu}$ = 3313, 3057, 2935, 2851, 1632, 1538, 1466, 692, 1313, 924, 715 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.77 (d, J = 7.5 Hz, 2 H, 2 × *CH-3*), 7.49 (t, J = 7.5 Hz, 1 H, *CH-1*), 7.42 (t, J = 7.5 Hz, 2 H, 2 × *CH-2*), 6.38 (br., 1 H, *NH-4*), 5.71 (br., 1 H, *NH-8*), 3.44 (q, J = 7.0 Hz, 2 H, CH_2-*5*), 3.22 (q, J = 7.0 Hz, 2 H, CH_2-*7*), 2.19 (q, J = 7.5 Hz, 2 H, CH_2-*9*), 1.68–1.29 [m, 12 H, $(CH_2)_6$-*6*], 1.15 (t, J = 7.5 Hz, 3 H, CH_3-*10*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.0 (C), 167.6 (C), 134.8 (C), 131.3 (CH), 128.5 (2 × CH), 126.9 (2 × CH), 40.0 (CH_2), 39.5 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.0 (CH_2), 29.0 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 10.0 (CH_3) ppm. EI-MS: m/z = 304 $[M]^+$. EI-HRMS: calcd. for $C_{18}H_{28}N_2O_2$ $[M]^+$ 304.2151; found 304.2157.

General Procedure for the Reaction of Amines 11a–11c with Succinic Anhydride: Succinic anhydride (150.1 mg, 1.5 mmol) was added in portions to a solution of an amine **11** (1.0 mmol) in Py (2.0 mL) at 0 °C. The resulting mixture was stirred at 100 °C for 3–4 h, cooled to room temperature, poured into HCl (aq), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate, 1:3) to afford the carboxylic acid.

3-{*N*-[2-(Phenylmethoxy)ethyl]carbamoyl}propanoic Acid (13a): Yield from **11a**: 203.6 mg, 0.81 mmol, 81%. A colorless solid; m.p. 75–76 °C (recrystallized from hexane/ethyl acetate). FTIR (KBr): $\tilde{\nu}$ = 3302, 3079, 2877, 1709, 1554, 1430, 1207, 1134, 918, 741, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.42–7.31 (m, 5 H, C_6H_5-*15*), 6.20 (t, J = 5.0 Hz, 1 H, *NH-11*), 4.54 (s, 2 H, CH_2-*14*), 3.59 (t, J = 5.0 Hz, 2 H, CH_2-*12*), 3.49 (t, J = 5.0 Hz, 2 H, CH_2-*13*), 2.69 (t, J = 7.0 Hz, 2 H, CH_2-*9*), 2.51 (t, J = 7.0 Hz, 2 H, CH_2-*10*) ppm; COOH signal not clearly observed. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.8 (C), 172.5 (C), 137.4 (C), 128.1 (2 × CH), 127.5 (2 × CH), 127.5 (CH), 72.6 (CH_2), 68.2 (CH_2), 39.1 (CH_2), 30.2 (CH_2), 29.2 (CH_2) ppm. EI-MS: m/z = 251 $[M]^+$. EI-HRMS: calcd. for $C_{13}H_{17}NO_4$ 251.1158; found 251.1210.

3-(*N*-{2-(Phenylmethoxy)-1-[(phenylmethoxy)methyl]ethyl}-carbamoyl)propanoic Acid (13b): Yield from **11b**: 274.8 mg, 0.74 mmol, 74%. A colorless solid; m.p. 93–95 °C (recrystallized from hexane/ethyl acetate). FTIR (KBr): $\tilde{\nu}$ = 3307, 3062, 2858, 1728, 1644, 1544, 1453, 1204, 1107, 831, 751, 700 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.37–7.25 (m, 10 H, 2 × C_6H_5-*15*), 6.09 (d, J = 8.0 Hz, 1 H, *NH-11*), 4.50 (s, 4 H, 2 × CH_2-*14*), 4.32–4.25 (m, 1 H, *CH-12*), 3.64 (dd, J = 14.5, 4.0 Hz, 2 H, 2 × one of CH_2-*13*), 3.54 (dd, J = 14.5, 5.5 Hz, 2 H, 2 × one of CH_2-*13*), 2.57 (t, J = 7.0 Hz, 2 H, CH_2-*9*), 2.49 (t, J = 7.0 Hz, 2 H, CH_2-*10*) ppm; COOH signal not clearly observed. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.8 (C), 171.6 (C), 137.7 (2 × C), 128.3 (4 × CH), 127.6 (4 × CH), 127.6 (2 × CH), 73.1 (2 × CH_2), 68.3 (2 × CH_2), 48.7 (CH), 30.6 (CH_2), 29.6 (CH_2) ppm. EI-MS: m/z = 371 $[M]^+$. EI-HRMS: calcd. for $C_{21}H_{25}NO_5$ 371.1733; found 371.1744.

