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Efficient and Flexible Solid-Phase Synthesis of *N*-Hydroxypolyamine Derivatives

Michaël Méret[a] and Stefan Bienz*[a]

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Orthogonally protected, *N*-hydroxylated, linear tri- and tetraamines were efficiently synthesised on Merrifield resin, which was modified with a phenethyl bromide linker. The polyamine frameworks were convergently prepared "from the centre" with reductive aminations and nucleophilic substitutions to elongate the polyamine backbone. The required *N*-hydroxy groups were introduced during the cleavage of the polyamine derivatives from the resin through Cope elimination.

Introduction

Aliphatic di- and polyamines are widespread natural products found in microorganisms, plants and animals. They often occur as conjugates to a number of different biological structures but also in free form (called biogenic amines). In addition to the almost ubiquitous spermine and the equally abundant putrescine and spermidine, a great number of other biogenic polyamines are known. Polyamines display a wide range of biological effects, and the last 30 years have witnessed increasing research activity in the field of polyamines, particularly concerning their biological functions in microorganisms as well as plant and animal systems. Polyamines play important roles in DNA stabilisation[1] and modification,[2] protein biosynthesis,[3] the modification of neuroreceptors and their associated ion channels in the mammalian central nervous system[4] and interact with phospholipids in biological membranes.[5] Because polyamine derivatives are therapeutic leads for the treatment of a variety of brain disorders such as Parkinson's[6] and Alzheimer's diseases,[7] new and efficient methods for their synthesis are being sought.

The synthesis of polyamines in solution is a laborious task since it involves the intensive use of protective group strategies[8] and often requires difficult purification steps due to the high polarity of the compounds. Solid-phase synthesis (SPS) of polyamines and polyamine derivatives facilitates the procedures; the work-up and purification operations are largely reduced to simple filtrations and washings.[9–11] So far, we have contributed to the topic of polyamine synthesis on solid-phase with the elaboration of a flexible method based on the inexpensive Merrifield resin.[12,13] Starting with the construction of the polyamine backbone from the centre, we were able to efficiently synthesise and derivatise a number of asymmetric polyamines.

Until now, our method has been applied to the preparation of terminally acylated polyamines only. A number of natural products, however, are additionally derivatised at the internal N atoms (e.g. the *N*-hydroxylated spider toxins Agel 448 and Agel 452 of *Agelenopsis aperta*, Figure 1).[14] In connection with our ongoing studies in the isolation and analysis of spider toxins, we were interested in extending our solid-phase strategy for the preparation of *N*-hydroxylated polyamine derivatives, too. We were confident that the Cope elimination provided an efficient transformation for the concurrent introduction of the desired *N*-hydroxy functionality and the cleavage of the final products from the resin. This reaction was already applied to the synthesis of *N*-hydroxylated compounds on solid-phase by Seo et al.,[15] but for simple systems only. The new challenge for us was to expand the method to the synthesis of more complex compounds, which requires not only an orthogonal protective group strategy – as for the synthesis of common polyamine derivatives on the solid phase – but also, and particu-

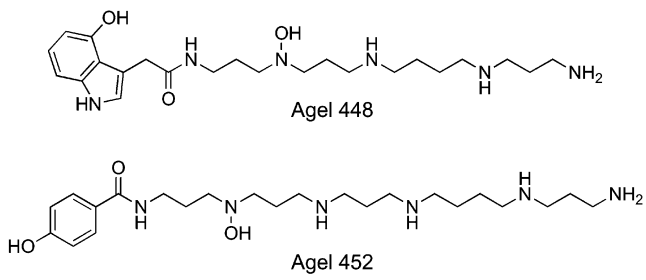

Figure 1. Two representatives of *N*-hydroxylated polyamine spider toxins from *Agelenopsis aperta*.

[a] Institute of Organic Chemistry, University of Zürich, Winterthurerstrasse 190, 8057 Zürich, Switzerland
Fax: +41-44-635-6812
E-mail: sbienz@oci.uzh.ch

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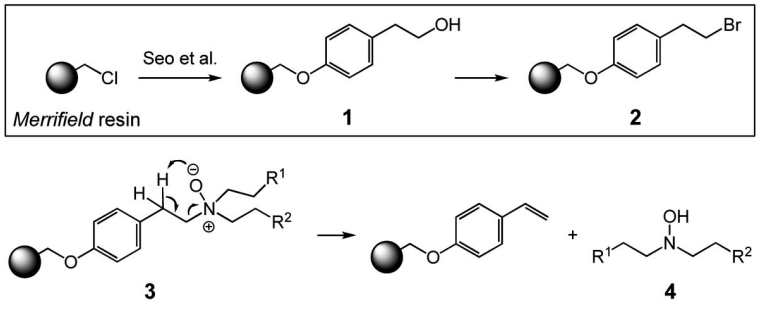
larly, protective groups that are resistant to oxidative conditions. In the following, we show that we were, in fact, able to efficiently apply solid-phase chemistry and the Cope elimination to the synthesis of a number of differently protected, asymmetric, *N*-hydroxylated tri- and tetra-amines.

Results and Discussion

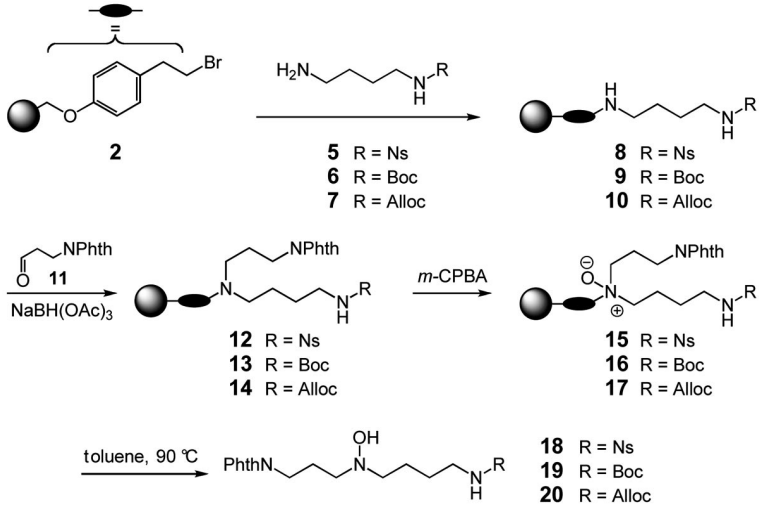
The linker introduced by Seo et al. contains the phenethyl bromide moiety we used to attach the amine to the resin.[15] The phenethyl group should secure the regioselectivity of the planned Cope elimination. Due to the enhanced acidity of the benzylic H atoms, the Cope elimination of an *N*-oxide of type **3** should predominantly proceed toward the linker side of the N atom – forming a styrene derivative together with the desired polyamine derivatives **4** – rather than to the side of the polyamine backbone (Scheme 1).

