Syntheses of crowned polyamines using isolable succinimidyl esters of *N*-tritylated linear amino acids and peptides

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Dedicated to Professor Gerasimos J. Karabatsos on the occasion of his 70th birthday
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Abstract
Partial and total syntheses of polyamines incorporating crown ether moieties have been effected using N-tritylated linear amino acids, like β-alanine (βAla) and γ-aminobutyric acid (γAba), to introduce the N–3-C and N–4-C polyamine structural units, respectively. The partial syntheses involve the acylation of commercially available crown bearing amino function(s) or aza-oxa crown ethers with the isolable succinimidyl esters of Trt-βAla-OH or Trt-βAla-γAba-OH, followed by $LiAlH_4$-mediated reduction of the resulting amides, whereas in the total syntheses the crown and the aza-oxa crown ether moieties are built-up from commercially available starting materials like polyethylene glycols, epichlorohydrin and dibenzylamine.

Keywords: Polyamines, crown ethers, aza-oxa crown ethers, amino acids, active esters, protecting groups

Introduction

Linear polyamines (PAs), like spermidine (SPD) and spermine (SPM) and their conjugates (PACs) with other natural products are widely distributed in the living organisms and are associated with interesting biological functions. For this reason, they have attracted considerable interest, and a variety of PA analogues and PACs have been already synthesized in order to determine structure-activity relationship and to identify possible leads for the development of PA-based pharmaceuticals.[1] On the other hand, the cyclic oligomers of ethylene oxide, collectively known as crown ethers (CEs), and their analogues and derivatives are widely used for complexing and separating metal or organic cations, as well as in the areas of phase transfer

catalysis, host-guest and supramolecular chemistry.[2] Different types of CEs have been synthesized in order to improve their properties and find suitable applications. In addition, a variety of pharmaceutically interesting compounds have been equipped with crown moieties in order to modify their physiological action.[3] Accordingly, we decided to examine the possibility of introducing CE moieties into PA molecules and study the complexing and biological properties of this new family of organic compounds, which we collectively coin as crowned polyamines (CRPAs). We now wish to report a general method that we have recently developed which facilitates access to CRPAs;. CEs is commercially available[4] but we have developed alternative methods of preparation. For the introduction of CE moieties into various polyamine skeletons as the purpose of this work, we have chosen the commercially available aza-oxa CEs **1** and **2** (Figure 1), the lariat aminomethyl CE **3** and the diaminodibenzo-CE **4**, a mixture of the isomers **4a** and **4b**.

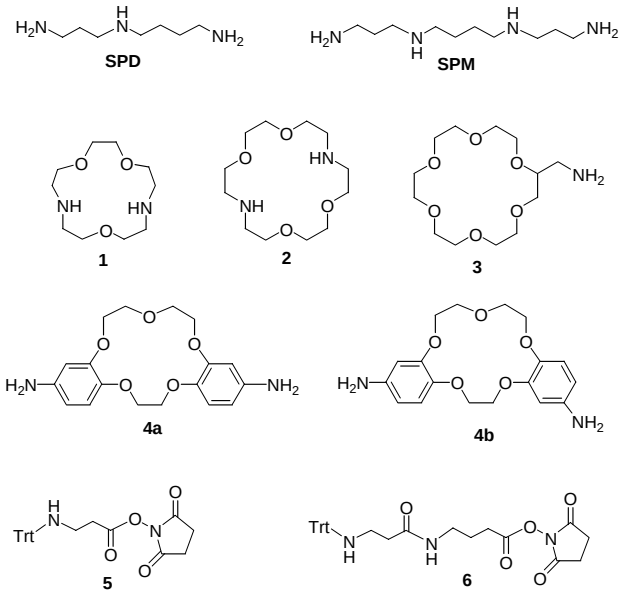


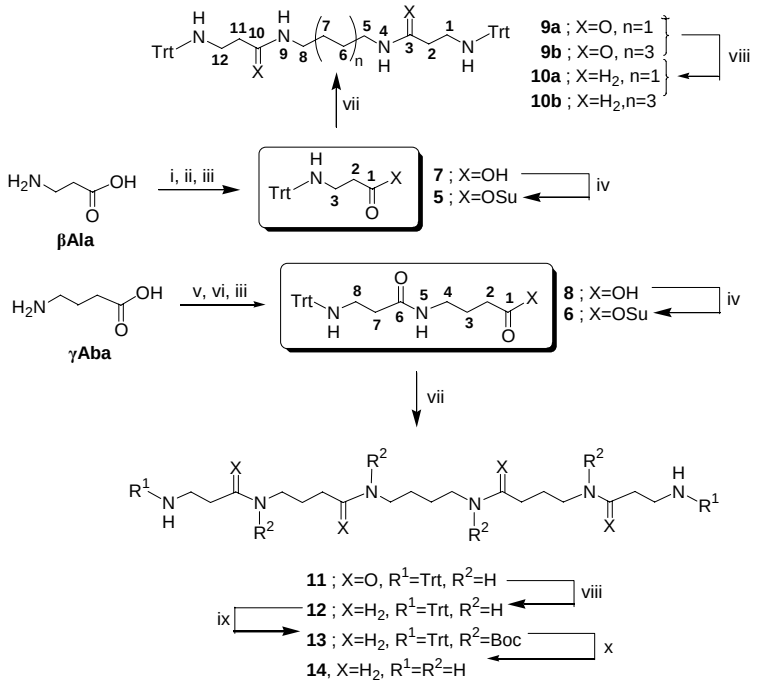
Figure 1. Structures of compounds related to this work.

Furthermore, we used simple commercially available building blocks, like polyethylene glycols, epichlorihydrin, and dibenzylamine, in order to build-up various CE skeletons to the appropriate size and content of N atoms, and the 'isolable′ active esters **5** and **6**, readily available from the corresponding linear amino acids β-alanine (βAla) and γ-aminobutyric acid (γAba),[5] as N–3-C and N–3-C–N–4-C synthons for the assembly of various PA skeletons.

Results and Discussion

Linear amino acids and α,ω-diaminoalkanes as building blocks for the assembly of linear polyamine skeletons

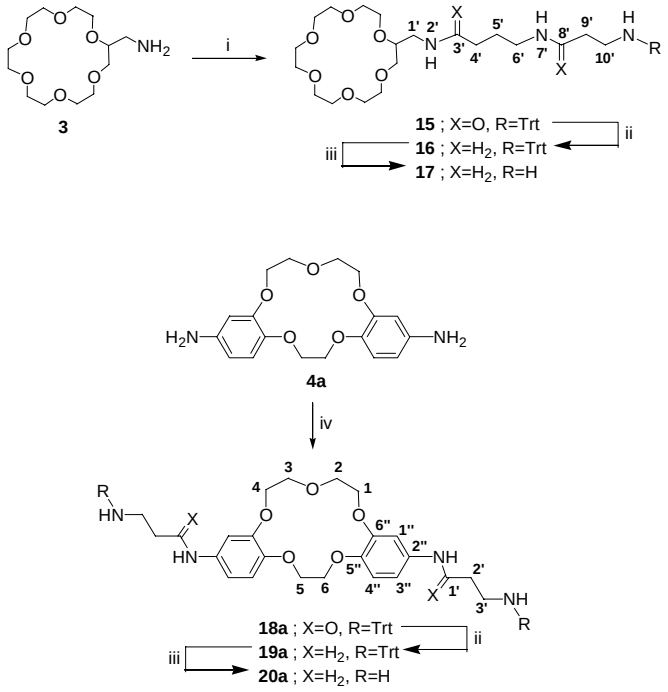
In a series of letters,[5,6] we have shown that the triphenylmethyl (trityl, Trt) N-protected linear amino acids, like βAla and γAba, and their dipeptides, e.g. βAla-γAba, in the form of their corresponding isolable succinimidyl 'active' esters (SAEs) **5** and **6** can be successfully employed for the synthesis of a variety of linear and cyclic SPD and SPM analogues and conjugates of the alkaloid kukoamine A type as well as their symmetric and asymmetric dimers, bridged by linear dicarboxylic acids, of the alkaloid tenuilobine type using the 'amide approach[4]. The required SAEs are readily obtained as depicted in Scheme 1.



Scheme 1. Syntheses of succinimidyl active esters and of linear polyamines (the numbers on the structures serve for the presentation of the NMR data).
(i) Me_3SiCl, CH_2Cl_2/MeCN (5:1), reflux, 30 min. (ii) Et_3N/TrtCl, 0 ºC, 1 h then 25 ºC, 3 h. (iii) MeOH, 97% (**7**) or 79% (**8**). (iv) HOSu/DCC, THF/DMF (3:1), 0 ºC, 1 h then 25 ^{o}C, 12 h, 85% (**5**) or 88% (**6**). (v) Me_3SiCl, CH_2Cl_2, 25 ºC, 10 min. (vi) **5**/Et_3N, 0 ºC, 45 min then 25 ºC, 15 min. (vii) PUT or DAO/Et_3N, DMF, 25 ºC, 12-24 h, 90% (**9a**) or 78% (**9b**) or 82% (**11**). (viii) $LiAlH_4$, THF, reflux, 2-4 d; 68% (**10a**) or 61% (**10b**). (ix) Boc_2O/Et_3N/cat. DMAP, $CHCl_3$, 0 ºC, 30 min then 25 ºC, 12 h, 30%. (x) TFA/CH_2Cl_2 (1:1), 25 ºC, 30 min, 75%.

O-Silylation of βAla, followed by N-tritylation and desilylation with MeOH,[7] provided Trt-βAla **7** in 97% yield. SAE **5** was then obtained in 85% yield by the condensation of **7** with of *N*-

hydroxysuccunimide (HOSu) in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC).[5a] On the other hand, O-silylation of γAba, followed by N-acylation with SAE **5** and desilylation with MeOH gave the N-tritylated dipeptide **8** in 79% yield. From this compound, SAE **6** was easily obtained in 88% yield upon routine activation also with HOSu in the presence of DCC.[5b] The applicability of these compounds to build any type of tetra- or hexa-amines of the 3-n-3 or the 3-4-n-4-3 types was readily exemplified by the facile preparation of the tetra-amine derivatives **10a** and **10b** (n = 4 and 8, respectively), and the hexa-amine **14** (n = 4). Thus, condensation of SAE **5** with 1,4-diaminobutane (putrescine, PUT) gave the expected bisamide **9a** in 90% yield. This was then reduced with $LiAlH_4$ to produce N^1,N^{12}-Trt_2-SPM **10a** in 68% yield.[5a] Later, the selective direct ditritylation of SPM to produce **10a** was reported.[8] On the other hand, bisacylation of 1,8-diaminooctane (DAO), followed by $LiAlH_4$ reduction of the bisamide **9b** produced the N^1,N^{16}-ditritylated tetra-amine **10b** in 61% yield.[4] Similarly, bisacylation of PUT with SAE **6** produced the tetra-amide **11** in 82% yield. $LiAlH_4$ reduction of all four amide functions took place unexceptionally and the thus obtained crude PA derivative **12** was per-*tert*-butoxycarbonylated to facilitate purification by flash column chromatography (FCC). The resulting pure, fully protected, hexa-amine **13** (30% overall yield) was deprotected with a 50% solution of trifluoroacetic acid (TFA) in CH_2Cl_2 to produce the 3-4-4-4-3 hexa-amine **14** as the hexatrifluoroacetate salt, in 75% yield.[4] In this general methodology, diversion may readily arise from the linear or even branched (e.g. chiral) amino acids or peptides, and the linear or branched or cyclic α,ω-diaminoalkanes used to furnish the N–C_n–N central core of the polyamine.



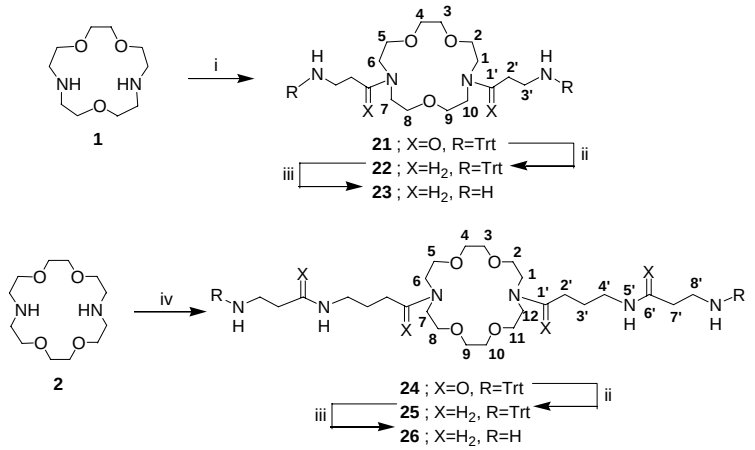
Scheme 2. Partial syntheses of crown ethers incorporating polyamine elements (the numbers on the structures serve for the presentation of the NMR data).