3-{*N*-[2-{2-(Phenylmethoxy)-1-[(phenylmethoxy)methyl]ethoxy}-1-({2-(phenylmethoxy)-1-[(phenylmethoxy)methyl]ethoxy}methyl)-ethyl]carbamoyl}propanoic Acid (13c): Yield from **11c**: 699.3 mg, 1.00 mmol, 100%. A colorless oil. FTIR (neat): $\tilde{\nu}$ = 3324, 3062, 3031, 2867, 1784, 1732, 1540, 1454, 1206, 1095, 907, 739, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.36–7.25 (m, 20 H, 4 × C_6H_5-*15*), 6.82 (d, J = 8.0 Hz, 1 H, *NH-11*), 4.50 (s, 4 H, 2 × CH_2-*14*), 4.50 (s, 4 H, 2 × CH_2-*14*), 4.16–4.09 (m, 1 H, *CH-12*), 3.82–3.50 (m, 14 H, 2 × CH_2-*13*, 2 × *CH-16*, 4 × CH_2-*17*), 2.44 (t, J = 6.5 Hz, 2 H, CH_2-*9*), 2.06 (t, J = 6.5 Hz, 2 H, CH_2-*10*) ppm; COOH signal not clearly observed. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.3 (C), 172.0 (C), 137.9 (2 × C), 137.7 (2 × C), 128.2 (4 × CH), 128.2 (4 × CH), 127.7 (4 × CH), 127.6 (4 × CH), 127.5 (2 × CH), 127.4 (2 × CH), 78.9 (2 × CH), 73.4 (2 × CH_2), 73.2 (2 × CH_2), 70.5 (2 × CH_2), 69.9 (2 × CH_2), 68.4 (2 × CH_2), 49.6 (CH), 30.1 (CH_2), 30.0 (CH_2) ppm. FAB-MS: m/z = 700 $[M + H]^+$. FAB-HRMS: calcd. for $C_{41}H_{50}NO_9$ $[M + H]^+$ 700.3486; found 700.3468.

2-[(*tert*-Butoxy)-*N*-({*N*-[2-{2-(phenylmethoxy)-1-[(phenylmethoxy)-methyl]ethoxy}-1-({2-(phenylmethoxy)-1-[(phenylmethoxy)-methyl]ethoxy}methyl)ethyl]carbamoyl}methyl)carbonylamino]-*N*-[2-{2-(phenylmethoxy)-1-[(phenylmethoxy)methyl]ethoxy}-1-({2-(phenylmethoxy)-1-[(phenylmethoxy)methyl]ethoxy}methyl)ethyl]acetamide (12d): PyBop (15.6 g, 30.01 mmol) was added to a mixture of $BocN(CH_2CO_2H)_2$ (3.50 g, 15.01 mmol), **7B** (19.8 g, 33.02 mmol), and DIEA (10.46 mL, 60.03 mmol) in DMF (50 mL) at room temperature. The mixture was stirred at room temperature for 3 h, poured into potassium hydrogen sulfate (5% aqueous solution, 100 mL), and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with $NaHCO_3$ (aq) and then brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate, 3:2) to afford **12d** as a colorless oil (18.66 g, 13.36 mmol, 89% yield). FTIR (neat): $\tilde{\nu}$ = 3031, 2866, 1702, 698, 1668, 1454, 1252, 1098, 737 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.83 (d, J = 8.0 Hz, 1 H, one of *NH-11*), 7.31–7.19 (m, 41 H, 8 × C_6H_5-*15*, one of *NH-11*), 4.48 (s, 16 H, 8 × CH_2-*14*), 4.19–4.08 (m, 2 H, 2 × *CH-12*), 3.81–3.40 (m, 32 H, 4 × CH_2-*13*, 4 × *CH-16*, 8 × CH_2-*17*, 2 × CH_2-*18*), 1.36 (s, 9 H, Boc) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 169.4 (C), 169.2 (C), 154.9 (C), 138.3 (2 × C), 138.3 (4 × C), 138.2 (2 × C), 128.3, 127.8, 127.7, 127.6, and 127.5 (40 × CH), 80.9 (C), 79.0 (2 × CH), 78.8 (2 × CH), 73.4 (2 × CH_2), 73.4 (2 × CH_2), 73.3 (4 × CH_2), 70.4 (2 × CH_2), 70.3 (2 × CH_2), 70.1 (2 × CH_2), 70.0 (2 × CH_2), 68.6 (2 × CH_2), 68.5 (2 × CH_2), 53.2 (CH_2), 52.4 (CH_2), 49.6 (CH), 49.6 (CH), 28.2 (3 × CH_3) ppm. FAB-MS: m/z = 1396 $[M + H]^+$. FAB-HRMS: calcd. for $C_{83}H_{102}N_3O_{16}$ $[M + H]^+$ 1396.7260; found 1396.7271.

3-[*N*,*N*-Bis({*N*-[2-{2-(phenylmethoxy)-1-[(phenylmethoxy)-methyl]ethoxy}-1-({2-(phenylmethoxy)-1-[(phenylmethoxy)-methyl]ethoxy}methyl)ethyl]carbamoyl}methyl)carbamoyl]propanoic Acid (13d): Trifluoroacetic acid (5 mL) was added to a solution of **12d** (2.0 g, 1.43 mmol) in CH_2Cl_2 (45 mL) at room temperature. The mixture was stirred at room temperature for 20 h, poured into $NaHCO_3$ (aq), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The residue, a crude amine (1.85 g, 1.43 mmol, 100% yield), was used in the next step without further purification. Succinic anhydride (286 mg, 2.85 mmol) was added portionwise a solution of the crude amine in Py (2.5 mL) and the mixture was stirred at 100 °C for 1.5 h. After being cooled to 0 °C, the resulting mixture was poured into HCl (aq) (2 N, 20 mL), extracted with CH_2Cl_2 (3 × 30 mL), washed with brine, dried with $MgSO_4$, and concen-