For the on-resin synthesis of the differently protected polyamine derivatives, resin **2**, prepared analogously to Seo et al., was initially loaded with several polyamine starters by nucleophilic substitution. The treatment of resin **2** with an excess of the monoprotected diamines **5**–**7**, prepared according to the literature,[16] in the presence of DIEA (*N*-diisopropylethylamine) in NMP (*N*-methylpyrrolidinone) at 50 °C gave rise to resins **8**–**10** (Scheme 2). A Volhard titration revealed the complete substitution of the halogens. In the case of resins **9** and **10** with their Boc- and Alloc-protected amines, FT-IR analysis showed the typical absorption for the carbamate carbonyl group at 1707 cm^{-1}. Concerning the Ns (2-nitrophenylsulfonyl) protecting group, FT-IR analysis showed the typical absorptions at 1509 and 1339 cm^{-1} for the nitro group and at 1362 and 1163 cm^{-1} for the sulfonamide. The elongation of the polyamine backbones was performed by reductive aminations with 3-phthalimidopropanal (**11**).[17] The treatment of resins **8**–**10** with aldehyde **11** for 2 h at 23 °C, followed by the reaction with $NaBH(OAc)_3$ in DMF for 2 h at 23 °C, afforded resins **12**–**14**. Their FT-IR spectra showed the typical absorptions for the carbonyls of the phthalimide groups at 1770 cm^{-1} in addition to the bands at 1708 cm^{-1} for the absorptions of the carbamates or the bands at 1509, 1362, 1339 and 1163 cm^{-1} for the absorptions of the Ns groups.

To obtain the first set of *N*-hydroxylated polyamine derivatives, resins **12**–**14** were oxidised at 23 °C with *m*-CPBA (3-chloroperbenzoic acid) in CH_2Cl_2. The intermediary *N*-oxide resins **15**–**17** were not further characterised but were immediately heated in toluene at 90 °C to effect the Cope elimination and liberate the desired *N*-hydroxylated spermidine derivatives **18**–**20**. These products were contaminated with approximately 1% of over-oxidised products – possibly nitrones such as the APCI decomposition products ob-



Scheme 1.



Scheme 2.

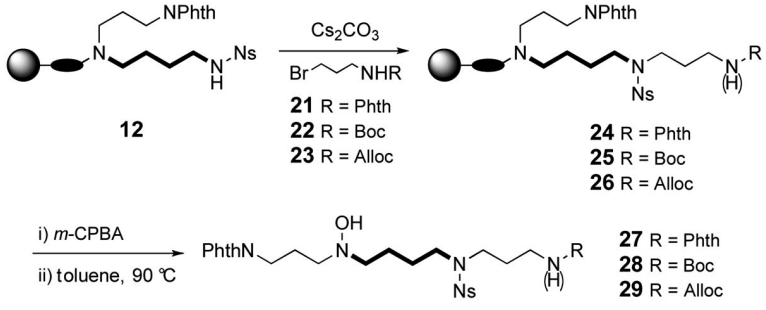
served with hydroxylamines[18] – as revealed by HPLC-MS of the crude mixtures. Reversed-phase HPLC finally furnished the bis-protected, *N*-hydroxylated triamines **18**–**20** in 30–32% overall yields (from resin **2**). Though apparently low, these yields are comparable to those obtained in the SPS of non-hydroxylated polyamine derivatives,[12] and they are very competitive with the yields obtained in the syntheses of *N*-hydroxylated polyamine derivatives in solution.[19] The products **18**–**20** were fully characterised by NMR, ESI-MS and MS/MS, which confirmed the proposed structures as shown in Scheme 2.

The synthetic process was extended to the preparation of a collection of triprotected *N*-hydroxylated tetra-amines (Scheme 3). To this purpose, intermediate **12** was alkylated at the Ns-protected N atom with three differently *N*-protected aminobromides. The treatment of the resin with **21**–**23** at 50 °C in the presence of Cs_2CO_3 in DMF gave tetra-amine resins **24**–**26**, which were submitted to the usual oxidation/cleavage conditions to furnish *N*-hydroxyl spermine derivatives **27**–**29** (28–30% yield from resin **2**).

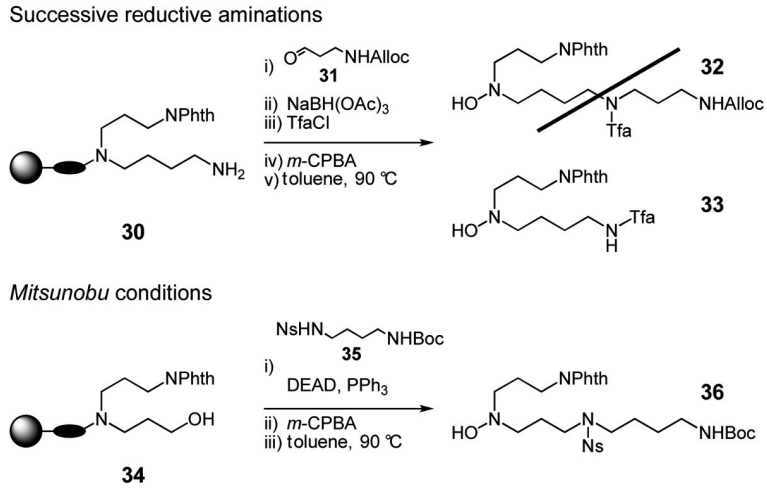
The extension of the polyamine backbone was not as trivial as it might appear from the Scheme shown above. For the synthesis of **27**–**29**, the combination of Cs_2CO_3 and protected aminobromides in the elongation step proved to be superior to a number of alternative conditions. Initially, we employed NaOMe as the base to deprotonate sulfonamide **12**, but HPLC-MS of mixtures obtained after the treatment of the anions with bromides **21**–**23** followed by oxidative cleavage revealed that the alkylation reactions did not proceed to completion; the major product was the non-alkylated *N*-hydroxy "starting material", triamine derivative **18**. The use of alkyl iodides instead of the bromides was not advantageous.

Other synthetic methods to effect the elongation of the polyamine backbone were tested, too, but proved to be no better (Scheme 4). Our attempts to construct the tetra-amine derivatives by successive reductive aminations failed completely: the successive treatment of resin **30** with allyl-*N*-(3-oxopropyl)carbamate **31** and $NaBH(OAc)_3$, analogously to the conversions of resins **8**–**10** into resins **12**–**14**, gave a resin showing "negative" Kaiser reaction[20] as was expected for the supposedly formed secondary amine. After treatment with trifluoroacetyl chloride and the usual oxidative cleavage, however, diprotected *N*-hydroxylated triamine derivative **33**, rather than the desired, triprotected, *N*-hydroxylated tetra-amine **32**, was obtained. Evidently, and despite the "negative" Kaiser test of the intermediate resin, the reductive amination was not successful.

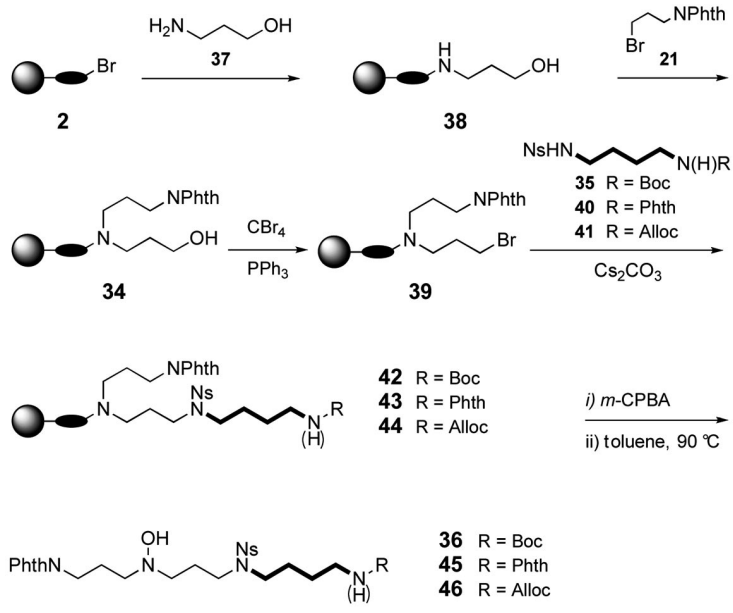
The alternative approach, applying the Mitsunobu reaction[10] to couple diprotected diamine **35** to the resin through substitution of alcoholic resin **34**, was problematic as well. In fact, after oxidative cleavage, tetra-amine deriva-



Scheme 3.