(i) **6**/Et_3N, DMF, 25 ºC, 1 h, 66%. (ii) $LiAlH_4$, THF, reflux, 12–48 h, 45% (**16**) or 82% (**19**). (iii) TFA/CH_2Cl_2 (1:1 or 1:3), 25 ºC, 1 h, 73% (**17**) or 91% (**20**). (iv) **5**/$^iPr_2NEt$, DMF, 60 ºC, 3 h, then 25 ºC, 12 h, 55% .

Partial syntheses of polyamines incorporating crown and diaza-oxa crown ether moieties

Oxapolyamines, i.e. polyamines incorporating O atom(s) in their skeleton have recently gained considerable interest.[9] Therefore, we decided to extent the above described method to include the cyclic counterparts of poly(ethylene glycols), i.e. CEs. Two possibilities were examined, namely CEs bearing one or two amino-handles and aza-oxy CEs incorporating two N atoms within the ring. Accordingly, condensation of 2-aminomethyl-18-CE-6 **3** with SAE **6** provided the bisamide **15** in 66% yield (Scheme 2). $LiAlH_4$ reduction of **15** gave the corresponding N-tritylated PA derivative **16** (45% yield); upon TFA detritylation the 8-N-monoalkylated SPD analogue **17** was obtained as its tris(trifluoroacetate) salt (73% yield). Similarly, bisacylation of diaminodibenzo-15-CE-5 **4** with SAE **5** gave bisamide **18** (only isomer **18a** is shown in Scheme 2) in 55% yield.

Reduction of **18** with $LiAlH_4$, followed by detritylation of the resulting CE derivative **19** (82%) gave CE **20** (91%). Compound **20a** may be considered as a conformationally restricted dioxa-analogue of the 3-12-3 tetra-amine core. Furthermore, bisacylation of the diaza-oxa-15-CE-5 **1** with SAE **5** gave the bisamide **21** in 59% yield (Scheme 3). Upon $LiAlH_4$ reduction of this compound the fully reduced analogue **22** was obtained in 62% yield.



Scheme 3. Partial syntheses of diaza-oxa crown ethers incorporating polyamine elements (the numbers on the structures serve for the presentation of the NMR data).
(i) **5**/Et_3N/cat. HOBt, DMF/$CHCl_3$ (1:1), 25 ºC, 12 h, 59%. (ii) $LiAlH_4$, THF, reflux, 1 d, 62% (**22**) or 64% (**25**). (iii) TFA/CH_2Cl_2 (1:3), 25 ºC, 1 h, 90% (**23**) or (**26**). (iv) **6**/Et_3N, DMF/$CHCl_3$ (3:1), 25 ºC, 2 d, 92%.

Finally, TFA detritylation gave the tetra(trifluoroacetate) salt of CE **23** as in 90% yield.[4] This compound may be considered as a crowned oxa-SPM analogue. When SAE **6** was used to bisacylate diaza-oxa-18-CE-6 **2**, the expected tetra-amide **24** was obtained in 92% yield. $LiAlH_4$

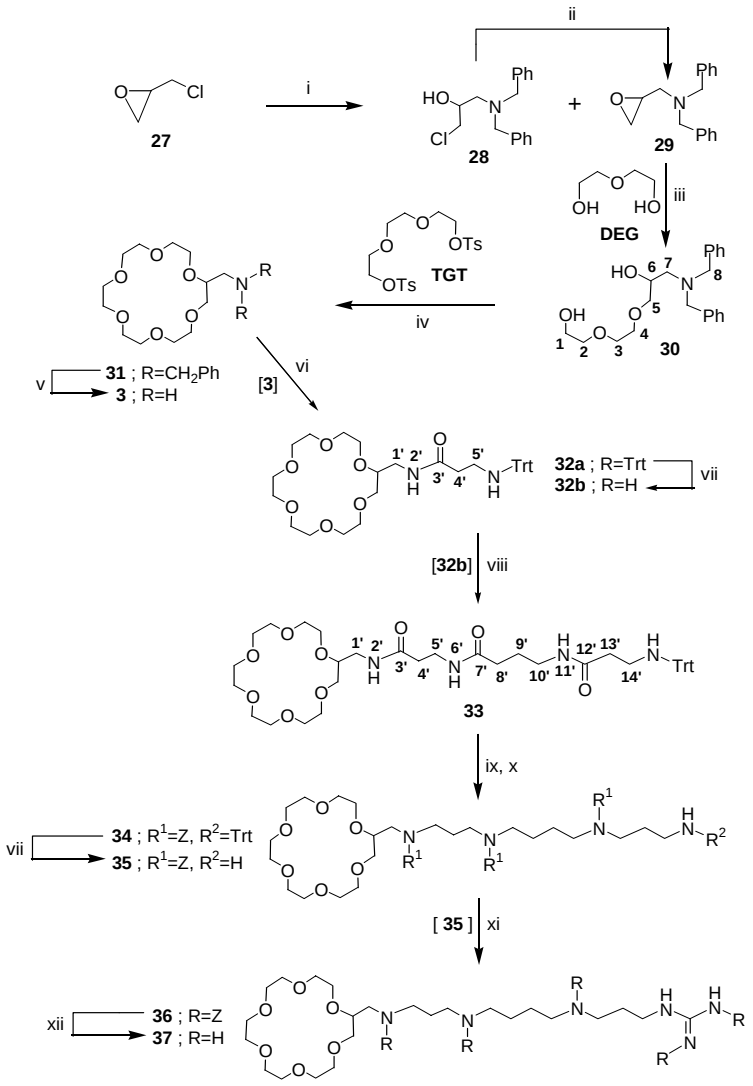
reduction of this compound gave a 64% yield of CE derivative **25**, from which the hexa(trifluoroacetate) salt of CRPA **26** was obtained in 90% yield.[4] This compound may be considered as a dioxa-3-4-8-4-3 PA analogue. It should be noted that the corresponding dioxa-3-8-3 PA analogue has been obtained by bisalkylation of CE **2** with acrylonitrile and subsequent catalytic hydrogenation over Raney Ni.[10]

Total syntheses of polyamines incorporating crown ether moieties

Having established the viability of this method we went on to synthesize more complex CRPAs. Taking into consideration the fact that the CEs so far used are commercially available compounds but very expensive for large scale applications, we decided to develop an alternative method for their preparation. For example, we envisaged that aminomethyl CE **3** could be readily produced using as a key-reaction the nucleophilic displacement of the Cl atom of epichlorohydrin (**27**) by a synthetically suitable amine. We have used two amines in the past, namely $TrtNH_2$[11] and Bn_2NH,[5b] to introduce the amino function into the γ-carboxy group of kainic acid, and at position 8 of SPD, respectively. It should be noted that aminomethyl CEs have been obtained so far either from the corresponding hydroxymethyl CEs through phthalimidation, followed by hydrazinolysis[12] or displacement of the Cl atom of chloromethylated glycol or oligoethylene glycols by ammonia or primary amines followed by CE formation by reaction with the appropriate oligoethylene glycol ditosylates or dichlorides.[13] In addition, it had been reported that the reaction of hindered amines with **27** leads to either 3-azetidinols in fair yields with primary amines and to a variety of products, some of which coming from EtOH used as the reaction solvent, with secondary amines.[14] To avoid these solvent-induced side-reactions we performed our exploratory experiments in **27** as the reaction medium. Much cleaner and reproducible results we obtained with Bn_2NH in place of $TrtNH_2$, and therefore, we used Bn_2NH for the preparation of aminomethyl CEs.

In fact, reaction of Bn_2NH with **27** in the presence of $^{i}Pr_2NEt$ as HCl scavenger, at 110 ºC for 2 h produced a mixture of two compounds which were readily separated in a small scale experiment by FCC and identified as the chlorohydrin **28** and the epoxide **29** (Scheme 4). Although this reaction mixture would have been used as such for the following transformation, namely the reaction with an oligoethylene glycol (OEG) in the presence of NaH, much better results were obtained when this mixture (ratio **28**:**29** = 3:2; or 2:3) by NMR, was first cleanly converted to the epoxide **29** (67% overall yield based on Bn_2NH) by treatment with NaH in THF at ambient temperature. NaH-catalyzed nucleophilic ring-opening of epoxides by OEGs have been used for the production of higher homologues of OEGs, suitable for CEs preparation.[15] Thus, treatment of epoxide **29** with diethylene glycol (DEG) in the presence of a catalytic quantity of NaH at refluxing THF for 2 days produced the anticipated triethylene glycol (TEG) derivative **30** in 75% yield. Preparation of the desired aminomethyl CE derivative **31** required as the final step the condensation of diol **30** with triethylene glycol ditosylate (TGT). Although several OEG ditosylates are commercially available, we used for the large scale preparation of DGT the method prescribed in ref. 2d, p. 84, an adaptation of the method by Ouchi *et al*,[16] TGT

and tetraethylene glycol ditosylate (TEGT; for its application cf. the following discussion). This method involves treatment of OEGs with tosyl chloride in the presence of NaOH in a mixture of THF/H_2O (2:1) as the solvent. On the other hand, an improved method has been recently published for the preparation of CEs exploiting the significant enhancement of the alkylation efficiency of alkoxides by ditosylates by using an unwashed 60% NaH dispersion in anhydrous DMSO.[17]



Scheme 4. Total synthesis of 2-aminomethyl-16-CE-6 and of related crowned polyamines (the numbers on the structures serve for the presentation of the NMR data).
(i) Bn_2NH/*i*Pr_2NEt, 110 ºC, 2 h, 40% **28** and 27% **29**. (ii) NaH/cat. imidazole, THF, 25 ºC, 1 h, 100%. (iii) NaH, THF, reflux, 2 d, 75%. (iv) 60% NaH dispersion, DMSO, 25 ºC, 2 d, 57%. (v) H_2(3 atm)/$Pd(OH)_2$ on C, MeOH, 25 ºC, 3 d, 96%. (vi) **5**/Et_3N, DMF, 25 ºC, 12 h, 93%. (vii) TFA/CH_2Cl_2 (1:1), 25 ºC, 30 min, 95% **32b** or 85% **35**. (viii) **6**/Et_3N, DMF, 0 ºC, 1 h then 25 ºC, 1 d, 79%. (ix) $LiAlH_4$, THF, reflux, 4 d. (x) ZCl/*i*Pr_2NEt, $CHCl_3$, 0 ºC, 30 min then 25 ºC, 12 h, 60%.

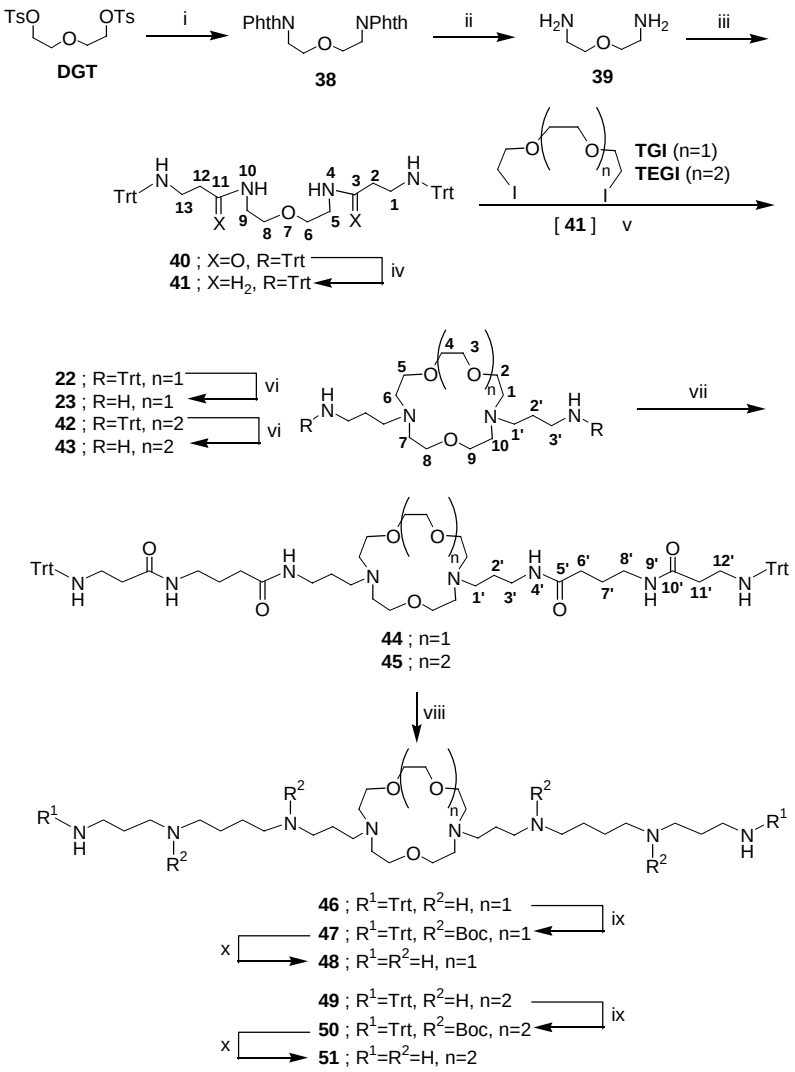
(xi) MeS-C(=NZ)-NHZ/ $^{i}Pr_2NEt$, $CHCl_3$, 0 ºC, 30 min then 25 ºC, 12 h, 82%. (xii) H_2(1 atm)/10% Pd-C, AcOH/MeOH/H_2O (4:1:0.1), 25 ºC, 6 h, then HCl/MeOH, 70% .