trated in vacuo. The residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate, 1:3) to afford **13d** as a pale yellow liquid (2.00 g, 1.43 mmol, 100% yield). FTIR (neat): $\tilde{\nu}$ = 3220, 3030, 2866, 1729, 1664, 1544, 1454, 1366, 1098, 739, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.84 (d, J = 8.0 Hz, 1 H, one of *NH-11*), 7.31–7.19 (m, 40 H, 8 × C_6H_5-*15*), 6.83 (d, J = 8.0 Hz, 1 H, one of *NH-11*), 4.46 (s, 16 H, 8 × CH_2-*14*), 4.21–4.09 (m, 2 H, 2 × *CH-12*), 3.76–3.45 (m, 32 H, 4 × CH_2-*13*, 4 × *CH-16*, 8 × CH_2-*17*, 2 × CH_2-*18*), 2.60–2.54 (m, 2 H, CH_2-*9*), 2.41–2.35 (m, 2 H, CH_2-*10*) ppm; COOH signal not clearly observed. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.8 (C), 173.8 (C), 169.1 (C), 168.7 (C), 138.8 (2 × C), 138.7 (4 × C), 138.7 (2 × C), 129.0, 129.0, 128.5, 128.4, 128.4, 128.3, 128.3, and 128.2 (40 × CH), 79.5 (2 × CH), 79.2 (2 × CH), 74.1 (2 × CH_2), 73.9 (2 × CH_2), 73.9 (4 × CH_2), 71.0 (2 × CH_2), 70.8 (2 × CH_2), 70.5 (4 × CH_2), 69.2 (2 × CH_2), 69.0 (2 × CH_2), 54.0 (CH_2), 52.7 (CH_2), 50.5 (CH), 50.2 (CH), 30.2 (CH_2), 28.4 (CH_2) ppm. FAB-MS: m/z = 1396 [M + H]$^+$. FAB-HRMS: calcd. for $C_{82}H_{98}N_3O_{17}$ [M + H]$^+$ 1396.7022; found 1396.6886.

General Procedure for the Preparation of Su Ester: HOSu (126.6 mg, 1.1 mmol), EDC (412.7 mg, 2.0 mmol), and Et_3N (0.11 mL, 0.8 mmol) were added to a solution of acid **13** (1.0 mmol) in anhydrous tetrahydrofuran (45 mL). The resulting mixture was stirred for 1.5–3.5 h at reflux, cooled to room temperature, poured into an aqueous solution of potassium hydrogen sulfate [$KHSO_4$ (aq)] (5%, 30 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with $NaHCO_3$ (aq) and then brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluted with hexane/ethyl acetate, 1:10) to afford *N*-hydroxysuccinimide ester.

2,5-Dioxopyrrolidinyl 3-{*N*-[2-(Phenylmethoxy)ethyl]carbamoyl}propanoate (14a): Yield from **13a**: 216.0 mg, 0.62 mmol, 62%. A colorless oil. FTIR (neat): $\tilde{\nu}$ = 3583, 3390, 1814, 1783, 1736, 1654, 1543, 1369, 1208, 1073, 747, 700, 665 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.42–7.31 (m, 5 H, C_6H_5-*15*), 6.25–6.13 (m, 1 H, *NH-11*), 4.55 (s, 2 H, CH_2-*14*), 3.59 (t, J = 6.5 Hz, 2 H, CH_2-*12*), 3.49 (t, J = 6.5 Hz, 2 H, CH_2-*13*), 3.19 (t, J = 9.5 Hz, 2 H, CH_2-*9*), 2.87 (s, 4 H, 2 × CH_2-*19*), 2.61 (t, J = 9.5 Hz, 2 H, CH_2-*10*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.1 (2 × C), 169.1 (C), 168.2 (C), 137.8 (C), 128.5 (2 × CH), 127.9 (2 × CH), 127.9 (CH), 73.2 (CH_2), 68.9 (CH_2), 39.5 (CH_2), 30.6 (CH_2), 26.8 (CH_2), 25.5 (2 × CH_2) ppm. EI-MS: m/z = 349 [M + H]$^+$. EI-HRMS: calcd. for $C_{17}H_{20}N_2O_6$ [M]$^+$ 348.1321; found 348.1327.

2,5-Dioxopyrrolidinyl 3-(*N*-{2-(Phenylmethoxy)-1-[(phenylmethoxy)methyl]ethyl}carbamoyl)propanoate (14b): Yield from **13b**: 346.7 mg, 0.74 mmol, 74%. A colorless crystal; m.p. 75–76 °C (recrystallized from hexane/ethyl acetate). FTIR (KBr): $\tilde{\nu}$ = 3252, 3079, 2945, 2909, 2868, 1818, 1784, 1732, 1651, 1557, 1384, 1211, 1104, 1075, 740, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.39–7.25 (m, 10 H, 2 × C_6H_5-*15*), 5.95 (d, J = 8.5 Hz, 1 H, *NH-11*), 4.51 (s, 4 H, 2 × CH_2-*14*), 4.34–4.27 (m, 1 H, *CH-12*), 3.64 (dd, J = 9.5, 4.0 Hz, 2 H, 2 × one of CH_2-*13*), 3.54 (dd, J = 9.5, 6.0 Hz, 2 H, 2 × one of CH_2-*13*), 2.98 (t, J = 7.0 Hz, 2 H, CH_2-*9*), 2.79 (s, 4 H, 2 × CH_2-*19*), 2.59 (t, J = 7.0 Hz, 2 H, CH_2-*10*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 169.3 (C), 168.7 (2 × C), 167.9 (C), 137.9 (2 × C), 128.2 (4 × CH), 127.6 (4 × CH), 127.5 (2 × CH), 73.1 (2 × CH_2), 68.3 (2 × CH_2), 48.6 (CH), 30.7 (2 × CH_2), 26.7 (CH_2), 25.5 (2 × CH_2) ppm. EI-MS: m/z = 467 [M – H]$^+$. EI-HRMS: calcd. for $C_{25}H_{28}N_2O_7$ [M]$^+$ 468.1897; found 468.1918.