Scheme 4.



Scheme 5.

tive **36** was obtained by this procedure, but the method was not reproducible in our hands.

Since spider toxins vary in the succession of the oligomethylene units in between the N atoms, a second set of protected *N*-hydroxytetra-amines with the $N(CH_2)_3N(OH)(CH_2)_3N$ moiety in the backbone was prepared (Scheme 5). To show the flexibility of our approach, the construction of the backbone followed a different scheme. Resin **2** was loaded with amino alcohol **37** in the presence of DIEA in NMP, affording resin **38**. Alternatively to the reductive amination performed before, the amine of this resin was directly alkylated by treatment with protected aminobromide **21** (DIEA, NMP), leading to resin **34**. Oxidative cleavage revealed that no over-alkylated product was formed in this transformation.

The hydroxy group of resin **34** was then substituted for a bromide by reaction with PPh_3 and CBr_4 in CH_2Cl_2 (resin **39**).[11,15,21] The treatment of this resin with nosyl derivatives **35**, **40** and **41** in the presence of Cs_2CO_3 in DMF – reversing the reactivities of the resin and the reagents relative to the alkylations of resin **12** with bromides **21**–**23** – resulted in resins **42**–**44**, which were oxidatively cleaved as before to furnish the spermine derivatives **36**, **45** and **46** (18–21% yield from resin **2**).

Conclusions

In conclusion, we succeeded in synthesising diprotected *N*-hydroxy spermidines and triprotected *N*-hydroxylated spermines and spermine analogues on solid support, and we have demonstrated that Ns, Boc, Alloc and phthaloyl protecting groups are compatible with the oxidative cleavage procedure. We have shown that the approach for the synthesis of the polyamine backbones on the solid support is flexible, allowing for the construction of the resin-bound polyamine portion by reductive aminations, direct alkylations of amines and sulfonamides as well as substitutions of halides. Thus, we have laid the basis for the SPS of any *N*-hydroxylated polyamine derivative. The synthesised *N*-hydroxypolyamine derivatives will be used as precursors for synthetic polyamine natural products and as reference compounds for the study and identification of constituents of venom samples from the spider *Agelenopsis aperta*, by HPLC-MS.

Experimental Section

General Methods: Unless otherwise stated, starting materials were obtained from commercial suppliers and used without further purification. Resin used: Merrifield polymer 200–400 mesh, 2% divinylbenzene, loading ca. 2.1 mmol Cl g^{-1} from Fluka. For the solid-phase reactions, an Advanced ChemTech PLS 6 Organic synthesiser was used. IR spectra were recorded with a Perkin–Elmer 1600 Series FT-IR spectrophotometer, and for the final products, an OMNILAB FT/IR 4100 spectrophotometer. *N*-Hydroxypolyamine derivatives were purified by preparative HPLC; chromatograms were recorded with a Dynamax solvent delivery system model SD-300 coupled with a Dynamax absorbance detector model UV-1; column: Kromasil KR100–10C18. ^{1}H NMR spectra were measured with a Bruker AV-600 (600 MHz) spectrometer; δ relative to $CHCl_3$ (δ = 7.26 ppm). ^{13}C-NMR spectra were measured with a Bruker AV-600 (150 MHz) spectrometer; δ relative to $CDCl_3$ (δ = 77.0 ppm); multiplicities were determined from DEPT-135 and DEPT-90 experiments; the assignment of carbon resonances followed from HSQC experiments. ESI mass spectroscopy was performed with a Bruker ESQUIRE-LC quadrupole ion-trap instrument (Bruker Daltonik GmbH, Bremen, Germany), equipped with a combined Hewlett–Packard Atmospheric Pressure Ion (API) source (Hewlett–Packard, Palo Alto, CA, USA). HR MS: High-resolution (≥10′000 FWHM) electrospray ionization mass spectrometry was performed with a Finnigan MAT 900 (Thermo Finnigan, San Jose, CA; USA) double-focusing, magnetic-sector, mass

spectrometer. Ten spectra were acquired for each sample. A mass accuracy ≤2 ppm was obtained in the peak-matching acquisition mode with a solution containing 2 μL PEG200, 2 μL PPG450 and 1.5 mg of NaOAc (all obtained from Sigma–Aldrich, Buchs, Switzerland) dissolved in 100 mL of MeOH (HPLC Supra grade, Scharlau, Barcelona, Spain) as an internal standard. Proof of the structure and purity of the final polyamine derivatives was provided by NMR spectra and MS/MS. Elemental analyses were not appropriate for the polyamine derivatives, since these compounds are waxy or glassy solids from which residual traces of solvents could not be removed.

Synthesis of Solid-Supported Tri- and Tetra-amine Derivatives

Loading with *N*-(2-Nitrophenylsulfonyl)-1,4-diaminobutane to Form Resin 8. General Procedure for the Loading of Resin 2: Resin **2** (3.2 mmol, prepared according to Seo et al.,[15] 1.6 g mol^{-1} as determined by Volhard titration)[22] was swelled in NMP (20 mL) for 15 min. DIEA (2.74 mL, 16.0 mmol) and *N*-(2-nitrophenylsulfonyl)-1,4-diaminobutane (**5**, 4.37 g, 16.0 mmol) were added, and the suspension was agitated for 24 h at 50 °C. Resin **8** was filtered off, washed successively with NMP, CH_2Cl_2 and MeOH and dried in vacuo. IR: $\tilde{\nu}$ = 1509 (NO_2), 1362 (SO_2), 1339 (NO_2), 1163 (SO_2) cm^{-1}.

Loading of Resin 2 with *tert*-Butyl *N*-(4-Aminobutyl)carbamate (6) to Form Resin 9: According to the general procedure, resin **2** (0.2 mmol) was loaded with **6** to give resin **9**. IR: $\tilde{\nu}$ = 1707 (CO) cm^{-1}.

Loading of Resin 2 with Allyl *N*-(4-Aminobutyl)carbamate (7) to Form Resin 10: According to the general procedure, resin **2** (0.2 mmol) was loaded with **7** to give resin **10**. IR: $\tilde{\nu}$ = 1708 (CO) cm^{-1}.

Loading of Resin 2 with 3-Amino-1-propanol (37) to Form Resin 38: According to the general procedure, resin **2** (1.6 mmol) was loaded with **37** to give resin **38**. IR: $\tilde{\nu}$ = 3260 (br., OH) cm^{-1}.