Indeed, using this method, the anticipated compound **31** was obtained in 57% yield. From this compound, the amino function was unmasked by catalytic hydrogenolysis at 3 atm and ambient temperature, using Pearlman′s catalyst [$Pd(OH)_2$ on C] to remove both benzyl groups.[5b,6b]

The aminomethyl CE **3** (obtained in 96% yield) was acylated without any further purification by SAE **5** to introduce the first N–3-C–N unit of SPM into CE. FCC purification afforded amide **32a** in 93% yield. This compound was detritylated with a solution of TFA in CH_2Cl_2, and the amino function was acylated with SAE **6** in the presence of Et_3N in order to introduce the remaining 4-C–N–3-C–N of SPM into CE. The expected trisamide **33** was obtained in 75% overall yield. Reduction of this amide with $LiAlH_4$, followed by complete benzyloxycarbonylation with benzyloxycarbonyl chloride (ZCl) produced the fully protected crowned SPM (CRSPM) **34** in 60% overall yield.[4] Complete benzyloxycarbonylation serves two purposes. It facilitates purification by FCC of the crude product produced by $LiAlH_4$ reduction of the amide functions and allows selective removal of the Trt group in the presence of the Z groups by mild acidolysis for further primary amino function modifications. For example, detritylation of CRSPM derivative **34** followed by guanidylation of the free primary amino group with the commercially available reagent 1,3-bis(benzyloxycarbonyl)-2-methyl-2-thiopseudourea (BZMTU) produced the fully protected guanidylated CRSPM derivative **36** in 70% yield. Complete deprotection is then readily effected by catalytic hydrogenolysis to produce the final product, the guanidylated CRSPM **37** in 70% yield. Natural and synthetic guanidylated polyamines[1a] and other types of organic compounds incorporating the guanidinium function[18] show very interesting biological properties, due to the fact that this function interacts strongly through hydrogen bonds and electrostatic interactions with other functional groups present in enzymes or receptors.

We then decided to synthesize diaza-oxa CEs incorporating PA elements in their skeleton, such as the CRPAs **23**, **43**, **48** and **51** (Scheme 5). We envisaged that CEs of this type might be readily available from a common precursor, i.e. the ditritylated oxo-SPM analogue **41**, by alkylation with various OEG diiodides (OEGIs). We based our reasoning on a well-established methodology (the Dale reaction) to produce aza-oxa CEs through the alkylation of primary or secondary diamines by OEGIs in the presence of anhydrous Na_2CO_3.[19] OEGIs are readily available from the corresponding ditosylates OEGTs through the classical displacement with NaI in acetone (see experimental section) whereas oxa-SPM derivative would be assembled from the diamine **39** and SAE **5**. Although several OEG α,ω-diamines (OEGAs) are commercially available, we obtained the required OEGA 39 from DGT through the classical two-steps sequence involving displacement with potassium phthalimide, followed by hydrazinolysis. For the purpose of this work, we isolated the bisphthalylhydrazide salt of OEGA **39** and used it as such for the coupling with SAE **5** in the presence of Et_3N. The expected bisamide **40** was

obtained in 77% yield. $LiAlH_4$ reduction of bisamide **40** proceeded unexceptionally to give the key-intermediate **41** in 85% yield. Bisalkylation of this intermediate with TGI in dry MeCN in the presence of anhydrous Na_2CO_3 produced ditritylated CRPA **22** in very good yield (73%), whereas its bisalkylation by TEGI in the presence of anhydrous K_2CO_3 gave access to the next higher CE homologue **42** in 66% yield. These CEs incorporate a symmetric oxa-3-5-3 tetra-amine skeleton and can be considered as oxa-SPM analogues.



Scheme 5. Total syntheses of diaza-oxa crowned polyamines. (the numbers on the structures serve for the presentation of the NMR data).
(i) PhthNK, DMF, 100-120 ºC, 12 h, 50%. (ii) $H_2NNH_2.H_2O$, MeOH, reflux, 30 min, 69%. (iii) SAE **5**/Et_3N, DMF, 0 ºC, 30 min then 25 ºC, 12 h, 77%. (iv) $LiAlH_4$, THF, reflux, 2 d, 85%. (v) Na_2CO_3 (TGI) or K_2CO_3 (TEGI), MeCN, reflux, 2 d, 73% (**22**) or 66% (**42**). (vi) TFA/CH_2Cl_2 (1:3), 1 h, 25 ºC, 90-100%. (vii) SAE **6**/Et_3N, DMF, 0 ºC, 30 min then 25 ºC, 1 d, 68% (**44**) or 55%

(**45**). (viii) $LiAlH_4$, THF, reflux, 4 d. (ix) Boc_2O/Et_3N/cat. DMPA, $CHCl_3$, 0 ^oC, 15 min then 25 ºC, 12 h, 35% (**47**) or 26% (**50**). (x) TFA/CH_2Cl_2 (1:1), 20 min, 25 ºC, 83–88%.

Detritylation of these compounds provided the corresponding CRPAs **23** and **43**, which upon coupling with the SAE **6**, also in the presence of Et_3N, gave the tetra-amides **44** and **45** in 68 and 55% yield, respectively. These tetra-amides were subsequently reduced with $LiAlH_4$ at refluxing THF to produce the corresponding crude ditritylated CRPAs **46** and **49**. For purification by FCC, these compounds were per-*tert*-butoxycarbonylated with bis(*tert*-butyl)dicarbonate (Boc_2O) in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) to give the fully protected CRPAs **47** and **50** in 35% and 26% overall yields, respectively, based on the starting tetra-amides. Finally, TFA-mediated detritylation of these intermediates gave the desired CRPAs **48** and **51** in 88% and 83% yield, respectively. These CEs incorporate a symmetric oxa-3-4-3-5-3-4-3 octa-amine skeleton.

Conclusions

Linear and crowned polyamines of variable length or ring-sizes and number of nitrogen functions in their skeleton can be readily assembled using the isolable succinimidyl active esters of the *N*-tritylated amino acid βAla and peptide βAla-γAba to couple to α,ω-diamino-alkanes and -dibenzocrown ethers, diaza-oxa crown ethers and aminomethyl crown ethers, followed by $LiAlH_4$-mediated reduction of the thus obtained polyamides. The required amino components were either commercially available or were readily synthesized in our laboratory employing, also commercially available, building blocks like oligoethylene glycols, epichlorohydrin and dibenzylamine and the alkylation of either oligoethylene alkoxides by oligoethylene tosylates or oligoethylene diamines by oligoethylene diiodides as key-reactions for the assembly of the crown or diaza-oxa crown ether skeleta, respectively. Further applications of this general approach to the synthesis of other types of crowned polyamines and conjugates and the evaluation of the metal-complexing and biological properties of the novel crowned polyamines described in this work are currently under investigation.

Experimental Section

General Procedures. Melting points were determined with a Buchi SMP-20 apparatus and are uncorrected. IR spectra were recorded for KBr pellets on a Perkin Elmer 16PC FT-IR spectrophotometer. ^{1}H-NMR spectra were obtained at 400.13 MHz and ^{13}C-NMR spectra at 100.62 MHz on a Bruker DPX spectrometer. $CDCl_3$ and tetramethylsilane (TMS) were used as the solvent and internal standard, respectively, unless otherwise stated. Chemical shifts are reported in δ units, parts per million () downfield from TMS. The assignments of the ^{1}H spectra

are based on chemical shift arguments, analysis of coupling patterns and signal intensities whereas the ^{13}C spectra were assigned taking into consideration chemical shift arguments. Data for the aromatic region (trityl group) are omitted for ^{1}H and ^{13}C NMR spectra of the *N*-tritylated compounds for the sake of brevity. The values observed for compound **7** are typical: ^{1}H NMR: δ 7.417 (6H, d, *J* = 8.0 Hz, *o*-H), 7.268 (6H, t, *J* = 7.6 Hz, *m*-H), 7.191 (3H, t, *J* = 7.2 Hz, *p*-H). ^{13}C NMR: δ 146.321 (*ipso*-C), 128.957 (*o*-C), 128.460 (*m*-C), 126.630 (*p*-C).

Electron-impact ionization mass spectra (EI-MS) were obrtained on a Fisons VG 7070E mass spectrometer with electron beam energy of 70 eV. Fast atom bombardment (FAB) mass spectra were recorded on a Fisons VG ZAB 2F operating at an accelerating potential of 8 kV and neutral xenon beam of 9 eV and using *m*-nitrobenzyl alcohol (NBA) as the matrix. Liquid secondary ion ionization (LSI) mass spectra in the positive mode were obtained on a Fisons VG ZAB-T four-sector instrument. The compounds were ionized using a caesium ion gun operated at an acceleration voltage of 30 kV. NBA was also used as the matrix solution which was carefully mixed with a 1 μL of sample solution in $CHCl_3$ on the tip of the probe prior to analysis. Electron-spray ionization (ESI) mass spectra were recorded on a Micromass-Platform LC spectrometer using MeOH or MeCN as solvents. The ESI high-resolution MS (HR-MS) experiments were carried out in a hybrid Q*q*TOF mass spectrometer equipped with an ion spray ionization source. Compounds were dissolved in a solution containing 0.1% acetic acid in methanol/water 50/50 and analyzed by direct infusion (5□L/min) at the optimum ion spray voltage of 4800V. The nitrogen gas flow was set at 30 psi, whereas the orifice, the focusing ring and the skimmer voltages were kept at 30, 50 and 25V, respectively. MS/MS experiments were performed in the collision cell *q* on the isotopically pure (^{12}C) peak of the selected precursor ions by keeping the Q1 at 20 or 30V and unit resolution, and scanning the TOF analyser. All the acquisitions were averaged over 50 scans at 8000 TOF resolution with a standard deviation of 0.01 cps. Microanalyses were performed on a Carlo Erba EA 1108 CHNS elemental analyzer in the Center of Instrumental Analysis of the University of Patras.

Flash column chromatography (FCC) was performed on Merck silica gel 60 (230-400 mesh) and TLC on 60 Merck $60F_{254}$ films (0.2 mm) precoated on aluminium foil. The solvent or solvent systems used for elution were: (A) PhMe/EtOAc (98:2), (B) PhMe/EtOAc (8:2), (C) PhMe/EtOAc (1:1), (D) PhMe/EtOAc (4:6), (E) EtOAc, (F) $CHCl_3$/MeOH (95:5), (G) $CHCl_3$/MeOH (9:1), (H) $CHCl_3$/MeOH/conc. NH_3 (95:5:0.5), (I) $CHCl_3$/MeOH/conc. NH_3 (9:1:0.05), (J) $CHCl_3$/MeOH/conc. NH_3 (9:1:0.1), (K) $CHCl_3$/MeOH/conc. NH_3 (85:15:1.5), (L) $CHCl_3$/MeOH/conc. NH_3 (8:2:0.2), (M) $CHCl_3$/MeOH/conc. NH_3 (9:2.5:0.2), (N) $CHCl_3$/MeOH/conc. NH_3 (7:3:0.3), (O) $CHCl_3$/MeOH/conc. NH_3 (6:4:0.4). Spots were visualized with UV light at 254 nm and the ninhydrin agent. All solvents (Merck) were dried and/or purified according to standard procedures prior to use. Anhydrous Na_2SO_4 was used for drying organic solvents, unless otherwise indicated, and subsequently solvents were routinely removed at ca. 40 ºC under reduced pressure (water aspirator). All reagents employed in the present work were purchased from either Aldrich or Fluka and used without further purification. NaH was purchased as a 60% dispersion in mineral oil. It was routinely washed off oil by

repeated washings with hexane prior to use, unless otherwise stated. With the exception of TFA-mediated deprotections, all other reactions were routinely carried out in an atmosphere of Ar.