2,5-Dioxopyrrolidinyl 3-{*N*-[2-{2-(Phenylmethoxy)-1-[(phenylmethoxy)methyl]ethoxy}-1-({2-(phenylmethoxy)-1-[(phenylmethoxy)methyl]ethoxy}methyl)ethyl]carbamoyl}propanoate (14c): Yield from **13c**: 613.6 mg, 0.77 mmol, 77%. A colorless oil. FTIR (neat): $\tilde{\nu}$ = 3337, 3062, 3030, 2919, 1815, 1784, 1739, 1673, 1528, 1454, 1366, 1092, 742, 699 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.35–7.27 (m, 20 H, 4 × C_6H_5-*15*), 6.68 (d, J = 8.5 Hz, 1 H, *NH-11*), 4.51 (s, 4 H, 2 × CH_2-*14*), 4.50 (s, 4 H, 2 × CH_2-*14*), 4.17–4.09 (m, 1 H, *CH-12*), 3.82–3.51 (m, 14 H, 2 × CH_2-*13*, 2 × *CH-16*, 4 × CH_2-*17*), 2.78 (t, J = 7.0 Hz, 2 H, CH_2-*9*), 2.77 (s, 4 H, 2 × CH_2-*19*), 2.12 (t, J = 7.0 Hz, 2 H, CH_2-*10*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 169.2 (C), 168.7 (2 × C), 167.8 (C), 138.0 (2 × C), 137.8 (2 × C), 128.3 (4 × CH), 128.2 (4 × CH), 127.7 (4 × CH), 127.6 (4 × CH), 127.4 (4 × CH), 79.0 (2 × CH), 73.4 (2 × CH_2), 73.3 (2 × CH_2), 70.6 (2 × CH_2), 70.0 (2 × CH_2), 68.5 (2 × CH_2), 49.4 (CH), 29.8 (CH_2), 26.5 (CH_2), 25.0 (2 × CH_2) ppm. FAB-MS: m/z = 797 [M – H]$^+$. FAB-HRMS: calcd. for $C_{45}H_{53}N_2O_{11}$ [M – H]$^+$ 797.3649; found 797.3641.

2,5-Dioxopyrrolidinyl 3-[*N*,*N*-Bis({*N*-[2-{2-(phenylmethoxy)-1-[(phenylmethoxy)methyl]ethoxy}-1-({2-(phenylmethoxy)-1-[(phenylmethoxy)methyl]ethoxy}methyl)ethyl]carbamoyl}methyl)carbamoyl]propanoate (14d): Yield from **13d**: 1150.2 mg, 0.79 mmol, 79%. A colorless oil. FTIR (neat): $\tilde{\nu}$ = 3258, 3030, 1740, 1657, 1544, 1454, 1366, 1096, 739, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.44 (d, J = 8.0 Hz, 1 H, one of *NH-11*), 7.31–7.19 (m, 40 H, 8 × C_6H_5-*15*), 6.95 (d, J = 8.0 Hz, 1 H, one of *NH-11*), 4.49 (s, 8 H, 4 × CH_2-*14*), 4.48 (s, 8 H, 4 × CH_2-*14*), 4.22–4.11 (m, 2 H, 2 × *CH-12*), 3.78–3.40 (m, 32 H, 4 × CH_2-*13*, 4 × *CH-16*, 8 × CH_2-*17*, 2 × CH_2-*18*), 2.78 (t, J = 7.0 Hz, 2 H, CH_2-*9*), 2.67 (s, 4 H, 2 × CH_2-*19*), 2.48 (t, J = 7.0 Hz, 2 H, CH_2-*10*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.8 (C), 169.5 (2 × C), 169.3 (C), 168.9 (C), 168.6 (C), 139.0 (2 × C), 138.9 (2 × C), 138.9 (2 × C), 138.8 (2 × C), 129.0, 129.0, 128.7, 128.4, 128.3, 128.2, 128.2, and 128.2 (40 × CH), 79.7 (2 × CH), 79.3 (2 × CH), 74.1 (2 × CH), 74.0 (2 × CH_2), 73.9 (4 × CH_2), 71.1 (2 × CH_2), 70.9 (2 × CH_2), 70.7 (2 × CH_2), 70.6 (2 × CH_2), 69.5 (2 × CH_2), 69.0 (2 × CH_2), 54.1 (CH_2), 53.0 (CH_2), 50.6 (CH), 50.1 (CH), 27.9 (CH_2), 26.9 (CH_2), 26.1 (2 × CH_2) ppm. FAB-MS: m/z = 1493 [M + H]$^+$. FAB-HRMS: calcd. for $C_{86}H_{101}N_4O_{19}$ [M + H]$^+$ 1493.7060; found 1493.7081.

General Procedure for Amide-Bond-Formation Reactions with 8: Amine **8** (284.8 mg, 1.0 mmol) and Et_3N (0.14 mL, 1.0 mmol) were added to a solution of *N*-hydroxysuccinimide ester **14** (1.0 mmol) in THF (20 mL). The mixture was stirred at room temperature for 3–6 h, poured into $KHSO_4$ (aq) (5%, 30 mL), and extracted with chloroform (3 × 30 mL). The combined organic layers were washed with $NaHCO_3$ (aq) and then brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluted with chloroform/methanol, 20:1) to afford *N*-benzoyl-*N*′-acylated 1,8-octamethylenediamine.