Reductive Amination of Resin 8 with 3-Phthalimidopropanal (11) to Form Resin 12. General Procedure for Reductive Aminations: Resin **8** (3.2 mmol) was swelled in DMF (20 mL) for 15 min. 3-Phthalimidopropanal (**11**, 3.26 g, 16.0 mmol) was added, and the suspension was agitated at 23 °C for 2 h. $NaBH(OAc)_3$ (3.38 g, 16.0 mmol) was added, and the suspension was agitated at 23 °C for an additional 2 h. Resin **12** was filtered off, washed successively with MeOH, DMF/AcOH (5%), CH_2Cl_2 and MeOH and dried in vacuo. IR: $\tilde{\nu}$ = 1770 (CO), 1707 (CO), 1509 (NO_2), 1362 (SO_2), 1339 (NO_2), 1163 (SO_2) cm^{-1}.

Reductive Amination of Resin 9 with 3-Phthalimidopropanal (11) to Form Resin 13: According to the general procedure, resin **9** (0.2 mmol) was elongated with **11** to give resin **13**. IR: $\tilde{\nu}$ = 1770 (CO of Phth), 1708 (CO of Boc/Phth) cm^{-1}.

Reductive Amination of Resin 10 with 3-Phthalimidopropanal (11) to Form Resin 14: According to the general procedure, resin **10** (0.2 mmol) was elongated with **11** to give resin **14**. IR: $\tilde{\nu}$ = 1770 (CO of Phth), 1708 (CO of Alloc/Phth) cm^{-1}.

Alkylation of Resin 12 with *N*-(3-Bromopropyl)phthalimide (21) to Form Resin 24. General Procedure for the Alkylations of Resin 12: Resin **12** (0.3 mmol) was swelled in DMF (10 mL) at 50 °C for 15 min. Cs_2CO_3 (1.30 g, 4.0 mmol) and *N*-(3-bromopropyl)phthalimide (**21**, 0.72 g, 2.7 mmol) were added, and the suspension was agitated at 50 °C for 24 h. Resin **24** was filtered off, washed successively with DMF, NMP/H_2O (1:1), NMP, MeOH and CH_2Cl_2 and dried in vacuo. IR: $\tilde{\nu}$ = 1770 (CO), 1708 (CO), 1509 (NO_2), 1362 (SO_2), 1339 (NO_2), 1163 (SO_2) cm^{-1}.

Alkylation of Resin 12 with *tert*-Butyl *N*-(3-Bromopropyl)carbamate (22) to Form Resin 25: According to the general procedure, resin **12** (0.3 mmol) was elongated with **22** to give resin **25**. IR: $\tilde{\nu}$ = 1770 (CO of Phth), 1707 (CO of Phth/Boc), 1509 (NO_2), 1364 (SO_2), 1339 (NO_2), 1162 (SO_2) cm^{-1}.

Alkylation of Resin 12 with Allyl *N*-(3-Bromopropyl)carbamate (23) to Form Resin 26: According to the general procedure, resin **12** (0.6 mmol) was elongated with **23** to give resin **26**. IR: $\tilde{\nu}$ = 1770 (CO of Phth), 1708 (CO of Phth/Alloc), 1509 (NO_2), 1363 (SO_2), 1340 (NO_2), 1163 (SO_2) cm^{-1}.

Alkylation of Resin 38 with *N*-(3-Bromopropyl)phthalimide to Form Resin 34: Resin **38** (1.6 mmol) was swelled in NMP (20 mL) for 15 min. DIEA (1.37 mL, 8.00 mmol) and *N*-(3-bromopropyl)-phthalimide (**21**, 2.14 g, 8.0 mmol) were added, and the suspension was agitated for 24 h at 50 °C. Resin **34** was filtered off, washed successively with NMP, CH_2Cl_2 and MeOH and dried in vacuo. IR: $\tilde{\nu}$ = 3350 (br., OH), 1770 (CO), 1708 (CO) cm^{-1}.

Bromination of Resin 34 to Resin 39: Resin **34** (1.6 mmol) was swelled in dry CH_2Cl_2 (15 mL). PPh_3 (2.098 g, 8.00 mmol) was added at 0 °C, followed by CBr_4 (2.653 g, 8.00 mmol) dissolved in dry CH_2Cl_2. The suspension was agitated for 12 h under Ar. Resin **39** was filtered off, washed successively with DMF, CH_2Cl_2 and MeOH and dried in vacuo. IR: $\tilde{\nu}$ = 1770 (CO), 1708 (CO) cm^{-1}.

Substitution of Bromo Resin 39 with *tert*-Butyl *N*-[4-(2-Nitrophenylsulfonamido)butyl]carbamate (35) to Form Resin 42. General Procedure for the Substitution of Resin 39: Resin **39** (0.3 mmol) was swelled in DMF (10 mL) at 50 °C for 15 min. Cs_2CO_3 (0.488 g, 1.5 mmol) and *tert*-butyl *N*-[4-(2-nitrophenylsulfonamido)butyl]-carbamate (**35**, 0.560 g, 1.5 mmol) were added, and the suspension was agitated at 50 °C for 24 h. Resin **42** was filtered off, washed successively with DMF, NMP/H_2O (1:1), NMP, MeOH and CH_2Cl_2 and dried in vacuo. IR: $\tilde{\nu}$ = 1770 (CO of Phth), 1707 (CO of Phth/Boc), 1509 (NO_2), 1364 (SO_2), 1162 (SO_2) cm^{-1}.

Substitution of Bromo Resin 39 with *N*-[4-(2-Nitrophenylsulfonamido)butyl]phthalimide (40) to Form Resin 43: According to the general procedure, resin **39** (0.3 mmol) was elongated with **40** to give resin **43**. IR: $\tilde{\nu}$ = 1770 (CO), 1709 (CO), 1509 (NO_2), 1363 (SO_2), 1339 (NO_2), 1163 (SO_2) cm^{-1}.

Substitution of Bromo Resin 39 with Allyl *N*-[4-(2-Nitrophenylsulfonamido)butyl]carbamate (41) to Form Resin 44: According to the general procedure, resin **39** (0.7 mmol) was elongated with **41** to give resin **44**. IR: $\tilde{\nu}$ = 1770 (CO of Phth), 1707 (CO of Phth/Alloc), 1509 (NO_2), 1363 (SO_2), 1340 (NO_2), 1162 (SO_2) cm^{-1}.

Liberation of the Tri- and Tetra-amine Derivatives from the Resins

Oxidation/Cope Elimination (General Procedure): The resin (obtained from 0.3 mmol of resin **2**) was swelled in CH_2Cl_2 (5 mL) for 15 min. *m*-CPBA (0.259 g, 1.50 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added, and the suspension was agitated for 3 h at 23 °C. The resulting resin was filtered off, washed successively with DMF, MeOH and CH_2Cl_2 and dried in vacuo. Toluene (10 mL) was added, and the suspension was heated to 90 °C for 2 h. The resin was filtered off and washed with toluene and CH_2Cl_2. The combined filtrates were concentrated to give a yellow oil, which was purified by HPLC as described below.