***N*-Trityl-β-alanine (7).** To a magnetically stirred suspension of βAla (17.82 g, 0.2 mol) in anhydrous CH_2Cl_2 (250 mL) and MeCN (50 mL) was added Me_3SiCl (27.9 mL, 0.22 mol), and the reaction mixture was refluxed with exclusion of moisture for 30 min. To the ice-cooled (0 ºC) resulting solution anhydrous Et_3N (61 mL, 0.44 mol) was added dropwise followed by the addition of TrtCl (58.5 g, 0.21 mol) in three equal portions within 15 min. Stirring was continued at 0 ºC for 1 h, and at ambient temperature for 3 h. MeOH (20 mL) was then introduced into the reaction mixture and the solvents were evaporated to dryness. To the resulting residue, aqueous NaOH solution (1N, 700 mL) was added and then extracted twice with Et_2O. The aqueous phase was then ice-cooled and brought to pH 5 by the dropwise addition of glacial AcOH. A 5% aqueous citric acid solution was then added to further acidify the reaction mixture until no more precipitate was formed. The precipitate was filtered and washed on the filter twice with H_2O and then with ice-cold Et_2O and finally dried under vacuo at 40 ºC overnight to give pure product **7** (64.3 g. 97%), mp 166–69 ºC; R_f (G) 0.33. FT-IR: 3455-2500 (CO-*OH*), 3298 (*NH*-Trt), 1708 (*CO*-OH), 1594 (Ph C=C) cm^{-1}. EI-MS (m/z): 331 (*M*), 243 (Trt), 165 (Trt-PhH). ^{1}H NMR: δ 4.900 (2H, br. s, N*H*, CO_2H), 2.506 (2H, t, *J* = 5.2 Hz, NCH_2), 2.451 (2H, t, *J* = 5.2 Hz, CH_2CO). ^{13}C NMR: δ 176.736 (CO_2H), 71.866 (Ph_3C), 39.785 (NCH_2), 35.061 (CH_2CO_2H). Anal. Calcd for $C_{22}H_{21}NO_2$ (331.42): C, 79.73; H, 6.39; N, 4.23. Found: C, 79.93; H, 6.11; N, 4.05.

2,5-Dioxopyrrolidin-1-yl *N*-trityl-β-alaninate (5). To an ice-cold suspension of Trt-βAla (24.4 g, 73.6 mmol) in THF (150 mL) and DMF (50 mL) was added HOSu (10.2 g, 88.3 mmol) and subsequently after 10 min DCC (16.7 g, 81 mmol). The resulting reaction mixture was stirred at 0 ºC for 1 h and then at ambient temperature overnight. The precipitated *N*,*N*′-dicyclohexylurea (DCU) was filtered off, and the residue on the filter was washed with hot THF. The filtrate was evaporated under reduced pressure, and the residue was taken up in EtOAc (300 mL) and washed twice with an ice-cold saturated aqueous NaCl solution (brine). Drying, evaporation to one third of the volume and refrigeration overnight gave crystalline product SAE **5** (26.8 g, 85%), mp 178–80 ºC; R_f(E) 0.63. FT-IR: 3326 (*NH*-Trt), 1818 and 1782 (*CO*-OSu), 1746 (N-*CO*)) cm^{-1}. LSI-MS (m/z): 451 (*M*Na), 429 (*M*H), 351 (*M*H-PhH), 243 (Trt), 165 (Trt-PhH). ^{1}H NMR: δ 2.788 (6H, m, H-2 and $CO(CH_2)_2CO$), 2.518 (2H, t, *J* = 6.4 Hz, H-3), 2.083 (1H, br. s, NH). ^{13}C NMR: δ 169.452 ($COCH_2$), 168.302 (C-1), 71.367 (Ph_3C), 39.496 (C-3), 32.947 (C-2), 25.982 ($COCH_2$). Anal. Calcd for $C_{26}H_{24}N_2O_4$ (428.49): C, 72.88; H, 5.65; N, 6.54. Found: C, 73.03; H, 5.75; N, 6.24.

***N*-Trityl-β-alanyl-γ-aminobutyric acid (8).** To a magnetically stirred suspension of γAba (6.6 g, 64 mmol) in anhydrous CH_2Cl_2 (90 mL) was added Me_3SiCl (8.9 mL, 70.4 mmol), and the reaction mixture was stirred at ambient temperature for 10 min. The resulting solution was ice-cooled and then treated with SAE **5** (24.9 g, 58 mmol) followed by the dropwise addition of anhydrous Et_3N (16 ml, 115 mmol) within 30 min. Stirring was continued at 0 ºC for 15 min and at ambient temperature for 15 min. MeOH (5 mL) was introduced, the resulting reaction mixture

was diluted with CH_2Cl_2 (300 mL) and then washed once with an ice-cold 5% aqueous citric acid solution and twice with H_2O. Drying and evaporation to dryness left a residue which, upon dissolution in a minimum volume of hot EtOAc and overnight refrigeration gave crystalline dipeptide acid **8** (19.1 g, 79%), mp 157–59 ºC; R_f(G) 0.16. FT-IR: 3300-2500 (OH), 3298 (NH), 1712 (*CO*-OH), 1634 (NH-*CO*)) cm^{-1}. EI-MS (m/z): 417 (*M*H), 339 (*M*H-PhH), 243 (Trt), 165 (Trt-PhH). ^{1}H NMR (DMSO-d_6): δ 7.848 (1H, unresolved t, H-5), 3.024 (2H, q, *J* = 6.0 Hz, H-4), 2.247 (2H, t, *J* = 6.4 Hz, H-8), 2.200 (2H, t, *J* = 7.2 Hz, H-2), 2.145 (2H, t, *J* = 6.4 Hz, H-7), 1.600 (2H, quintet, *J* = 7.2 Hz, H-3). ^{13}C NMR: δ 175.082 (C-1), 172.263 (C-6), 71.127 (Ph_3C), 40.342 (C-4), 38.664 (C-8), 36.995 (C-2), 31.944 (C-7), 24.869 (C-3). Anal. Calcd for $C_{26}H_{28}N_2O_3$ (416.52): C, 74.98; H, 6.78; N, 6.72. Found: C, 75.14; H, 6.50; N, 6.44.

Succinimidyl *N*-trityl-β-alanyl-γ-aminobutyrate (6). To an ice-cold suspension of Trt-βAla-γAba (19.6 g, 47 mmol) in THF (110 mL) and DMF (40 mL) was added HOSu (6.1 g, 53 mmol) followed after 10 min by DCC (10.5 g, 51 mmol). The resulting reaction mixture was stirred at 0 ºC for 1 h and then at ambient temperature overnight. The precipitated DCU was filtered off and washed on the filter with hot THF. The filtrate was evaporated under reduced pressure, and the residue was taken up in EtOAc (200 mL) and washed twice with ice-cold brine. Drying, evaporation to dryness, dissolution of the oily residue in CH_2Cl_2, overnight refrigeration and filtration removed an additional amount of DCU. Evaporation of CH_2Cl_2 and addition of Et_2O followed by overnight refrigeration gave the crystalline product SAE **6** (21.2 g, 88%), mp 101–04 ºC; R_f(E) 0.57. FT-IR: 3326 and 3296 (NH), 1816 and 1788 (*CO*-OSu), 1740 (N-*CO*) and 1630 (NH-*CO*) cm^{-1}. LSI-MS (m/z): 536 (*M*Na), 514 (*M*H), 436 (*M*H-PhH), 339 [*M*H-N$(COCH_2)_2$-Ph], 243 (Trt), 165 (Trt-PhH). ^{1}H NMR: δ 6.720 (1H, unresolved t, H-5), 3.363 (2H, q, *J* = 6.4 Hz, H-4), 2.790 (4H, br. s, CO$(CH_2)_2$CO), 2.638 (2H, t, *J* = 6.8 Hz, H-2), 2.473 (2H, t, *J* = 5.6 Hz, H-8), 2.372 (2H, t, *J* = 5.6 Hz, H-7), 1.980 (2H, quintet, *J* = 6.8 Hz, H-8). ^{13}C NMR: δ 172.268 (C-6), 169.627 (*C*O$(CH_2)_2$*C*O), 168.767 (C-1), 71.558 (Ph_3C), 46.342 (C-4), 38.646 (C-8), 37.057 (C-2), 29.062 (C-7), 26.448 (CO$(CH_2)_2$CO), 25.927 (C-3). Anal. Calcd for $C_{30}H_{31}N_3O_5$ (513.59): C, 70.16; H, 6.08; N, 8.18. Found: C, 69.93; H, 6.30; N, 8.29.

1*N*,12*N*-Bis(tritylamino)-4,9-diazadodecane-3,10-dione (9a). To a magnetically stirred solution of SAE **5** (25.71 g, 60 mmol) in DMF (230 mL) was added PUT (2.64 g, 30 mmol). After 15 min at ambient temperature, the pH of the reaction mixture was adjusted to 8 by the addition of Et_3N, followed by stirring at for 24 h. The reaction mixture was then diluted with H_2O (600 mL), and the precipitated product was extracted with CH_2Cl_2. The organic phase was washed sequentially once with H_2O, twice with a 5% aqueous $NaHCO_3$ solution and finally twice with H_2O, dried and evaporated to a volume that induced crystallization. Refrigeration, filtration of the precipitated solid and washing on the filter initially with ice-cold CH_2Cl_2 followed by Et_2O and hexane gave pure bisamide **9a** (19.3 g, 90%), mp 182–85 ºC; R_f(G) 0.68. FT-IR: 3328 and 3277 (NH), 1634 (NH-*CO*) cm^{-1}. FAB-MS (m/z): 716 (*M*H), 473 (*M*-Trt), 395 (*M*-Trt-PhH), 243 (Trt). ^{1}H NMR: δ 6.503 (2H, unresolved t, H-4 and H-9), 3.371 (4H, q, *J* = 5.6 Hz, H-5 and H-8), 2.434 (4H, t, *J* = 6.0 Hz, H-1 and H-12), 2.295 (4H, t, *J* = 6.0 Hz, H-2 and H-11), 1.546 (4H, m, H-6, H-7). ^{13}C NMR: δ 172.782 (C-3 and C-10), 71.381 (Ph_3C), 40.334 (C-5

and C-8), 39.377 (C-1 and C-12), 37.526 (C-2 and C-11), 27.417 (C-6 and C-7). Anal. Calcd for $C_{48}H_{50}N_4O_2$ (714.96): C, 80.64; H, 7.05; N, 7.84. Found: C, 80.84; H, 6.87; N, 7.60.

1*N*,12*N*-Bis[3-(tritylamino)propyl]butane-1,4-diamine (10a). To a magnetically stirred suspension of $LiAlH_4$ (6.4 g, 168 mmol) in anhydrous THF (220 mL) at reflux temperature was added bisamide **9a** (20 g, 28 mmol) in *ca.* equal portions within 30 min, and refluxing was continued for 4 d. The resulting reaction mixture was ice-cooled, and excess $LiAlH_4$ was carefully quenched by dropwise addition of a saturated aqueous Na_2SO_4 solution. The resulting salts were filtered off by vacuum filtration and washed on the filter with distilled THF. The filtrate was concentrated to dryness, and the resulting oily residue was dissolved in EtOAc and washed twice with brine. Drying and evaporation gave an oily residue which upon trituration with Et_2O and refrigeration gave SPM derivative **10a** (13 g, 68%). This product was recrystallized from MeOH (700 mL), mp 116–17 ºC; R_f(M) 0.78. FT-IR: 3268 (*NH*) cm^{-1}. FAB-MS (m/z): 688 (*M*H), 609 (*M*-PhH), 445 (*M*-Trt), 367 (*M*-Trt-PhH), 243 (Trt). HR-MS: Found 687.4441 (M^++1), $C_{48}H_{55}N_4$ requires M^++1 = 687.4427. ^{1}H NMR: δ 2.656 (4H, t, *J* = 7.2 Hz, H-1 and H-12), 2.580 (4H, unresolved t, H-3 and H-10), 2.184 (4H, unresolved t, H-5 and H-8), 1.752 (2H, br. s, H-4 and H-9), 1.650 (4H, quintet, *J* = 6.8 Hz, H-2 and H-11), 1.475 (4H, unresolved quintet, H-6 and H-7). ^{13}C NMR: δ 71.320 (Ph_3C), 50.440 (C-1 and C-12), 48.966 (C-3 and C-10), 42.528 (C-5 and C-8), 31.498 (C-2 and C-11), 28.499 (C-6 and C-7) . Anal. Calcd for $C_{48}H_{54}N_4$ (686.99): C, 83.92; H, 7.92; N, 8.16. Found: C, 83.71; H, 8.05; N, 8.30.