***N*′-[8-(Phenylcarbonylamino)octyl]-*N*-[2-(phenylmethoxy)ethyl]butane-1,4-diamide (15a):** Yield from **14a**: 303.4 mg, 0.63 mmol, 63%. A colorless solid; m.p. 147–148 °C (recrystallized from hexane/chloroform). FTIR (KBr): $\tilde{\nu}$ = 3313, 3060, 2922, 2854, 1627, 1539, 1334, 1215, 1104, 1028, 997, 729, 694 cm^{-1}. ^1H NMR ($CDCl_3$/CD_3OD = 1:1, 400 MHz): δ = 8.07 (t, J = 5.5 Hz, 1 H, *NH*), 7.83–7.26 (m, 10 H, *CH-1*, 2 × *CH-2*, 2 × *CH-3*, C_6H_5-*15*), 7.76 (t, J = 5.0 Hz, 1 H, *NH*), 7.69 (t, J = 5.0 Hz, 1 H, *NH*), 4.53 (s, 2 H, CH_2-*14*), 3.56 (t, J = 5.5 Hz, 2 H, CH_2-*12*), 3.45–3.35 (m, 4 H, CH_2-*13*, CH_2-*5*), 3.16 (dt, J = 7.0, 5.5 Hz, 2 H, CH_2-*7*), 2.48 (t, J = 6.0 Hz, 2 H, CH_2-*10*), 2.45 (t, J = 6.0 Hz, 2 H, CH_2-*9*), 1.63 (quint, J = 7.0 Hz, 2 H, CH_2-*6*), 1.49 (quint, J = 7.0 Hz, 2 H, CH_2-*6*), 1.43–

1.27 (m, 8 H, 4× *CH*$_2$-*6*) ppm. ^{13}C NMR ($CDCl_3$/CD_3OD, 10:1, 75 MHz): δ = 172.9 (C), 172.7 (C), 168.1 (C), 137.8 (C), 134.7 (C), 131.5 (CH), 128.6 (2× CH), 128.5 (2× CH), 127.9 (2× CH), 127.9 (2× CH), 126.9 (CH), 73.2 (CH_2), 68.7 (CH_2), 40.0 (CH_2), 39.5 (CH_2), 39.4 (CH_2), 31.8 (CH_2), 31.7 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 26.8 (CH_2), 26.7 (CH_2) ppm. EI-MS: *m*/*z* = 481 $[M]^+$. EI-HRMS: calcd. for $C_{28}H_{39}N_3O_4$ $[M]^+$ 481.2941; found 481.2934.

***N*′-[8-(Phenylcarbonylamino)octyl]-*N*-{2-(phenylmethoxy)-1-[(phenylmethoxy)methyl]ethyl}butane-1,4-diamide (15b):** Yield from **14b**: 463.4 mg, 0.77 mmol, 77%. A colorless solid; m.p. 110–112 °C (recrystallized from hexane/chloroform). FTIR (KBr): $\tilde{\nu}$ = 3320, 3060, 2931, 2860, 1643, 1542, 1475, 1453, 1204, 1104, 1028, 734, 696 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.78–7.27 (m, 15 H, *CH-1*, 2× *CH-2*, 2× *CH-3*, 2× C_6H_5-*15*), 6.20–5.95 (m, 3 H, *NH-4*, *NH-8*, *NH-11*), 4.50 (s, 4 H, 2× *CH*$_2$-*14*), 4.32–4.24 (m, 1 H, *CH-12*), 3.62 (dd, *J* = 9.8, 4.0 Hz, 2 H, 2× one of *CH*$_2$-*13*), 3.51 (dd, *J* = 9.8, 6.0 Hz, 2 H, 2× one of *CH*$_2$-*13*), 3.44 (q, *J* = 6.5 Hz, 2 H, *CH*$_2$-*5*), 3.19 (q, *J* = 6.5 Hz, 2 H, *CH*$_2$-*7*), 2.64–2.45 (m, 4 H, *CH*$_2$-*9*, *CH*$_2$-*10*), 1.67–1.22 (m, 12 H, 6× *CH*$_2$-*6*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.1 (C), 172.0 (C), 167.6 (C), 137.8 (2× C), 134.6 (C), 131.2 (CH), 128.4 (2× CH), 128.3 (6× CH), 127.6 (2× CH), 127.5 (2× CH), 126.7 (2× CH), 73.1 (2× CH_2), 68.4 (2× CH_2), 48.6 (CH), 40.0 (CH_2), 39.5 (CH_2), 31.9 (CH_2), 31.8 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 29.0 (CH_2), 26.8 (CH_2), 26.6 (CH_2) ppm. EI-MS: *m*/*z* = 601 $[M]^+$. EI-HRMS: calcd. for $C_{36}H_{47}N_3O_5$ $[M]^+$ 601.3516; found 601.3497.

***N*′-[8-(Phenylcarbonylamino)octyl]-*N*-[2-{2-(phenylmethoxy)-1-[(phenylmethoxy)methyl]ethoxy}-1-({2-(phenylmethoxy)-1-[(phenylmethoxy)methyl]ethoxy}methyl)ethyl]butane-1,4-diamide (15c):** Yield from **14c**: 920.9 mg, 0.99 mmol, 99%. A colorless oil. FTIR (neat): $\tilde{\nu}$ = 3312, 3062, 2927, 2858, 1644, 1542, 1453, 1099, 1028, 738, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.79–7.28 (m, 25 H, *CH-1*, 2× *CH-2*, 2× *CH-3*, 4× C_6H_5-*15*), 6.73 (d, *J* = 8.0 Hz, 1 H, *NH*), 6.45–6.30 (m, 2 H, 2× *NH*), 4.50 (s, 4 H, 2× *CH*$_2$-*14*), 4.45 (s, 4 H, 2× *CH*$_2$-*14*), 4.15–4.07 (m, 1 H, *CH-12*), 3.84–3.65 (m, 4 H, 2× *CH-16*, 2× one of *CH*$_2$-*13*), 3.65–3.52 (m, 10 H, 2× one of *CH*$_2$-*13*, 4× *CH*$_2$-*17*), 3.42 (q, *J* = 6.5 Hz, 2 H, *CH*$_2$-*5*), 3.15 (q, *J* = 6.5 Hz, 2 H, *CH*$_2$-*7*), 2.34 (t, *J* = 6.5 Hz, 2 H, *CH*$_2$-*10*), 2.17 (t, *J* = 6.5 Hz, 2 H, *CH*$_2$-*9*), 1.68–1.23 (m, 12 H, 6× *CH*$_2$-*6*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.1 (C), 172.0 (C), 167.5 (C), 138.1 (2× C), 138.0 (2× C), 134.8 (C), 131.6 (CH), 128.4 (2× CH), 128.4 (4× CH), 128.3 (4× CH), 127.7 (4× CH), 127.7 (2× CH), 127.6 (2× CH), 127.6 (4× CH), 126.9 (2× CH), 79.0 (2× CH), 73.4 (2× CH_2), 73.3 (2× CH_2), 70.5 (CH_2), 70.4 (CH_2), 70.0 (CH_2), 70.0 (CH_2), 68.5 (2× CH_2), 49.4 (CH), 40.0 (CH_2), 39.4 (CH_2), 31.7 (CH_2), 31.4 (CH_2), 29.5 (CH), 29.4 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 26.8 (CH_2), 26.7 (CH_2) ppm. FAB-MS: *m*/*z* = 931 $[M + H]^+$. FAB-HRMS: calcd. for $C_{56}H_{72}N_3O_9$ $[M + H]^+$ 930.5269; found 930.5262.