***N*-[4-Hydroxy-8-(2-nitrophenylsulfonamido)-4-azaoctyl]phthalimide (18) from Resin 12 (obtained from 0.3 mmol of resin 2):** HPLC (H_2O/MeCN/TFA, 60:40:0.1, 25 mL min^{-1}, λ = 280 nm) gave **18** as a colourless oil (0.043 g, 0.09 mmol, 30% from resin **2**). IR: $\tilde{\nu}$ = 1771 (CO), 1708 (CO), 1364 (SO_2), 1340 (NO_2), 1163 (SO_2) cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$, 278 K): δ = 8.10–8.09 (m, 1 H, arom. H

o to NO_2), 7.85–7.83 (m, 3 H, arom. H *o* to SO_2 and 2 arom. CC*H*CH of Phth), 7.77–7.76 (m, 2 H, arom. H *p* to NO_2 and arom. H *p* to SO_2), 7.75–7.73 (m, 2 H, 2 arom. CCHC*H* of Phth), 3.81 (t, $^3J_{H,H}$ = 6.3 Hz, 2 H, PhthNCH_2), 3.39–3.20 (m, 4 H, CH_2NOHCH_2), 3.13–3.09 (m, 2 H, NsNHCH_2), 2.24–2.11 (m, 2 H, PhthNCH$_2$CH_2), 1.93–1.78 (m, 2 H, NsNHCH$_2$CH$_2$CH_2), 1.65 [quint, $^3J_{H,H}$ = 7.2 Hz, 2 H, NsNHCH$_2$CH_2] ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 278 K): δ = 168.5 (s, 2×CO), 147.9 (s, arom. CNO_2), 134.4 (d, 2 arom. CCH*C*H of Phth), 133.8 (d, arom. CH *p* to NO_2), 133.1 (s, arom. CSO_2), 132.9 (d, arom. CH *p* to SO_2), 131.7 (s, 2 arom. C of Phth), 131.1 (d, arom. CH *o* to NO_2), 125.5 (d, arom. CH *o* to SO_2), 123.6 (d, 2 arom. C*C*H of Phth), 59.2, 57.1 (2 t, CH_2NOHCH_2), 42.9 (t, NsNHCH$_2$), 34.6 (t, PhthN*C*H$_2$), 26.4 (t, NsNHCH$_2$*C*H$_2$), 23.6 (t, PhthCH$_2$*C*H$_2$), 20.6 (t, NsNHCH$_2$CH$_2$*C*H$_2$) ppm. ESI-MS: *m*/*z* (%) = 477.2 (100) [M + H]$^+$. HRMS: calcd. for $C_{21}H_{25}N_4O_7S_1$ 477.1444; found 477.1449.

***tert*-Butyl *N*-(5-Hydroxy-8-phthalimido-5-azaoctyl)carbamate (19) from Resin 13 (obtained from 0.2 mmol of resin 2):** HPLC (H_2O/MeCN/TFA, 60:40:0.1, 25 mL min^{-1}, λ = 280 nm) gave **19** as a colourless oil (0.025 g, 0.06 mmol, 32% from resin **2**). IR: $\tilde{\nu}$ = 1773 (CO of Phth), 1710 (CO of Boc/Phth) cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$, 278 K): δ = 7.90–7.88 (m, 2 H, 2 arom. CC*H*CH of Phth), 7.79–7.77 (m, 2 H, 2 arom. CCHC*H* of Phth), 4.67 (br. s, 1 H, NH), 3.85 (t, $^3J_{H,H}$ = 6.2 Hz, 2 H, PhthNCH_2), 3.35–3.26 (m, 4 H, CH_2NOHCH_2), 3.19–3.14 (m, 2 H, BocNHCH_2), 2.28–2.15 (m, 2 H, PhthNCH$_2$CH_2), 1.95–1.75 (m, 2 H, BocNHCH$_2$CH$_2$CH_2), 1.59 (quint, $^3J_{H,H}$ = 7.1 Hz, 2 H, BocNHCH$_2$CH_2), 1.45 (s, 9 H, CMe_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 278 K): δ = 168.3 (s, 2×CO of Phth), 156.1 (s, CO of Boc), 134.4 (d, 2 arom. CCH*C*H of Phth), 131.8 (s, 2 arom. C of Phth), 123.6 (d, 2 arom. C*C*H of Phth), 79.6 (s, Me_3C), 59.2, 57.0 (2 t, 2×CH_2), 39.4 (t, BocNH*C*H$_2$), 34.8 (t, PhthN*C*H$_2$), 28.3 (*q*, *Me*$_3$C), 27.0 (t, BocNHCH$_2$*C*H$_2$), 26.6 (t, PhthNCH$_2$*C*H$_2$), 20.6 (t, BocNHCH$_2$CH$_2$*C*H$_2$) ppm. ESI-MS: *m*/*z* (%) = 392.3 (100) [M + H]$^+$, 336.3 (13). HRMS: calcd. for $C_{20}H_{30}N_3O_5$ 392.2185; found 392.2186.

Allyl *N*-(5-Hydroxy-8-phthalimido-5-azaoctyl)carbamate (20) from Resin 14 (obtained from 0.2 mmol of resin 2): HPLC (H_2O/MeCN/TFA, 60:40:0.1, 25 mL min^{-1}, λ = 280 nm) gave **20** as a colourless oil (0.022 g, 0.06 mmol, 30% from resin **2**). IR: $\tilde{\nu}$ = 1771 (CO of Phth), 1705 (CO of Alloc/Phth) cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$, 278 K): δ = 7.88–7.84 (m, 2 H, 2 arom. CC*H*CH of Phth), 7.77–7.72 (m, 2 H, 2 arom. CCHC*H* of Phth), 5.90 (ddt, $^3J_{trans}$ = 17.1, $^3J_{cis}$ = 10.6, $^3J_{vic}$ = 5.3 Hz, 1 H, CH_2=C*H*), 5.30 (dd, $^3J_{trans}$ = 17.1, $^3J_{gem}$ = 1.5 Hz, 1 H, CH_2=CH), 5.21 (d, $^3J_{cis}$ = 10.6 Hz, 1 H, CH_2=CH), 4.87 (br. s, 1 H, NH), 4.54 (d, $^3J_{H,H}$ = 5.3 Hz, 2 H, OCH_2), 3.83 (t, $^3J_{H,H}$ = 6.2 Hz, 2 H, PhthNCH_2), 3.32–3.22 (m, 4 H, CH_2NOHCH_2), 3.19–3.22 (m, 2 H, AllocNHCH_2), 2.22–2.10 (m, 2 H, PhthNCH$_2$CH_2), 1.94–1.74 (m, 2 H, AllocNHCH$_2$CH$_2$CH_2), 1.60 (quint, $^3J_{H,H}$ = 7.0 Hz, 2 H, AllocNHCH$_2$CH_2) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 278 K): δ = 168.4 (s, 2×CO of Phth), 156.4 (s, CO of Alloc), 134.3 (d, 2 arom. CCH*C*H of Phth), 132.8 (d, CH_2=*C*H), 131.8 (s, 2 arom. C of Phth), 123.6 (d, 2 arom. C*C*H of Phth), 117.8 (t, *C*H$_2$=CH), 65.7 (t, CH_2=CH*C*H$_2$), 59.2, 57.1 (2 t, 2×CH_2), 39.9 (t, AllocNH*C*H$_2$), 34.8 (t, PhthN*C*H$_2$), 26.9 (t, NHCH$_2$*C*H$_2$), 23.6 (t, PhthNCH$_2$*C*H$_2$), 20.6 (t, NHCH$_2$CH$_2$*C*H$_2$) ppm. ESI-MS: *m*/*z* (%) = 376.3 (100) [M + H]$^+$, 360.3 (10). HRMS: calcd. for $C_{19}H_{26}N_3O_5$ 376.1872; found 376.1871.