1*N*,16*N*-Bis(tritylamino)-4,13-diazahexadecane-3,14-dione (9b). To a magnetically stirred ice-cold solution of DAO (0.72 g, 5 mmol) in dry DMF (8 mL) was added anhydrous Et_3N (1.4 mL, 10 mmol), followed by SAE **5** (4.46 g, 10.4 mmol). The reaction mixture was stirred at 0 ºC for 30 min and then at ambient temperature overnight.. It was then diluted with $CHCl_3$ and washed sequentially twice with a 5% aqueous $NaHCO_3$ solution and thrdee times with H_2O, dried, evaporated, and the residue was triturated with Et_2O. Overnight refrigeration gave pure bisamide **9b** (3 g, 78%), mp 158–59 ºC; R_f(E) 0.43. FT-IR: 3290 (NH), 1629 (NH*CO*) cm^{-1}. ESI-MS (m/z): 772.13 (*M*H). ^{1}H NMR: δ 6.332 (2H, t, *J* 5.20 Hz, H-4 and H-9), 3.210 (4H, t, *J* = 6.4 Hz, H-5 and H-8), 2.446 (4H, t, *J* = 6.0 Hz, H-1 and H-12), 2.311 (4H, t, *J* = 6.0 Hz, H-2 and H-11), 1.487 (4H, quintet, *J* = 6.8 Hz, H-6 and H-7), 1.284 (8H, br. s, H-6′, H-7′, H-6″ and H-7″). ^{13}C NMR: δ 172.454 (C-3 and C-10), 71.437 (Ph_3C), 40.362 (C-5 and C-8), 39.789 (C-1 and C-12), 37.638 (C-2 and C-11), 30.046 (C-6 and C-7), 29.520 (C-6′ and C-7′), 27.277 (C-6″ and C-7″). Anal. Calcd for $C_{52}H_{58}N_4O_2$ (771.06): C, 81.00; H, 7.58; N, 7.27. Found: C, 81.20; H, 7.32; N, 7.15.

1*N*,16*N*-Bis[3-(tritylamino)propyl]octane-1,8-diamine (10b). Bisamide **9b** (1.55 g, 2 mmol) was treated with $LiAlH_4$ (0.46 g, 12 mmol) in anhydrous THF (25 mL) for 2 d as described for **9a**. Following identical work-up procedure followed by FCC purification using the solvent system I as eluant,. pure tetra-amine **10b** was obtained as an oil (0.9 g, 67%), R_f(I) 0.5. ESI-MS (m/z): 743.05 (*M*H), 501.39 (*M*H-Trt), 243 (Trt). HR-MS (m/z): Found 743.5053 (M^++1), $C_{52}H_{63}N_4$ requires M^++1 = 743.5056. ^{1}H NMR: δ 2.741 (4H, t, *J* = 7.2 Hz, H-3 and H-10), 2.627 (4H, t, *J* = 7.2 Hz, H-1 and H-12), 2.204 (4H, t, *J* = 6.8 Hz, H-5 and H-8), 1.734 (4H, quintet, *J* =

6.0 Hz, H-2 and H-11), 1.517 (4H, quintet, *J* = 6.8 Hz, H-6 and H-7), 1.299 (8H, m, (C-6′,7′,6″,7″). ^{13}C NMR: δ 71.338 (Ph_3C), 50.287 (C-3 and C-10), 48.898 (C-1 and C-12), 42.449 (C-5 and C-8), 30.584 (C-2 and C-11), 29.815 (C-6 and C-7), 29.449 (C-6′,7′), 27.388 (6″,7″). Anal. Calcd for $C_{52}H_{62}N_4$ (743.09): C, 84.05; H, 8.41; N, 7.54. Found: C, 84.20; H, 8.15; N, 7.41.

1*N*,22*N*-Bis(tritylamino)-1,4,9,14,19,22-hexaazadocosane-3,8,15,20-tetraone (11). To a magnetically stirred ice-cold solution of PUT (0.32 g, 3.6 mmol) in dry DMF (10 mL) was added anhydrous Et_3N (1 mL, 7.2 mmol), followed by SAE **6** (3.7 g, 7.2 mmol). The reaction mixture was stirred at 0 ºC for 30 min and then at ambient temperature overnight.. It was then diluted with $CHCl_3$ and washed sequentially with a 5% aqueous $NaHCO_3$ solution (twice) and with H_2O (three times), dried, evaporated to a volume that induced crystallization. Overnight refrigeration gave pure tetra-amide **11** (2.61 g, 82 %), mp 185–86 ºC; R_f(E) 0.32. FT-IR: 3290 (NH), 1635 (NH*CO*) cm^{-1}. ESI-MS (m/z): 886.41 (MH), 243.12 (Trt). Anal. Calcd for $C_{56}H_{64}N_6O_4$ (885.17): C, 75.99; H, 7.29; N, 9.49. Found: C, 75.80; H, 7.49; N, 9.67.

***N*^{4},*N*^{9},*N*^{14},*N*^{19}-Tetra(*tert*-butoxycarbonyl)-*N*^{1},*N*^{22}-ditrityl-1,22-diamino-4,9,14,19-tetraazadocosane (13).** Tetra-amide **11** (1.28 g, 1.45 mmol) was treated with $LiAlH_4$ (0.55 g, 14.5 mmol) in anhydrous THF (10 mL) for 4 d as described for **9a**. Identical work-up afforded the crude product **12** as an oil, R_f (O) 0.16. To a solution of this product in anhydrous $CHCl_3$ (4 mL) were added dry Et_3N (1 mL, 7.25 mmol) and DMAP (0.1 g, 0.8 mmol), the mixture was cooled to 0 ºC and treated with Boc_2O (1.58 g, 7.25 mmol) for 30 min at this temperature and at ambient temperature overnight. The resulting solution was diluted with more $CHCl_3$ and washed sequentially with a 5% aqueous $NaHCO_3$ solution and with H_2O (twice), dried and evaporated to leave a residue. From this residue upon FCC purification using solvent system B as eluant pure product **13** (0.54 g, 30%) was obtained as a white foam, R_f(B) 0.37. ESI-MS (m/z): 1,229.82 (*M*), 987.81 (*M*-Trt), 243 (Trt). $C_{76}H_{104}N_6O_8$ requires M^+ = 1,229.70.

4,9,14,19-Tetraazadocosane-1,22-diamine (14). A solution of the protected hexa-amine **13** (0.39 g, 0.32 mmol) in CH_2Cl_2/TFA (1:1, 4 mL) was kept at ambient temperature for 30 min. Evaporation to dryness, trituration with Et_2O and overnight refrigeration gave the hexa(trifluoroacetate) salt of hexa-amine **14** (0.25 g, 75%) as an oil. HR-MS: Found 345.3715 (M^++1), $C_{18}H_{45}N_6$ requires M^++1 = 345.3706.

2-(10′-Tritylamino-3′,8′-dioxo-2′,7′-diazadecyl)-1,4,7,10,13,16-hexaoxacyclohexadecane (15). To a magnetically stirred solution of commercial crown ether **5** (1 g, 3.41 mmol) in anhydrous DMF (4 mL) at ambient temperature were added sequentially dry Et_3N (0.5 mL, 3.6 mmol) and SAE **6** (1.75 g, 3.41 mmol). After an additional 1 h the reaction mixture was diluted with $CHCl_3$ and washed sequentially with a 5% aqueous $NaHCO_3$ solution and with brine (twice). Drying and evaporation to dryness furnished a residue from which upon FCC purification with solvent system G as eluant bisamide **15** (1.56 g, 66%) was obtained as an oil, R_f(G) 0.08. ESI-MS (m/z): 731,35 (*M*K), 715.08 (*M*Na), 693.02 (*M*H), 243.11 (Trt). $C_{39}H_{53}N_3O_8$ requires M^+ = 691.83.

2-(10′-Tritylamino-2′,7′-diazadecyl)-1,4,7,10,13,16-hexaoxacyclohexadecane (16). A solution of bisamide **15** (1.56 g, 2.25 mmol) in anhydrous THF (13 mL) was added dropwise within 45 min to a magnetically stirred suspension of $LiAlH_4$ (0.44 g, 13.5 mmol) in refluxing THF (5 mL). The reaction mixture was stirred at this temperature overnight and was worked-up as described for the preparation of **10a**. From the resulting crude reaction product upon FCC purification using the solvent system L as eluant pure product **16** (0.66 g, 45%) was obtained as an oil, R_f(N) 0.21. ESI-MS (m/z): 687 (*M*Na), 665 (*M*H), 422 (*M*H-Trt), 243 (Trt). $C_{39}H_{57}N_3O_6$ requires M^+ = 663.90. ^{1}H NMR: δ 3.907 (1H, ddd, J= 6.6, 4.4 and 3.6 Hz, C*H*-O), 3.678 (22H, m, CH_2-O), 2.695 (4H, m, H-1′ and H-3′), 2.614 (4H, m, H-6′ and H-8′), 2.179 (2H, t, *J* = 6.8 Hz, H-10′), 2.054 (3H, br. s, N*H*), 1.687 (2H, t, *J* = 6.4 Hz, H-9′), 1.520 (4H, m, H-4′ and H-5′) . ^{13}C NMR: δ 78.880 (*C*H-O), 71.337 (Ph_3C), 73.395, 71.251-70.959 and 70.187 (11C, CH_2-O), 51.466 (C-1′), 50.298 and 50.255 (C-6′ and C-8′), 48.786 (C-3′), 42.490 (C-10′), 31.287 (C-9′), 28.307 (C-4′ and C-5′) .

2-(10′-Amino-2′,7′-diazadecyl)-1,4,7,10,13,16-hexaoxacyclohexadecane (17). A solution of tritylated triamine **16** (0.45 g, 0.68 mmol) in 6 mL of CH_2Cl_2/TFA (1:1) was kept at ambient temperature for 1 h. Evaporation to dryness, trituration with Et_2O and refrigeration for several days gave pure triamine **17** as tristrifluoroacetate salt (0.38 g, 73%), mp 136–40 ºC; R_f(N) 0.06. HR-MS (m/z): Found 422.2647 (M^++1), $C_{20}H_{44}N_3O_6$ requires M^++1 = 422.2656.

***N*$^{4'}$,*N*$^{4''(5'')}$-Bis(3-tritylaminopropanoyl)-4′,4″(5″)-diaminodibenzo-15-crown ether-5 (18).** To a magnetically stirred suspension of crown ether **6** (1 g, 2.89 mmol) in anhydrous DMF (6 mL) *i*Pr_2NEt (1 mL, 6 mmol) and SAE **5** (2.49 g, 5.8 mmol) were added sequentially, and the resulting reaction mixture was kept at 60 ºC for 2 h. It was then treated with an additional quantity of SAE **5** (0.43 g, 1 mmol) for a further 1 h at that temperature and for overnight at ambient temperature. The reaction mixture was diluted with $CHCl_3$ and washed sequentially with a 5% aqueous K_2CO_3 solution (twice) and with H_2O, dried ($MgSO_4$) and evaporated to leave a residue. Upon FCC purification using EtOAc as eluant pure **18** (1.55 g, 55%) was obtained as a beige foam, R_f(E) 0.27. ESI-MS (m/z): 996 (*M*Na), 316 [TrtNH$(CH_2)_2$CHO+H], 288 (TrtNHCH_2CH_3+H), 243 (Trt). $C_{62}H_{60}N_4O_7$ requires M^+ = 973.18.

***N*$^{4'}$,*N*$^{4''(5'')}$-Bis(3-tritylaminopropyl)-4′,4″(5″)-diaminodibenzo-15-crown ether-5 (19).** Bisamide **18** (1.5 g, 1.54 mmol) was added portionwise within 30 min to a magnetically stirred suspension of $LiAlH_4$ (0.3 g, 9 mmol) in refluxing THF (10 mL). The reaction mixture was stirred at this temperature for 2 d. Excess hydride was destroyed at –10 ºC` by the dropwise addition of a saturated aqueous K_2SO_4 solution. Filtration, washing with distilled THF, and finally evaporation of the filtrates left a residue. This was taken-up in EtOAc and washed twice with the above mentioned K_2SO_4 solution, dried ($MgSO_4$) and evaporated to dryness. FCC purification using initially solvent system C followed by solvent system D gave pure product **19** (1.19 g, 82%) as an oil, R_f(C) 0.25. ESI-MS (m/z): 946 (*M*H), 258(TrtNH), 243 (Trt). $C_{62}H_{64}N_4O_5$ requires M^+ = 945.11. ^{1}H NMR: δ 6.819 (2H, d, *J* = 8.8 Hz, H-4″), 6.219 (2H, unresolved d, H-1″), 6.143 (2H, dd, *J* = 8.8 and 2.4 Hz, H-3″), 4.26-4.25 (4H, m, H-5 and H-6), 4.128 (4H, t, *J* = 4.0 Hz, H-1 and H-4), 3.919 (4H, t, *J* = 4.4 Hz, H-2 and H-3), 3.163 (4H, t, *J* =

6.4 Hz, H-1′), 2.270 (4H, t, *J* = 6.0 Hz, H-3′), 1.755 (4H, quintet, *J* = 6.0 Hz, H-2′). ^{13}C NMR: δ 151.311 (C-6″), 144.896 (C-5″), 142.095 (C-2″), 102.564 (C-1″), 105.542 (C-3″), 119.113 (C-4″), 71.511 (Ph_3C), 70.873 (C-5 and C-6), 70.298 and 70.255 (4C, C-1/2/3/4), 43.648 (C-1′), 42.280 (C-3′), 30.869 (C-2′) .