***N*′-[8-(Phenylcarbonylamino)octyl]-*N*,*N*-bis({*N*-[2-{2-(phenylmethoxy)-1-[(phenylmethoxy)methyl]ethoxy}-1-({2-(phenylmethoxy)-1-[(phenylmethoxy)methyl]ethoxy}methyl)ethyl]carbamoyl}methyl)butane-1,4-diamide (15d):** Yield from **14d**: 1562 mg, 0.96 mmol, 96%. A colorless oil. FTIR (neat): $\tilde{\nu}$ = 3307, 3062, 3030, 2925, 1651, 1543, 1454, 1206, 1100, 1028, 739, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.29 (d, *J* = 8.0 Hz, 1 H, CONH), 7.77 (d, *J* = 7.0 Hz, 2 H, 2× *CH-3*), 7.46 (t, *J* = 7.0 Hz, 1 H, *CH-1*), 7.40 (t, *J* = 7.0 Hz, 2 H, 2× *CH-2*), 7.41–7.35 (m, 40 H, 8× C_6H_5-*15*), 7.08 (d, *J* = 8.0 Hz, 1 H, *NH*), 6.36 (br., *J* = 5.0 Hz, 1 H, *NH*), 5.97 (br. d, *J* = 5.0 Hz, 1 H, *NH*), 4.50 (s, 16 H, 8× *CH*$_2$-*14*), 4.22–4.0 (m, 2 H, 2× *CH-12*), 3.80–3.40 (m, 34 H, *CH*$_2$-*5*, 4× *CH*$_2$-*13*, 4× *CH-16*, 8× *CH*$_2$-*17*, 2× *CH*$_2$-*18*), 3.10 (q, *J* = 6.5 Hz, 2 H, *CH*$_2$-*7*), 2.45 (t, *J* = 6.5 Hz, 2 H, *CH*$_2$-*9*), 2.30 (t, *J* = 6.5 Hz, 2 H, *CH*$_2$-*10*), 1.68–1.23 (m, 12 H, 6× *CH*$_2$-*6*) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.1 (C), 171.7 (C), 168.5 (C), 168.0 (C), 167.3 (C), 138.1 (2× C), 138.0 (4× C), 137.9 (2× C), 134.7 (C), 131.1 (CH), 128.3, 128.2, 128.2, 127.6, 127.6, 127.5, 127.5, 127.5, 127.4, 127.4, and 126.7 (44× CH), 78.9 (2× CH), 78.8 (2× CH), 73.3 (2× CH_2), 73.3 (2× CH_2), 73.2 (4× CH_2), 70.3 (2× CH_2), 70.2 (2× CH_2), 69.9 (2× CH_2), 69.9 (2× CH_2), 68.8 (2× CH_2), 68.3 (2× CH_2), 53.4 (CH_2), 52.3 (CH_2), 49.9 (CH), 49.6 (CH), 40.0 (CH_2), 39.4 (CH_2), 31.1 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.2 (CH_2), 26.8 (CH_2), 26.7 (CH_2) ppm. TOF-HRMS: calcd. for $C_{97}H_{119}N_5NaO_{17}$ $[M + Na]^+$ 1648.8493; found 1648.8534.

General Debenzylation Procedure: A solution of benzyl ether **15** (or **14d**) (1.0 mmol) in ethanol (15 mL) in the presence of a catalytic amount of palladium hydroxide/carbon (20 wt-% Pd, 30 mg) was stirred at room temperature under hydrogen for 3–6 h. The resulting suspension was filtered through Celite™ 535 and the filtrate was concentrated in vacuo to give the desired debenzylated product.