[4-Hydroxy-9-(2-nitrophenylsulfonyl)-4,9-diazadodecane]-1,12-diphthalimide (27) from Resin 24 (obtained from 0.3 mmol of resin 2): HPLC (H_2O/MeCN/TFA, 60:40:0.1, 25 mL min^{-1}, λ = 280 nm) gave **27** as a colourless solid (0.059 g, 0.09 mmol, 30% from resin **2**). M.p. 67–70 °C. IR: $\tilde{\nu}$ = 1769 (CO), 1708 (CO), 1370 (SO_2), 1341 (NO_2), 1161 (SO_2) cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$, 278 K): δ = 7.96 (dd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.3 Hz, 1 H, arom. H *o* to NO_2), 7.86–7.81 (m, 4 H, 4 arom. CC*H*CH of Phth), 7.75–7.72 (m, 4 H, 4 arom. CCHC*H* of Phth), 7.71 (app. td, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.3 Hz, 1 H, arom. H *p* to NO_2), 7.66 (app. td, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.3 Hz, 1 H, arom. H *p* to SO_2), 7.61 (dd, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.3 Hz, 1 H, arom. H *o* to SO_2), 3.83 [t, $^3J_{H,H}$ = 6.2 Hz, 2 H, PhthNCH_2(CH$_2$)$_2$NOH], 3.67 [t, $^3J_{H,H}$ = 7.5 Hz, 2 H, PhthNCH_2(CH$_2$)$_2$NNs], 3.38–3.34 (m, 4 H, CH_2NNsCH_2), 3.33–3.28 (m, 4 H, CH_2NOHCH_2), 2.23–2.16 (m, 2 H, PhthNCH$_2$CH_2CH$_2$OH), 1.92 (quint, $^3J_{H,H}$ = 7.5 Hz, 2 H, NsNCH$_2$CH_2CH$_2$-NPhth), 1.86–1.78 [m, 2 H, OHNCH$_2$CH_2-(CH$_2$)$_2$NNs], 1.77–1.71 [m, 2 H, OHN(CH$_2$)$_2$CH_2CH$_2$NNs] ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 278 K): δ = 168.3, 168.2 (2 s, 2×CO of Phth), 148.0 (s, arom. CNO_2), 134.3, 134.1 (2 d, 2×2 arom. CCH*C*H of Phth), 133.8 (d, arom. CH *p* to NO_2), 132.8 (s, arom. CSO_2), 131.9 (d, arom. CH *p* to SO_2), 131.8 (s, 4 arom. C of Phth), 130.7 (d, arom. CH *o* to NO_2), 124.3 (d, arom. CH *o* to CSO_2), 123.5, 123.3 (2 d, 2×2 arom. C*C*H of Phth), 58.9, 56.9 (2 t, CH_2NNsCH_2), 47.1, 45.8 (2 t, CH_2NOHCH_2), 35.6 [t, PhthN*C*H$_2$-(CH$_2$)$_3$NNs], 34.7 [t, PhthN*C*H$_2$(CH$_2$)$_2$NOH], 27.4 (t, OHNCH$_2$CH$_2$*C*H$_2$CH$_2$NNs), 25.6 (t, PhthNCH$_2$*C*H$_2$CH$_2$NNs), 23.6 (t, PhthNCH$_2$*C*H$_2$CH$_2$NOH), 20.4 [t, OHNCH$_2$*C*H$_2$-(CH$_2$)$_2$NNs] ppm. ESI-MS: *m*/*z* (%) = 702.3 (12) [M + K]$^+$, 686.3 (28) [M + Na]$^+$, 664.4 (100) [M + H]$^+$, 646.3 (9). HRMS: calcd. for $C_{32}H_{34}N_5O_9S_1$ 664.2077; found 664.2086.

***tert*-Butyl *N*-[9-Hydroxy-4-(2-nitrophenylsulfonyl)-12-phthalimido-4,9-diazadodecyl]carbamate (28) from Resin 25 (obtained from 0.3 mmol of resin 2):** HPLC (H_2O/MeCN/TFA, 55:45:0.1, 25 mL min^{-1}, λ = 280 nm) gave **28** as a colourless oil (0.053 g, 0.08 mmol, 28% from resin **2**). IR: $\tilde{\nu}$ = 1773 (CO of Phth), 1712 (CO of Phth/Boc), 1367 (SO_2), 1345 (NO_2), 1163 (SO_2) cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$, 278 K): δ = 7.96 (d, $^3J_{H,H}$ = 7.2 Hz, 1 H, arom. H *o* to NO_2), 7.87–7.86 (m, 2 H, 2 arom. CC*H*CH of Phth), 7.77–7.75 (m, 2 H, 2 arom. CCHC*H* of Phth), 7.74 (ap. td, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.6 Hz, 1 H, arom. H *p* to NO_2), 7.71 (ap. td, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.6 Hz, 1 H, arom. H *p* to SO_2), 7.65 (d, $^3J_{H,H}$ = 7.4 Hz, 1 H, arom. H *o* to SO_2), 3.82 (t, $^3J_{H,H}$ = 6.3 Hz, 2 H, PhthNCH_2), 3.35–3.23 (m, 10 H, CH_2NOHCH_2, CH_2NNsCH_2, CH_2NHBoc), 2.18–2.11 (m, 2 H, PhthNCH$_2$CH_2), 1.82–1.63 [m, 6 H, OHNCH$_2$(CH_2)$_2$CH$_2$NNs, BocNHCH$_2$CH_2], 1.42 (s, 9 H, *Me*$_3$C) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 278 K): δ = 168.5 (s, 2×CO of Phth), 156.2 (s, CO of Boc), 147.9 (s, arom. CNO_2), 134.4 (d, 2 arom. CCH*C*H of Phth), 133.8 (d, arom. CH *p* to NO_2), 132.6 (s, arom. CSO_2), 131.9 (d, arom. CH *p* to SO_2), 131.6 (s, 2 arom. C of Phth), 130.4 (d, arom. CH *o* to NO_2), 124.3 (d, arom. CH *o* to SO_2), 123.6 (d, 2 arom. C*C*H of Phth), 79.5 (s, Me_3C), 58.9, 57.0 (2 t, CH_2NNsCH_2), 46.8, 45.4 (2 t, CH_2NOHCH_2), 37.2 (t, BocNH*C*H$_2$), 34.6 (t, PhthN*C*H$_2$), 28.5 (t, CH_2), 28.3 (q, *Me*$_3$C), 25.2 (t, BocNHCH$_2$*C*H$_2$), 23.5 (2 t, PhthNCH$_2$*C*H$_2$, BocNHCH$_2$*C*H$_2$), 20.4 (t, CH_2) ppm. ESI-MS: *m*/*z* (%) = 672.3 (10) [M + K]$^+$, 656.3 (10) [M + Na]$^+$, 634.3 (100) [M + H]$^+$. HRMS: calcd. for $C_{29}H_{40}N_5O_9S_1$ 634.2547; found 634.2543.