***N*$^{4'}$,*N*$^{4''(5'')}$-Bis(3-aminopropyl)-4′,4″(5″)-diaminodibenzo-15-crown ether-5 (20).** A solution of tritylated tetra-amine **19** (1.1 g, 1.16 mmol) in CH_2Cl_2/TFA (3:1, 10 mL) was kept at ambient temperature for 1 h. Evaporation to dryness, trituration with Et_2O and refrigeration for 1 d, followed by decantation of the supernatant liquor and repetition of this procedure gave pure tetra-amine **20** (0.97 g, 91%) as the tetra(trifluoroacetate) salt in the form of a beige foam, R_f(G) 0.02. HR-MS (m/z): Found 461.2044 (M^++1), $C_{24}H_{37}N_4O_5$ requires M^++1 = 461.2039.

***N*^{7},*N*^{13}-Bis(3-tritylaminopropanoyl)-1,4,10-trioxa-7,13-diazacyclopentadecane (21).** To a magnetically stirred solution of aza-oxy crown ether **1** (1 g, 4.58 mmol) in anhydrous DMF (5 mL) and $CHCl_3$ (5 mL) were added dry Et_3N (1.4 mL, 10 mmol), SAE **5** (4.28 g, 10.mmol) and a catalytic amount of HOBt (54 mg, 0.4 mmol), and the resulting reaction mixture was stirred at ambient temperature overnight. Dilution with $CHCl_3$, washing with H_2O (twice), drying and evaporation left a residue from which upon FCC purification using $CHCl_3$ as eluant and followed by solvent system G pure bisamide **21** (2.28 g, 59%) was obtained as an oil, R_f(G) 0.85. ESI-MS (m/z): 846.27 (*M*H), 243.11 (Trt). $C_{54}H_{60}N_4O_5$ requires M^+ = 845.09. From the same column, monoacylated **1** (0.34 g, 14%) was also eluted; ESI-MS (m/z): 532.44 (*M*H), 243.11 (Trt). $C_{32}H_{41}N_3O_4$ requires M^+ = 531.62.

***N*^{7},*N*^{13}-Bis(3-tritylaminopropanoyl)-1,4,10-trioxa-7,13-diazacyclopentadecane (22).** A solution of bisamide **21** (2.28 g, 2.7 mmol) in anhydrous THF (10 mL) was added dropwise within 1 h to a magnetically stirred suspension of $LiAlH_4$ (0.46 g, 14 mmol) in refluxing THF (5 mL). The reaction mixture was stirred at this temperature for 1 d and was then worked-up under an identical manner to that for product **19**. Upon FCC purification using solvent system J for elution pure product **22** (1.37 g, 62%) was obtained as an oil, R_f(J) 0.57. ESI-MS (m/z): 840.18 (*M*Na), 817.96 (*M*H), 243 (Trt). HR-MS (m/z): Found 817.5049 (M^++1), $C_{54}H_{64}N_4O_3$ requires M^++1 = 817.5057. ^{1}H NMR: δ 3.557 and 3.497 (12H, two m, H-2-5, H-8 and H-9), 2.714 (8H, m, H-1, H-6, H-7 and H-10), 2.526 (4H, t, *J* = 6.8 Hz, H-3′), 2.131 (4H, t, *J* = 6.4 Hz, H-1′), 1.951 (2H, br. s, NH), 1.649 (4H, quintet, *J* = 6.8 Hz, H-2′). ^{13}C NMR: δ 71.362 (Ph3C), 71.065 (C-2, C-5, C-8 and C-9), 70.037 (C-3 and C-4), 55.363 (C-1′), 54.681 (C-3′), 42.624 (C-1, C-6, C-7 and C-10), 28.733 (C-2′).

***N*^{4},*N*^{13}-Bis(3′-aminopropyl)-l1,7,10-trioxa-4,13-diazacyclopentadecane (23).** A solution of crown ether derivative **22** (1.47 g, 1.8 mmol) in CH_2Cl_2/TFA (3:1; 8 mL) was kept at ambient temperature for 1 h and was then concentrated to dryness. The residue was triturated with Et_2O and refrigerated whereby the product separated as an oil. The supernatant liquor was decanted and this procedure was repeated once more. Thus, the tetra(trifluoroacetate) salt of **23** (1.38 g, 90%) was obtained in the form of a yellowish powder, R_f(J) 0.22. ESI-MS (m/z): 356.11 (*M*Na), 334.29 (*M*H). HR-MS (m/z): Found 333.2861 (M^++1), $C_{16}H_{37}N_4O_3$ requires M^++1 = 333.2866.

***N*^{7},*N*^{16}-Bis(8-tritylamino-6-oxo-5-azaoctanoyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (24).** To a magnetically stirred solution of aza-oxy crown ether **2** (0.52 g, 2 mmol) in anhydrous DMF (3 mL) and $CHCl_3$ (1 mL) were added dry Et_3N (0.56 mL, 4 mmol) and SAE **6** (2.05 g, 4.mmol). The resulting reaction mixture was stirred at ambient temperature for 2 d. Dilution with $CHCl_3$, washing with a 5% aqueous $NaHCO_3$ solution (twice) and with H_2O (once), drying and evaporation left a residue from which upon FCC purification using the solvent system F as eluant pure bisamide **24** (1.95 g, 92%) was obtained as a viscous oil, R_f(F) 0.23. ESI-MS (m/z): 1,060.31 (*M*H), 817.47 (*M*H-Trt), 243.09 (Trt). $C_{64}H_{78}N_6O_8$ requires M^+ = 1,059.36.

***N*^{7},*N*^{16}-Bis(8-tritylamino-5-azaoctyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (25).** A solution of tetra-amide **24** (1.91 g, 1.8 mmol) in anhydrous THF (15 mL) was added dropwise within 20 min to a magnetically stirred suspension of $LiAlH_4$ (0.72 g, 22 mmol) in refluxing THF (5 mL). The reaction mixture was stirred at this temperature for 1 d, and then excess $LiAlH_4$ was carefully destroyed at –10 ºC by the dropwise addition of a saturated aqueous Na_2SO_4 solution. Filtration and washing with more distilled THF followed by evaporation of the filtrates gave a residue which was taken-up in EtOAc. The organic layer was washed twice with brine, dried and evaporated to leave crude hexa-amine derivative **25**. Upon FCC purification using solvent system J, then system L and finally system N for elution pure product **25** (1.15 g, 64%) was obtained as a viscous oil, R_f(N) 0.47. ESI-MS (m/z): 1026 (*M*Na), 1004 (*M*H), 656 [*M*Na-TrtNH$(CH_2)_3$NH$(CH_2)_2$CH=CH_2], 633 656 [*M*H-TrtNH$(CH_2)_3$NH$(CH_2)_2$CH=CH_2], 243 (Trt). $C_{64}H_{86}N_6O_4$ requires M^+ = 1003.42. ^{1}H-NMR: δ 3.594 (16H, m, H-2-5 and H-8-11), 2.753 (8H, t, *J* = 5.6 Hz, H-1, H-6, H-7 and H-12), 2.674 (4H, t, *J* = 6.8 Hz, H-1′), 2.589 (4H, m, H-4′), 2.489 (4H, m, H-6′), 2.183 (4H, t, *J* = 6.4 Hz, H-8′), 1.671 (4H, quintet, *J* = 6.4 Hz, H-7′), 1.464 (8H, m, H-2′ and H-3′). ^{13}C NMR: δ 71.364 (Ph_3C), 71.148 (C-3, C-4, C-9 and C-10), 70.420 (C-2, C-5, C-8 and C-11), 56.250 (C-1′), 54.410 (C-1, C-6, C-7 and C-12), 50.335 (C-4′), 48.824 (C-6′), 42.512 (C-8′), 31.323 (C-2′), 28.446 (C-3′), 25.698 (C-7′) .

***N*^{7},*N*^{16}-Bis(8-amino-5-azaoctyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (26).** A solution of bistritylated hexa-amine **25** (1.1 g, 1.1 mmol) in CH_2Cl_2/TFA (3:1, 10 m) was kept at ambient temperature for 1 h and was then concentrated to dryness. The residue was triturated with Et_2O and refrigerated whereby the product separated as an oil. The supernatant liquor was decanted and this procedure was repeated once more to furnish **26** (1.19 g,. 90%) as the hexa(trifluoroacetate) salt in the form of a brownish powder, R_f(N) 0.07. HR-MS (m/z): Found 519.4589 (M^++1), $C_{26}H_{59}N_6O_4$ requires M^++1 = 519.4598.

Reaction of epichlohydrin (27) with dibenzylamine, Formation of a mixture of 1-dibenzylamino-3-chloro-2-propanol (28) and dibenzylaminomethyloxirane (29). A solution consisting of 27 (30 mL, 0.38 mol), Bn2NH (20 mL, 0.1 mol) and anhydrous iPr2NEt (20 mL, 0.11.mol) was kept at 110 ºC (bath temperature) for 2 h. It was then diluted with Et2O and washed sequentially with a 5% aqueous NaHCO3 solution, with H2O (twice), and with brine (once), dried and evaporated to dryness to leave an oily residue. From this oil, upon purification by FCC using PhMe as the eluant mixture consisted of chlorohydrin 28 and epoxide 29 (18.34 g; ratio 3:2 by 1H NMR) was obtained. This mixture was used as such for the next experiment.

However, in a small scale experiment (2 mL from each of Bn2NH and iPr2NEt and 3 mL of 27), the resulting mixture was separated by FCC using solvent system A as eluant to give pure alcohol 28 and epoxide 29, both as oils.

Chlorohydrin **28**: R_f(PhMe/EtOAc =98:2) 0.24. ^{1}H NMR: δ 7.35–7.23 (10H, m, Ph-H), 3.751 (1H, dq, *J* = 8.6 and 5.2 Hz, C*H*-OH), 3.753 and 3.503 (4H, two d-ABq, *J* = 13.4 Hz, NCH_2Ph), 3.450 (2H, dd, *J* = 5.0 and 3.1 Hz, CH_2Cl), 3.225 (1H, br. s, OH), 2.631 (1H, dd, *J* = 11.9 and 4.8 Hz, CHCH_2N) and 2.587 (1H, dd, *J* = 11.9 and 8.5 Hz, CHCH_2N). ^{13}C NMR: δ 138.754 (*ipso* C), 129.470 (*o*-C), 128.938 (*m*-C), 127.835 (*p*-C), 68.211 (*C*H-OH), 59.298 (N*C*H_2Ph), 57.178 (*C*H_2Cl), 45.451 (N*C*H_2CH). Anal. Calcd for $C_{17}H_{20}ClNO$ (289.81): C, 70.46; H, 6.96; N, 4.83. Found: C, 70.26; H, 7.10; N, 4.97.

Epoxide **29**: R_f(PhMe/EtOAc =98:2) 0.32. ^{1}H NMR: δ 7.37–7.20 (10H, m, Ph-H), 3.796 and 3.557 (4H, two d-ABq, *J* = 13.7 Hz, NCH_2Ph), 3.067 (1H, dq, *J* = 6.4 and 3.7 Hz, C*H*-O), 2.760 (1H, dd, *J* = 13.8 and 3.6 Hz, CH_2O), 2.652 (1H, t, *J* = 4.5 Hz, NCH_2CH), 2.405 (1H, dd, *J* = 13.8 and 6.3 Hz, CH_2O), 2.391 (1H, dd, *J* = 5.0 and 2.8 Hz, NCH_2CH). ^{13}C NMR: δ 139.802 (*ipso* C), 129.265 (*o*-C), 128.701 (*m*-C), 127.427 (*p*-C), 59.410 (N*C*H_2Ph), 56.315 (*C*H-O), 51.520 (*C*H_2O), 45.443 (N*C*H_2CH) .Anal. Calcd for $C_{17}H_{19}NO$ (253.34): C, 80.60; H, 7.56; N, 5.53. Found: C, 80.38; H, 7.70; N, 5.81.

Conversion of the mixture of chlorohydrin 28 and epoxide 29 to epoxide 29 and reaction of the latter with DEG. Preparation of 9-dibenzylamino-3,6-dioxanonane-1,8-diol (30). A solution consisted of chlorohydrin **28** (3.5 g, 12 mmol) and epoxide **29** (2 g, 8 mmol) in anhydrous THF (15 mL) was added dropwise within 30 min to two-necked round bottom flask equipped with a side-armed dropping funnel containing NaH (0.29 g, 12 mmol) and a catalytic amount of imidazole. The resulting reaction mixture was stirred at ambient temperature for a further 1 h and then filtered. The precipitate was washed with THF (10 mL), and the filtrate containing pure (by TLC) epoxide **29** was used as such to the following experiment.