***N*-(2-Hydroxyethyl)-*N*′-[8-(phenylcarbonylamino)octyl]butane-1,4-diamide (16):** Yield from **15a**: 391.5 mg, 1.0 mmol, 100%. A colorless solid; m.p. 161–163 °C (recrystallized from ethanol/diethyl ether). FTIR (KBr): $\tilde{\nu}$ = 3317, 3056, 2937, 2849, 1623, 1539, 1462, 1315, 1216, 1062, 715, 692 cm^{-1}. ^{1}H NMR (CD_3OD, 400 MHz): δ = 7.81–7.77 (m, 2 H, 2× *CH-3*), 7.53–7.41 (m, 3 H, 2× *CH-2*, *CH-1*), 3.58 (t, *J* = 6.0 Hz, 2 H, *CH*$_2$-*12*), 3.38 (t, *J* = 7.0 Hz, 2 H, *CH*$_2$-*5*), 3.30 (t, *J* = 6.0 Hz, 2 H, *CH*$_2$-*13*), 3.16 (t, *J* = 7.0 Hz, 2 H, *CH*$_2$-*7*), 2.50–2.46 (m, 4 H, *CH*$_2$-*9, CH*$_2$-*10*), 1.62 (quint, *J* = 7.0 Hz, 2 H, *CH*$_2$-*6*), 1.49 (quint, *J* = 7.0 Hz, 2 H, *CH*$_2$-*6*), 1.41–1.28 (m, 8 H, 4× *CH*$_2$-*6*) ppm. ^{13}C NMR ($CDCl_3$/CD_3OD = 1:10, 75 MHz): δ = 174.7 (C), 174.3 (C), 170.1 (C), 135.6 (C), 132.3 (CH), 129.3 (2× CH), 128.0 (2× CH), 61.4 (CH_2), 42.8 (CH_2), 40.9 (CH_2), 40.3 (CH_2), 32.2 (CH_2), 32.1 (CH_2), 30.3 (CH_2), 30.2 (CH_2), 30.2 (2× CH_2), 27.8 (CH_2), 27.7 (CH_2) ppm. EI-MS: *m*/*z* = 391 $[M]^+$. EI-HRMS: calcd. for $C_{21}H_{33}N_3O_4$ $[M]^+$ 391.2471; found 391.2449.

***N*-[2-Hydroxy-1-(hydroxymethyl)ethyl]-*N*′-[8-(phenylcarbonylamino)octyl]butane-1,4-diamide (17):** Yield from **15b**: 421.5 mg, 1.0 mmol, 100%. A colorless solid; m.p. 170–171 °C (recrystallized from chloroform/diethyl ether). FTIR (KBr): $\tilde{\nu}$ = 3303, 3062, 2930, 2852, 1631, 1543, 1469, 1220, 1073, 974, 668 cm^{-1}. ^{1}H NMR (CD_3OD, 400 MHz): δ = 7.81–7.77 (m, 2 H, 2× *CH-3*), 7.53–7.41 (m, 3 H, *CH-1*, 2× *CH-2*), 3.90 (q, *J* = 5.5 Hz, 1 H, *CH-12*), 3.65–3.55 (m, 4 H, 2× *CH*$_2$-*13*), 3.38 (t, *J* = 7.0 Hz, 2 H, *CH*$_2$-*5*), 3.16 (t, *J* = 7.0 Hz, 2 H, *CH*$_2$-*7*), 2.52–2.46 (m, 4 H, *CH*$_2$-*9*, *CH*$_2$-*10*), 1.62 (quint, *J* = 7.0 Hz, 2 H, *CH*$_2$-*6*), 1.49 (quint, *J* = 7.0 Hz, 2 H, *CH*$_2$-*6*), 1.41–1.28 (m, 8 H, 4× *CH*$_2$-*6*) ppm. ^{13}C NMR ($CDCl_3$/CD_3OD = 3:7, 75 MHz): δ = 173.9 (C), 173.4 (C), 169.2 (C), 134.9 (C), 131.8 (CH), 128.8 (2× CH), 127.4 (2× CH), 61.6 (2× CH_2), 53.3 (CH), 40.4 (CH_2), 39.8 (CH_2), 31.9 (CH_2), 31.6 (CH_2), 29.7 (CH_2), 29.5 (3× CH_2), 27.2 (CH_2), 27.1 (CH_2) ppm. EI-MS: *m*/*z* = 421 $[M]^+$. EI-HRMS: calcd. for $C_{22}H_{35}N_3O_5$ $[M]^+$ 421.2577; found 421.2573.

***N*-(2-[2-Hydroxy-1-(hydroxymethyl)ethoxy]-1-{[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl}ethyl)-*N*′-[8-(phenylcarbonylamino)octyl]butane-1,4-diamide (18):** Yield from **15c**: 569.7 mg, 1.0 mmol, 100%. A colorless solid; m.p. 92–94 °C. FTIR (KBr): $\tilde{\nu}$ = 3321, 2928, 2868, 1625, 1539, 1476, 1216, 1045, 926, 722, 693 cm^{-1}. ^{1}H NMR (CD_3OD, 400 MHz): δ = 7.84 (d, *J* = 7.0 Hz, 2 H, 2× *CH-3*), 7.71 (t, *J* = 7.0 Hz, 1 H, *CH-1*), 7.62 (t, *J* = 7.0 Hz, 2 H, 2× *CH-*

2), 4.29–4.21 (m, 1 H, *CH-12*), 3.88–3.59 (m, 14 H, 2× *CH-16*, 2× CH_2-*13*, 4× CH_2-*17*), 3.49 (t, *J* = 6.0 Hz, 2 H, CH_2-*5*), 3.23 (t, *J* = 6.0 Hz, 2 H, CH_2-*7*), 2.67–2.55 (m, 4 H, CH_2-*9*, CH_2-*10*), 1.72 (quint, *J* = 6.0 Hz, 2 H, CH_2-*6*), 1.57 (quint, *J* = 6.0 Hz, 2 H, CH_2-*6*), 1.51–1.34 (m, 8 H, 4× CH_2-*6*) ppm. ^{13}C NMR (CD_3OD, 75 MHz): δ = 174.5 (C), 174.3 (C), 169.9 (C), 135.7 (C), 132.4 (CH), 129.4 (2× CH), 128.1 (2× CH), 82.9 (2× CH), 69.5 (2× CH_2), 62.4 (2× CH_2), 62.3 (2× CH_2), 51.0 (CH), 40.9 (CH_2), 40.5 (CH_2), 32.3 (CH_2), 32.2 (CH_2), 30.4 (2× CH_2), 30.2 (2× CH_2), 27.9 (CH_2), 27.8 (CH_2) ppm. FAB-MS: *m*/*z* = 570 $[M + H]^+$. FAB-HRMS: calcd. for $C_{28}H_{48}N_3O_9$ $[M + H]^+$ 570.3391; found 570.3390.