Allyl *N*-[9-Hydroxy-4-(2-nitrophenylsulfonyl)-12-phthalimido-4,9-diazadodecyl]carbamate (29) from Resin 26 (obtained from 0.2 mmol of resin 2): HPLC (H_2O/MeCN/TFA, 60:40:0.1, 25 mL min^{-1}, λ = 280 nm) gave **29** as a colourless oil (0.022 g, 0.06 mmol, 30% from resin **2**). IR: $\tilde{\nu}$ = 1772 (CO of Phth), 1711 (CO of Phth/Alloc), 1371 (SO_2), 1142 (SO_2) cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$, 278 K): δ = 7.96 (dd, $^3J_{H,H}$ = 7.4, $^4J_{H,H}$ = 1.7 Hz, 1 H, arom. H *o* to NO_2), 7.88–7.86 (m, 2 H, 2 arom. CC*H* of Phth), 7.77–7.76 (m, 2 H, 2

arom. CCHC*H* of Phth), 7.75 (ap. td, $^3J_{H,H}$ = 7.4, $^4J_{H,H}$ = 1.5 Hz, 1 H, arom. H *p* to NO_2), 7.72 (ap. td, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 1.5 Hz, 1 H, arom. H *p* to SO_2), 7.66 (dd, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 1.5 Hz, 1 H, arom. H *o* to SO_2), 5.90 (ddt, $^3J_{trans}$ = 17.3, $^3J_{cis}$ = 10.7, $^3J_{vic}$ = 5.5 Hz, 1 H, CH_2=C*H*), 5.30 (dd, $^3J_{trans}$ = 17.1, $^3J_{gem}$ = 1.3 Hz, 1 H, C*H*$_2$=CH), 5.21 (dd, $^3J_{cis}$ = 10.7, $^3J_{gem}$ = 1.3 Hz, 1 H, C*H*$_2$=CH), 4.53 (d, $^3J_{vic}$ = 5.5 Hz, 2 H, OC*H*$_2$), 3.83 (t, $^3J_{H,H}$ = 6.3 Hz, 2 H, PhthNC*H*$_2$), 3.36–3.21 (m, 10 H, C*H*$_2$NOHC*H*$_2$, C*H*$_2$NNsC*H*$_2$, AllocNHC*H*$_2$), 2.19–2.14 (m, 2 H, PhthNCH$_2$C*H*$_2$), 1.82–1.73 (m, 4 H, OHNCH$_2$C*H*$_2$C*H*$_2$CH$_2$NNs), 1.72–1.65 (m, 2 H, AllocNHCH$_2$C*H*$_2$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 278 K): δ = 168.4 (s, 2×CO of Phth), 156.4 (s, CO of Alloc), 147.8 (s, arom. CNO_2), 134.4 (d, 2 arom. CCH*C*H of Phth), 133.9 (d, arom. CH *p* to NO_2), 132.8 (d, *C*H=CH_2), 132.5 (s, arom. CSO_2), 131.9 (d, arom. CH *p* to SO_2) 131.6 (s, 2 arom. C of Phth), 130.5 (d, arom. CH *o* to NO_2), 124.4 (d, arom. CH *o* to SO_2), 123.6 (d, 2 arom. C*C*H of Phth), 117.7 (t, *C*H$_2$=CH), 65.6 (t, CH$_2$=CH*C*H$_2$), 58.9, 57.1 (2 t, CH_2NNsCH_2), 46.9, 45.3 (2 t, CH_2NOHCH_2), 37.5 (t, AllocNHCH$_2$), 34.5 (t, PhthNCH$_2$), 28.3 (t, CH$_2$), 25.3 (t, AllocNHCH$_2$*C*H$_2$), 23.5 (t, PhthNCH$_2$*C*H$_2$), 20.4 (t, CH$_2$) ppm. ESI-MS: *m*/*z* (%) = 618.3 (100) $[M + H]^+$. HRMS: calcd. for $C_{28}H_{36}N_5O_9S_1$ 618.2234; found 618.2228.

***tert*-Butyl *N*-[9-Hydroxy-5-(2-nitrophenylsulfonyl)-12-phthalimido-5,9-diazadodecyl]carbamate (36) from Resin 42 (obtained from 0.3 mmol of resin 2):** HPLC (H_2O/MeCN/TFA, 55:45:0.1, 25 mL min^{-1}, λ = 280 nm) gave **36** as a colourless oil (0.032 g, 0.05 mmol, 18% from resin **2**). IR: $\tilde{\nu}$ = 1772 (CO of Phth), 1710 (CO of Phth/Boc), 1398 (SO_2), 1345 (NO_2), 1144 (SO_2) cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$, 278 K): δ = 8.26 (d, $^3J_{H,H}$ = 8.3 Hz, 1 H, arom. H *o* to NO_2), 7.85–7.84 (m, 2 H, 2 arom. CC*H*CH of Phth), 7.75–7.70 (m, 4 H, 2 arom. CCHC*H* of Phth, arom. H *p* to NO_2, arom. H *p* to SO_2), 7.62 (dd, $^3J_{H,H}$ = 7.4, $^4J_{H,H}$ = 1.5 Hz, 1 H, arom. H *o* to SO_2), 4.68 (app. t, $^3J_{H,H}$ = 6.0 Hz, 1 H, BocNH), 3.87–3.79 (m, 2 H, PhthNCH$_2$), 3.67–3.62 (m, 1 H, NOHCH$_2$-CH$_2$C*H*$_2$NNs), 3.52–3.47 (m, 1 H, NOHCH$_2$CH$_2$C*H*$_2$NNs), 3.40–3.23 [m, 6 H, C*H*$_2$NOHC*H*$_2$, NsNC*H*$_2$(CH$_2$)$_3$NHBoc], 3.10 (app. td, $^3J_{H,H}$ = 6.6, $^3J_{H,H}$ = 6.0 Hz, 2 H, BocNHC*H*$_2$), 2.27–2.16 (m, 2 H, PhthNCH$_2$C*H*$_2$), 2.07–2.03 (m, 2 H, NOHCH$_2$C*H*$_2$CH$_2$NNs), 1.62–1.51 (m, 2 H, NsNCH$_2$C*H*$_2$CH$_2$CH$_2$NHBoc), 1.50–1.43 (m, 2 H, NsNCH$_2$CH$_2$C*H*$_2$CH$_2$NHBoc), 1.41 (s, 9 H, *Me*$_3$C) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 278 K): δ = 168.4 (s, 2×CO of Phth), 156.1 (s, CO of Boc), 147.8 (s, arom. CNO_2), 134.3 (d, 2 arom. CCH*C*H of Phth), 133.8 (d, arom. CH *p* to NO_2), 132.3 (s, arom. CSO_2), 132.1 (d, arom. CH *p* to SO_2), 131.7 (s, 2 arom. C of Phth), 131.3 (d, arom. CH *o* to NO_2), 124.0 (d, arom. CH *o* to SO_2), 123.5 (d, 2 arom. C*C*H of Phth), 57.9 [t, NsN*C*H$_2$(CH$_2$)$_3$NPhth], 56.9 [t, NOH(CH$_2$)$_2$*C*H$_2$], 47.9 [t, PhthN(CH$_2$)$_2$*C*H$_2$NOH], 44.2 [t, NOH*C*H$_2$(CH$_2$)$_2$NNs], 39.6 (t, BocNHCH$_2$), 34.6 (t, PhthNCH$_2$), 28.3 (q, *Me*$_3$C), 27.1 (t, BocNHCH$_2$*C*H$_2$), 25.7 (t, BocNHCH$_2$CH$_2$*C*H$_2$), 23.5 (t, PhthNCH$_2$*C*H$_2$), 22.6 (t, NOHCH$_2$*C*H$_2$CH$_2$NNs) ppm. ESI-MS: *m*/*z* (%) = 634.3 (100) $[M + H]^+$. HRMS: calcd. for $C_{29}H_{40}N_5O_9S_1$ 634.2547; found 634.2552.