DEG (19 mL, 0.2 mol) was added dropwise within 15 min to a magnetically stirred suspension of NaH (0.1 g, 4 mmol) in anhydrous THF (10 mL) placed in a two-necked round bottom flask equipped with a side-armed dropping funnel and a reflux condenser. It was then heated to reflux, and the above described solution of **29** was added dropwise from the dropping funnel within 2.5 h. Reflux was kept on for additional 2 d. THF was then evaporated, and the residue was dissolved in EtOAc and washed three times with brine. Drying and evaporation left an oily residue from which after FCC using the solvent system F as eluant pure TEG derivative **30** (5.4 g, 75%) was obtained as an oil, R_f(F) 0.38. ESI-MS (m/z): 741.65 (2M+Na), 719.69 (2M+H), 382.34 (*M*Na), 360.42 (*M*H). ^{1}H NMR: δ 7.33–7.23 (10H, m, Ph-H), 3.912 (1H, m, H-6), 3.741 (2H, d, *J* = 13.4 Hz, H-8), 3.680 (2H, t, *J* = 4.6 Hz, H-1), 3.609-3.551 (6H, m, H-2-4), 3.520 (2H, d, *J* = 13.5 Hz, H-8′), 3.483 (1H, dd, *J* = 10.2 and 3.7 Hz, H-5), 3.533 (1H, dd, *J* = 10.2 and 6.4 Hz, H-5′), 2.557 (1H, dd, *J* = 12.8 and 8.4 Hz, H-7), 2.504 (1H, dd, *J* = 12.9 and 5.1 Hz, H-7′). ^{13}C NMR: δ 139.095 (*ipso* C), 129.429 (*o*-C), 128.793 (*m*-C), 127.611 (*p*-C), 74.847 (C-6), 72.915 (C-1), 71.182 (C-2), 70.711 (C-5), 67.569 (C-4), 62.111 (C-3), 59.028 (C-8),

56.413 (C-7). Anal. Calcd for $C_{21}H_{29}NO_4$ (359.46): C, 70.17; H, 8.13; N, 3.90. Found: C, 70.47; H, 7.94; N, 3,70.

2-Dibenzylaminomethyl-18-crown ether-6 (31). To a solution of diol **30** (4.8 g, 13.4 mmol) in anhydrous DMSO (50 mL) was first added NaH (2.68 g of a 60% dispersion in oil, 67 mmol) and then TGT (6.15 g, 13.4 mmol). The resulting reaction mixture was stirred at ambient temperature for 2 d and then diluted with H_2O (150 mL) and brine (50 mL). The resulting mixture was extracted three times with Et_2O, the organic layers were combined, washed three times with brine and finally dried (anhydrous $MgSO_4$) and evaporated to dryness to leave an oily residue. This residue was subjected to FCC using solvent system G as eluant to give pure product **31** (3.62 g, 57%) as an oil, R_f(G) 0.20. ESI-MS (m/z): 513.46 (*M*K), 496.49 (*M*Na), 474.46 (*M*H). ^{1}H NMR: δ 7.34–7.20 (10H, m, Ph-H), 3.81–3.32 (24H, m, C*H*O, C*H*$_2$O and NC*H*$_2$Ph), 2.563 (1H, dd, *J* = 12.6 and 5.7 Hz, OCHC*H*$_2$N), 2.506 (1H, dd, *J* = 12.6 and 4.8 Hz, OCHC*H*$_2$N). Anal. Calcd for $C_{27}H_{39}NO_6$ (473.60): C, 68.47; H, 8.30; N, 2.96. Found: C, 68.70; H, 8.05; N, 2.69.

2-Aminomethyl-18-crown ether-6 (3). To a solution of crown ether **31** (2.2 g, 4.6 mmol) in MeOH (30 mL) was added of Pearlman′s catalyst (0.5 g), and the resulting mixture was subjected to catalytic hydrogenation at 3 atm pressure at ambient temperature for 3 d. Filtration of the catalyst and evaporation of the MeOH filtrate to dryness left the oily crown ether **3** (1.3 g, 96%), R_f (G) 0.11. This product **3** was identical in all respects with a commercially available sample and was used without any further purification in the preparation of amide **32a**.

2-(5′-Tritylamino-3′-oxo-2′-azapentyl)-1,4,7,10,13,16-hexaoxacyclohexadecane (32a). To a solution of aminomethyl crown **3** (1.3 g, 4.43 mmol) and dry Et_3N (0.62 mL, 4.43 mmol) in anhydrous DMF (5 mL) was added in three equal portions within 30 min SAE **5** (1.9 g, 4.43 mmol). The resulting solution was kept at ambient temperature overnight and was then diluted with $CHCl_3$ and washed sequentially with a 5% aqueous $NaHCO_3$ solution (twice) and with brine (once), dried ($MgSO_4$) and evaporated to dryness to leave an oily residue. Following FCC purification with solvent system J as eluant pure amide **32a** (2.5 g, 93%) was obtained as a foam, R_f(J) 0.19. FT-IR: 3322 (NH), 1652 (NH*CO*) cm^{-1}. ESI-MS (m/z): 1,214.08 (2M+H), 646.48 (*M*K), 629.71 (*M*Na), 607.76 (*M*H), 243 (Trt). $C_{35}H_{46}N_2O_7$ requires M^+ = 606.76.

2-(14′-Tritylamino-3′,7′,12′-trioxo-2′,6′,11′-triazatetradecyl)-1,4,7,10,13,16-hexaoxa-cyclohexadecane(33). A solution of amide **32a** (1.2 g, 2 mmol) in CH_2Cl_2/TFA (1:1; 8 mL) was kept at ambient temperature for 30 min. It was then evaporated to dryness, triturated with Et_2O and refrigerated overnight. The supernatant liquor was decanted and the residue was trituration with Et_2O followed by refrigeration; finally decantation was repeated to leave the trifluoroacetate salt of **32b** (0.91 g, 95%) as a thick oil. HR-MS (m/z): Found 365.2231 (M^++1), $C_{16}H_{33}N_2O_7$ requires M^++1 = 365.2228.

This oil was dissolved in anhydrous DMF (3 mL) and treated at 0 ºC in turn with Et_3N (0.5 mL, 3.8 mmol) and SAE **6** (0.98 g, 1.9 mmol) for 1 h and then at ambient temperature for 1 d. Identical work-up as for **32a** and FCC purification using solvent system G for elution gave pure trisamide **33** (1.13 g, 79%) as a foam, R_f(G) 0.26. FT-IR: 3284 (NH), 1652 (NH*CO*) cm^{-1}.

ESI-MS (m/z): 801.62 (*M*K), 785.60 (*M*Na), 763.75 (*M*H), 243 (Trt). HR-MS (m/z): Found 763.4292 (M^++1), $C_{42}H_{59}N_4O_9$ requires M^++1 = 763.4282.

2-(*N*$^{2'}$,*N*$^{6'}$,*N*$^{11'}$-Tris(benzyloxycarbonyl)-14′-tritylamino-2′,6′,11′-triazatetradecyl)-1,4,7,10,13,16-hexaoxacyclohexadecane (34). A solution of trisamide **33** (0.7 g, 0.92 mmol) in anhydrous THF (8 mL) was added dropwise within 30 min to a magnetically stirred suspension of $LiAlH_4$ (0.31 g, 8.3 mmol) in refluxing THF (3 mL). The reaction mixture was stirred at this temperature for 4 d and was then worked-up as described for the preparation of **10a** to give crude tetra-amine **34** (0.45 g, 0.63 mmol). This was dissolved in dry $CHCl_3$ (5 mL) and treated at 0 ºC in turn with anhydrous $^{i}Pr_2NEt$ (0.43 mL, 2.5 mmol) and ZCl (0.29 mL, 2 mmol) for 30 min and at ambient temperature for overnight. The resulting solution was diluted with $CHCl_3$ and washed sequentially twice with a 5% aqueous $NaHCO_3$ solution and once with H_2O, dried ($MgSO_4$) and evaporated to leave an oily residue. Upon FCC purification using solvent system F for elution pure product **34** (0.60 g, 60% based on trisamide **33**) was obtained as an oil, R_f(F) 0.36. HR-MS (m/z): Found 1,123.6032 (M^++1), $C_{66}H_{83}N_4O_{12}$ requires M^++1 = 1,123.6008.

2-(*N*$^{2'}$,*N*$^{6'}$,*N*$^{11'}$-Tris(benzyloxycarbonyl)-14′-[bis(benzyloxycarbonyl)guanidyl]-2′,6′,11′-triazatetradecyl-1,4,7,10,13,16-hexaoxacyclohexadecane (36). Intermediate **34** (0.16 g, 0.14 mmol) was detritylated under identical way to that for amide **32a** to give the trifluoroacetate salt of **35** (0.12, g 85%) as an oil. ESI-MS (m/z): 882.50 (*M*H), 881.51 (*M*). $C_{47}H_{68}N_4O_{12}$ requires M^+ = 881.08. This oil was dissolved in anhydrous $CHCl_3$ (0.5 mL) and treated at 0 ºC in turn with *i*Pr_2NEt (0.044 mL, 0.25 mmol) and the reagent BZMTU (0.043 g, 0.12 mmol) for 30 min and at ambient temperature overnight. Identical work-up as for **34** and final FCC purification with solvent system F gave pure, fully protected, intermediate **36** (0.13 g, 82%) as a foam, R_f(F) 0.11. ESI-MS (m/z): 1,230.64 (*M*K), 1,214.63 (*M*Na), 1,191.67 (*M*), 608.02 [(M+H+Na)/2]. $C_{64}H_{82}N_6O_{16}$ requires M^+ = 1,191.39.

2-(14′-guanidyl-2′,6′,11′-triazatetradecyl)-1,4,7,10,13,16-hexaoxacyclohexadecane (37). To a solution of fully protected polyamine **36** (0.12 g, 0.1 mmol) in glacial AcOH (4 mL), MeOH (1 mL) and H_2O (0.1 mL) was added Pd on C (10%; 0.03 g), and the resulting reaction mixture was hydrogenated at ambient temperature for 6 h. Filtration and evaporation gave pure product **37**, R_f(L) 0.27. This product was dissolved in a solution of HCl in anhydrous MeOH (1.8 M, 1 mL). Trituration with Et_2O and refrigeration gave the tetrahydrochloride of polyamine **37** (0.054 g, 70%) as a powder. HR-MS (m/z): Found 521.4038 (M^++1), $C_{24}H_{53}N_6O_6$ requires M^++1 = 521.4027.

1,8-Diido-3,6-dioxaoctane (TGI) and 1,11-Diido-3,6,9-trioxaundecane (TEGI). To a magnetically stirred solution of either TGT (4.59 g, 10 mmol) or TEGT (5.03 g, 10 mmol) in acetone (60 mL). NaI (6 g, 40 mmol) was added, and the resulting reaction mixture was stirred at ambient temperature for 1 d. Filtration and evaporation of the solvent left a residue which was triturated with Et_2O and refrigerated for overnight. Filtration and evaporation of the solvent left the pure diiodides in quantitative yield as pale red liquids which were used as such without any further purification for the preparation of the aza-oxa crown ethers.

Preparation of 3-oxapentane-1,5-diamine (39) as bisphthalylhydrazide.salt. A solution of DGT (11.03 g, 26.6 mmol) and potassium phthalimide (9.85 g, 53.2 mmol) in DMF (25 mL) was heated at 100-20 ºC (bath temperature) overnight. It was then diluted with $CHCl_3$ and washed in turn with a aqueous NaOH (2N) and with brine (twice) and H_2O (twice). Drying and evaporation left a residue which upon trituration with Et_2O and overnight refrigeration gave pure bisphthalimide **38** (4.85 g, 50%), R_f(C) 0.36.

Bisphthalimide **38** (4.8 g, 13.2 mmol) and hydrazine monohydrate (1.28 mL, 26.4 mmol) were heated under reflux in MeOH (15 mL) for 30 min. The reaction mixture was then refrigerated overnight and the precipitated product the bisphthalyl-hydrazide salt of **39** (3.9 g, 69%) was obtained by filtration and washing with ice-cold MeOH. This salt was used as such for the preparation of bisamide **40**.