***N*,*N*-Bis{[*N*-(2-[2-hydroxy-1-(hydroxymethyl)ethoxy]-1-{[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl}ethyl)carbamoyl]methyl}-*N*′-[8-(phenylcarbonylamino)octyl]butane-1,4-diamide (19):** Yield from **15d**: 1627.0 mg, 1.0 mmol, 100%. A pale yellow amorphous solid. FTIR (neat): $\tilde{\nu}$ = 3307, 3086, 2930, 2878, 1644, 1554, 1468, 1216, 1122, 1051, 697 cm^{-1}. ^{1}H NMR (CD_3OD, 400 MHz): δ = 7.80 (d, *J* = 7.0 Hz, 2 H, 2× *CH-3*), 7.52 (t, *J* = 7.0 Hz, 1 H, *CH-1*), 7.45 (t, *J* = 7.0 Hz, 2 H, 2× *CH-2*), 4.27 (s, 2 H, CH_2-*18*), 4.22 (quint, *J* = 5.0 Hz, 1 H, *CH-12*), 4.15 (quint, *J* = 5.0 Hz, 1 H, *CH-12*), 4.05 (s, 2 H, CH_2-*18*), 3.82–3.52 (m, 28 H, 4× CH_2-*13*, 4× *CH-16*, 8× CH_2-*17*), 3.38 (t, *J* = 7.0 Hz, 2 H, CH_2-*5*), 3.16 (t, *J* = 7.0 Hz, 2 H, CH_2-*7*), 2.60 (t, *J* = 6.5 Hz, 2 H, CH_2-*9*), 2.48 (t, *J* = 6.5 Hz, 2 H, CH_2-*10*), 1.62 (quint, *J* = 6.5 Hz, 2 H, CH_2-*6*), 1.49 (quint, *J* = 6.5 Hz, 2 H, CH_2-*6*), 1.41–1.28 (m, 8 H, 4× CH_2-*6*) ppm. ^{13}C NMR (CD_3OD, 75 MHz): δ = 175.6 (C), 174.2 (C), 171.65 (C), 171.37 (C), 170.0 (C), 135.7 (C), 132.4 (CH), 129.4 (2× CH), 128.1 (2× CH), 83.1 (2× CH), 82.9 (2× CH), 69.7 (2× CH_2), 69.5 (2× CH_2), 62.6 (2× CH_2), 62.5 (2× CH_2), 62.4 (4× CH_2), 54.5 (CH_2), 54.0 (CH_2), 51.6 (CH), 51.3 (CH), 41.0 (CH_2), 40.5 (CH_2), 31.7 (CH_2), 30.5 (CH_2), 30.3 (2× CH_2), 30.3 (CH_2), 29.2 (CH_2), 28.0 (CH_2), 27.9 (CH_2) ppm. FAB-MS: *m*/*z* = 906 $[M + H]^+$. FAB-HRMS: calcd. for $C_{41}H_{72}N_5O_{17}$ $[M + H]^+$ 906.4923; found 906.4971.

2,5-Dioxopyrrolidinyl 3-(*N*,*N*-Bis{[*N*-(2-[2-hydroxy-1-(hydroxymethyl)ethoxy]-1-{[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl}ethyl)carbamoyl]methyl}carbamoyl)propanoate (24): Yield from **14d**: 906.0 mg, 1.0 mmol, 100%. A colorless oil. FTIR (neat): $\tilde{\nu}$ = 3307, 3030, 2930, 2878, 1740, 1657, 1544, 1454, 1366, 1216, 1122, 1096, 739, 697 cm^{-1}. ^{1}H NMR (CD_3OD, 300 MHz): δ = 4.22–4.05 (m, 6 H, 2× CH_2-*18*, 2× *CH-12*), 3.80–3.43 (m, 28 H, 4× CH_2-*13*, 4× *CH-16*, 8× CH_2-*17*), 2.96 (t, *J* = 5.0 Hz, 2 H, CH_2-*9*), 2.82 (s, 4 H, 2× CH_2-*19*), 2.74 (t, *J* = 5.0 Hz, 2 H, CH_2-*10*) ppm. ^{13}C NMR (CD_3OD, 75 MHz): δ = 174.1 (C), 171.8 (C), 171.7 (2× C), 171.5 (C), 169.9 (C), 83.0 (2× CH), 82.9 (2× CH), 69.7 (2× CH_2), 69.4 (2× CH_2), 62.5 (4× CH_2), 62.4 (4× CH_2), 54.4 (CH_2), 54.1 (CH_2), 51.6 (CH), 51.3 (CH), 28.6 (CH_2), 27.2 (CH_2), 26.5 (2× CH_2) ppm. FAB-MS: *m*/*z* = 773 $[M + H]^+$. FAB-HRMS: calcd. for $C_{30}H_{52}O_{19}N_4$ $[M + H]^+$ 773.3304; found 773.3314.

Condensation Reaction between 8 and 24: BGL modification of **8** (28.5 mg, 0.1 mmol) with **24** (115.9 mg, 0.15 mmol) was performed in water in the presence of Et_3N (20.2 mg, 0.2 mmol). After concentration to remove water and Et_3N, **19** was obtained in quantitative yield along with HOSu, any unreacted **24**, and the carboxylic acid obtained by hydrolysis of the CO_2Su moiety of **24**.

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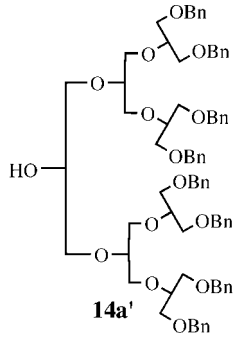

14a'

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