***N*[1],*N*[13]-Ditritylamino-3,11-dioxo-7-oxa-4,10-diazatridecane (40).** To a magnetically stirred, ice-cold solution of salt **39** (3.43 g, 8 mmol) in dry DMF (30 mL) was added anhydrous Et_3N (4.5 mL, 32 mmol), followed by SAE **5** (6.86 g, 16 mmol). The reaction mixture was stirred at this temperature for 30 min and then at ambient temperature overnight.. It was then diluted with $CHCl_3$, washed in turn with aqueous $NaHCO_3$ solution (5%, twice) and with H_2O (three times), dried, evaporated, and the residue was triturated with EtOAc. Overnight refrigeration gave pure bisamide **40** (4.5 g, 77%), mp 164–65 ºC; R_f(G) 0.71. FT-IR: 3328 and 3254 (NH), 1646 (NH-*CO*) cm^{-1}. ESI-MS (m/z): 731.87 (*M*H), 489.64 (*M*-Trt), 243 (Trt). ^{1}H NMR: δ 6.678 (2H, t, *J* = 5.2 Hz, H-4 and H-10), 3.544 (4H, t, *J* = 5.2 Hz, H-6 and H-8), 3.395 (4H, q, *J* = 5.2 Hz, H-5 and H-9), 2.364 (4H, t, *J* = 6.0 Hz, H-1 and H-13), 2.131 (4H, t, *J* = 6.0 Hz, H-2 and H-12). ^{13}C NMR: δ 172.796 (C-3 and C-11), 71.452 (Ph_3C), 70.540 (C-6 and C-8), 40.226 (C-5 and C-9), 39.512 (C-1 and C-13), 37.259 (C-2 and C-12) .Anal. Calcd for $C_{48}H_{50}N_4O_3$ (730.96): C, 78.87; H, 6.90; N, 7.76. Found: C, 78.59; H, 7.05; N, 7.99.

***N*[1],*N*[13]-Dityrityl-1,13-diamino-7-oxa-4,10-diazatridecane (41).** Bisamide **40** (4.53 g, 6.2 mmol) was treated with $LiAlH_4$ (1.4 g, 37 mmol) in anhydrous THF (50 mL) for 2 d, and the resulting reaction mixture was worked-up in an identical way to that described for **9a** to give pure product **41** (3.7 g, 85%), 111–12 ºC, R_f (J) 0.42. ESI-MS (m/z): 703.80 (*M*H). ^{1}H NMR: δ 3.530 (4H, t, *J* = 5.2 Hz, H-6 and H-8), 2.733 (4H, t, *J* = 5.2 Hz, H-5 and H-9), 2.643 (4H, t, *J* = 6.8 Hz, H-1 and H-13), 2.148 (4H, unresolved t, H-3 and H-11), 1.696 (2H, br. s, H-4 and H-10), 1.621 (4H, quintet, *J* = 6.8 Hz, H-2 and H-12). ^{13}C NMR: δ 71.310 (Ph_3C), 70.997 (C-6 and C-8), 49.869 (C-5 and C-9), 48.974 (C-1 and C-13), 42.552 (C-3 and C-11), 31.480 (C-2 and C-12). Anal. Calcd for $C_{48}H_{54}N_4O$ (702.99): C, 82.01; H, 7.74; N, 7.97. Found: C, 82.21; H, 7.35; N, 7.77.

***N*[4],*N*[13]-Di(3′-tritylaminopropyl)-l1,7,10-trioxa-4,13-diazacyclopentadecane (22) from tetra-amine derivative 41.** To a solution of tetra-amine derivative **41** (1.2 g, 1.7 mmol) and diiodide TGI (0.63 g, 1.7 mmol) in anhydrous MeCN (30 mL) was added Na_2CO_3 (1.04 g, 10 mmol), and the resulting mixture was refluxed in an atmosphere of Ar for 2 d. It was then refrigerated, filtered, and the residue on the filter was washed with ice-cold MeCN. The filtrate was evaporated, and the residue was dissolved in EtOAc and washed with H_2O (twice). Drying

($MgSO_4$), filtration and evaporation left a residue from which after FCC purification and using solvent system J as eluant the pure product **22** (1.01 g, 73%) was obtained as a foam.

***N*^{4},*N*^{16}-Di(3′-tritylaminopropyl)-1,7,10,13-tetraoxa-4,16-diazacyclooctadecane (42).** Under identical reaction conditions and work-up, compound **41** (0.98 g, 1.4 mmol), diiodide TEGI (0.58 g, 1.4 mmol) and K_2CO_3 (1.11 g, 8 mmol) in anhydrous MeCN (30 mL) gave after FCC purification with solvent system H as eluant the pure product **42** (0.80 g, 66%) as a foam, R_f(H) 0.33. ESI-MS (m/z): 862.04 (*M*H). HR-MS (m/z): Found 861.5332 (M^++1), $C_{56}H_{69}N_4O_4$ requires M^++1 = 861.5319. ^{1}H NMR: δ 3.586 and 3.509 (16 H, two m, CH_2O), 2.776 (8H, m, C-1, C-6, C-7 and C-10), 2.596 (4H, m, C-1′), 2.118 (4H, t, *J* = 6.8 Hz, H-3′), 1.654 (4H, quintet, *J* = 6.4 Hz, H-2′) .

***N*^{4},*N*^{16}-Di(3′-aminopropyl)-1,7,10,13-tetraoxa-4,16-diazacyclooctadecane (43).** Under identical reaction conditions and work-up procedure as for **23**, aza-crown derivative **42** (0.8 g, 0.94 mmol) in CH_2Cl_2/TFA (3:1; 4 mL) **43** was obtained as the tetra(trifluoroacetate) salt (0.74 g, ca. 100%), R_f(J) 0.21. This salt was used as such for the next step. ESI-MS (m/z): 377.54 (*M*H). HR-MS (m/z): Found 377.3142 (M^++1), $C_{18}H_{41}N_4O_4$ requires M^++1 = 377.3128.

***N*^{4},*N*^{13}-Di(12′-tritylamino-5′,10′-dioxo-4′,9′-diazadodecyl)-l1,7,10-trioxa-4,13-diaza-cyclopentadecane (44).** To an ice-cold solution of the tetratrifluoroacetate salt **23** (0.70 g, 0.89 mmol) in anhydrous DMF (5 mL) Et_3N (0.77 mL, 5.5 mmol) was added followed by SAE **6** (0.92 g, 1.8 mmol). The resulting reaction mixture was stirred at this temperature for 30 min and then overnight at ambient temperature. Additional SAE **6** (0.10 g, 0.2 mmol) was then added, and stirring was continued for 1 d. Dilution with EtOAc, washing sequentially with a aqueous K_2CO_3 solution (5%) and with a saturated aqueous $MgSO_4$ solution (twice), drying ($MgSO_4$) and evaporation left a residue. This residue was subjected to FCC purification and using solvent system J as eluant to furnish pure tetra-amide **44** (1 g, 68%) as a white foam, R_f(L) 0.55. FT-IR: 3307 (NH), 1657 (NH*CO*) cm^{-1}. ESI-MS (m/z): 1,169.16 (*M*K), 1,153.22 (*M*Na), 1,130.27 (*M*H), 565.80 [(M+2H)/2]. $C_{68}H_{88}N_8O_7$ requires M^+ = 1,129.50.

***N*^{4},*N*^{16}-Di(12′-tritylamino-5′,10′-dioxo-4′,9′-diazadodecyl)-1,7,10,13-tetraoxa-4,16-diaza-cyclooctadecane (45).** Identical reaction conditions and work-up procedure as for **44** were employed with the exception of using an aqueous $NaHCO_3$ solution (5%) instead of K_2CO_3. Thus, from the tetratrifluoroacetate salt **43** (0.74 g, 0.89 mmol) after FCC purification using solvent system K as eluant of pure tetra-amide **45** (1.21 g, 55%) was obtained as white foam, R_f(K) 0.42. FT-IR: 3276 (NH), 1657 (NH*CO*) cm^{-1}. ESI-MS (m/z): 1,213.10 (*M*K), 1,174.17 (*M*H), 587.76 [(M+2H)/2]. $C_{70}H_{92}N_8O_8$ requires M^+ = 1,173.55. ^{1}H NMR: δ 3.59–3.54 and 3.276 (16H, two m, CH_2O), 2.643 (8H, m, H-3′ and H-8′), 2.499, 2.409 and 2.347 (12H, three m, H-1, H-6, H-7, H-10 and H-1′), 2.237 and 2.128 (10H, two m, NH, H-8′ and H-11′), 1.633 (4H, m, H-2′), 1.811 (4H, quintet, *J* 6.8 Hz, H-7′) .

***N*^{4},*N*^{13}-Di[*N*$^{4'}$,*N*$^{9'}$-di(*tert*-butoxycarbonyl)-12′-tritylamino-4′,9′-diazadodecyl]-l1,7,10-trioxa-4,13-diaza-cyclopentadecane (47).** To a magnetically stirred suspension of $LiAlH_4$ (0.36 g, 9.6 mmol) in refluxing anhydrous THF (4 mL) a solution of tetra-amide **44** (0.9 g, 0.8 mmol) in THF (6 mL) was added dropwise within 30 min. Refluxing was continued for 4 d and then the

resulting reaction mixture was ice-cooled. Excess $LiAlH_4$ was destroyed carefully by the dropwise addition of a saturated aqueous K_2SO_4 solution, the precipitated salts were filtered off and washed on the filter with distilled THF. The filtrate was evaporated under reduced pressure and the residue was taken-up in EtOAc and was washed twice with a saturated aqueous KCl solution. Drying ($MgSO_4$), filtration and evaporation left the crude product **46** (0.73 g, 0.68 mmol). ESI-MS (m/z): 1,074.36 (*M*H). This product was dissolved in anhydrous $CHCl_3$ (3 mL) and treated sequentially at 0 ºC with Et_3N (0.57 mL, 4.08 mmol), a catalytic amount of DMAP and Boc_2O (0.74 g, 3.4 mmol) and was then left at ambient temperature overnight. Dilution with $CHCl_3$, sequential washing once with a 5% aqueous K_2CO_3 solution and with H_2O (twice), drying ($MgSO_4$), filtration and evaporation left an oily residue. From this residue, after FCC purification with solvent system I as eluant pure product **47** (0.41g, 35% overall yield based on tetra-amide **44**) was obtained as a foam, R_f(J) 0.34. ESI-MS (m/z): 1,475.62 (*M*H). HR-MS (m/z): Found 1,473.9772 (M^++1), $C_{88}H_{129}N_8O_{11}$ requires M^++1 = 1,473.9781.

***N*^{4},*N*^{13}-Di(12′-amino-4′,9′-diazadodecyl)-l1,7,10-trioxa-4,13-diazacyclopentadecane (48).** A solution of fully protected octa-amine derivative **47** (0.41 g, 0.28 mmol) in CH_2Cl_2/TFA (1:1; 4 mL) was kept at ambient temperature for 20 min. Evaporation to dryness, trituration with Et_2O and overnight refrigeration gave the octatrifluoroacetate salt of octa-amine **48** (0.37 g, 88%) as a foam, R_f(L) 0.19. HR-MS (m/z): Found 589.5498 (M^++1), $C_{30}H_{69}N_8O_3$ requires M^++1 = 589.5493.

***N*^{4},*N*^{16}-Di[*N*$^{4'}$,*N*$^{9'}$-di(*tert*-butoxycarbonyl)-12′-tritylamino-4′,9′-diazadodecyl]-1,7,10,13-tetraoxa-4,16-diazacyclooctadecane (50).** Identical reaction conditions and work-up procedure, with the exception that Na_2SO_4 was used instead of both K_2SO_4 and KCl, as for the preparation of **46** were used for the preparation of product **49**. Thus, from of tetra-amide **45** (0.9 g, 0.77 mmol) the crude product **49** (0.4 g) was obtained. ESI-MS (m/z): 1,119.49 (*M*H), 1,118.48 (*M*), 560.55 [(M+2H)/2]. This product was directly converted into the corresponding per(*tert*-butoxycarbonylated) oily product **50** (0.3 g, 26% overall yield based on the tetra-amide **45b**) after FCC purification with solvent system J as eluant. R_f(J) 0.22. ESI-MS (m/z): 1,519.96 (*M*H). HR-MS (m/z): Found 1,518.0031 (M^++1), $C_{90}H_{133}N_8O_{12}$ requires M^++1 = 1,518.0043.

***N*^{4},*N*^{16}-Di(12′-amino-4′,9′-diazadodecyl)-1,7,10,13-tetraoxa-4,16-diazacyclooctadecane (51).** A solution of fully protected octa-amine derivative **50** (0.3 g, 0.2 mmol) in CH_2Cl_2/TFA (1:1; 4 mL) was kept at ambient temperature for 20 min. Evaporation to dryness, trituration with Et_2O and overnight refrigeration gave the octa(trifluoroacetate) salt of octa-amine **51** (0.25 g, 83%) as a thick oil, R_f(L) 0.19. HR-MS (m/z): Found 633.5767 (M^++1), $C_{32}H_{73}N_8O_4$ requires M^++1 = 633.5755.

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