[4-Hydroxy-8-(2-nitrophenylsulfonyl)-4,8-diazadodecane]-1,12-diphthalimide (45) from Resin 43 (obtained from 0.3 mmol of resin 2): HPLC (H_2O/MeCN/TFA, 60:40:0.1, 25 mL min^{-1}, λ = 280 nm) gave **45** as a colourless solid (0.040 g, 0.06 mmol, 21% from resin **2**). M.p. 66–69 °C. IR: $\tilde{\nu}$ = 1771 (CO of Phth), 1709 (CO of Phth/Alloc), 1371 (SO_2), 1155 (SO_2) cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$, 278 K): δ = 8.26–8.25 (m, 1 H, arom. H *o* to NO_2), 7.85–7.83 (m, 4 H, 4 arom. CC*H*CH of Phth), 7.75–7.68 (m, 6 H, 4 arom. CCHC*H* of Phth, 1 arom. H *p* to NO_2, 1 arom. H *p* to SO_2), 7.56–7.55 (m, 1 H, arom. H *o* to SO_2), 3.85–3.82 [m, 2 H, PhthNC*H*$_2$(CH$_2$)$_2$NOH], 3.68–3.64 [m, 2 H, PhthNC*H*$_2$-(CH$_2$)$_3$NNs], 3.53–3.22 (m, 8 H, C*H*$_2$NOHC*H*$_2$CH$_2$C*H*$_2$NNsC*H*$_2$), 2.28–2.03 (m, 2 H, PhthNCH$_2$C*H*$_2$CH$_2$NOH), 2.08–2.03 (m, 2 H, NOHCH$_2$C*H*$_2$CH$_2$NNs), 1.70–1.65 (m, 2 H, NsNCH$_2$CH$_2$C*H*$_2$-CH$_2$NPhth), 1.61–1.51 (m, 2 H, NsNCH$_2$C*H*$_2$CH$_2$CH$_2$NPhth) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 278 K): δ = 168.4, 168.3 (2 s, 2×2 CO of Phth), 147.8 (s, arom. CNO_2), 134.2, 134.1 (2 d, 2×2 arom. CCH*C*H of Phth), 133.8 (d, arom. CH *p* to NO_2), 132.2 (s, arom. CSO_2), 132.0 (d, arom. CH *p* to SO_2), 131.8, 131.7 (2 s, 2×2 arom. C of Phth), 131.3 (d, arom. CH *o* to NO_2), 123.9 (d, arom. CH *o* to CSO_2), 123.5, 123.3 (2 d, 2×2 arom. C*C*H of Phth), 57.8, 56.9 (2 t, CH_2NNsCH_2), 47.7, 44.3 (2 t, CH_2NOHCH_2), 36.9 [t, PhthN*C*H$_2$(CH$_2$)$_3$NNs], 34.7 [t, PhthN*C*H$_2$(CH$_2$)$_2$NOH], 25.6 (2 t, PhthNCH$_2$*C*H$_2$*C*H$_2$CH$_2$NNs), 23.4 (t, PhthNCH$_2$*C*H$_2$CH$_2$NOH), 22.7 (t, OHNCH$_2$*C*H$_2$CH$_2$NNs) ppm. ESI-MS: *m*/*z* (%) = 702.2 (12) $[M + K]^+$, 686.2 (18) $[M + Na]^+$, 664.3 (100) $[M + H]^+$. HRMS: calcd. for $C_{32}H_{34}N_5O_9S_1$ 664.2077; found 664.2074.

Allyl *N*-[9-Hydroxy-5-(2-nitrophenylsulfonyl)-12-phthalimido-5,9-diazadodecyl]carbamate (46) from Resin 44 (obtained from 0.3 mmol of resin 2): HPLC (H_2O/MeCN/TFA, 60:40:0.1, 25 mL min^{-1}, λ = 280 nm) gave **46** as a colourless oil (0.037 g, 0.06 mmol, 20% from resin **2**). IR: $\tilde{\nu}$ = 1770 (CO of Phth), 1708 (CO of Phth/Alloc), 1368 (SO_2), 1345 (NO_2), 1142 (SO_2) cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$, 278 K): δ = 8.22 (dd, $^3J_{H,H}$ = 7.2, $^4J_{H,H}$ = 1.5 Hz, 1 H, arom. H *o* to NO_2), 7.86–7.84 (m, 2 H, 2 arom. CC*H*CH of Phth), 7.75–7.70 (m, 3 H, 2 arom. CCHC*H* of Phth, 1 arom. H *p* to NO_2), 7.71 (dd, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.7 Hz, 1 H, arom. H *p* to SO_2), 7.62 (dd, $^3J_{H,H}$ = 7.0, $^4J_{H,H}$ = 2.0 Hz, 1 H, arom. H *o* to SO_2), 5.89 (ddt, $^3J_{trans}$ = 17.2, $^3J_{cis}$ = 10.4, $^3J_{vic}$ = 5.4 Hz, 1 H, CH_2=C*H*), 5.28 (dd, $^3J_{trans}$ = 17.2, $^3J_{gem}$ = 1.5 Hz, 1 H, C*H*$_2$=CH), 5.20 (dd, $^3J_{cis}$ = 10.5, $^3J_{gem}$ = 1.4 Hz, 1 H, C*H*$_2$=CH), 4.52 (dt, $^3J_{vic}$ = 5.4, $^4J_{H,H}$ = 1.3 Hz, 2 H, OC*H*$_2$), 3.87–3.79 (m, 2 H, PhthNCH$_2$), 3.64–3.59 (m, 1 H, NOHCH$_2$CH$_2$C*H*$_2$NNs), 3.52–3.47 (m, 1 H, NOHCH$_2$CH$_2$-C*H*$_2$NNs), 3.41–3.25 [m, 6 H, C*H*$_2$NOHC*H*$_2$, NsNC*H*$_2$-(CH$_2$)$_3$NHAlloc], 3.18 (td, $^3J_{H,H}$ = 6.5, $^3J_{H,H}$ = 6.5 Hz, 2 H, AllocNHC*H*$_2$), 2.24–2.19 (m, 2 H, PhthNCH$_2$C*H*$_2$), 2.08–2.04 (m, 2 H, NOHCH$_2$C*H*$_2$CH$_2$NNs), 1.62–1.56 (m, 2 H, NsNCH$_2$-C*H*$_2$CH$_2$CH$_2$NHAlloc), 1.52–1.48 (m, 2 H, NsNCH$_2$CH$_2$C*H*$_2$-CH$_2$NHAlloc) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 278 K): δ = 168.4 (s, 2×CO of Phth), 156.6 (s, CO of Alloc), 148.0 (s, arom. CNO_2), 134.5 (d, 2 arom. CCH*C*H of Phth), 134.1 (d, arom. CH *p* to NO_2), 133.0 (d, *C*H=CH_2), 132.4 (s, arom. CSO_2), 132.3 (d, arom. CH *p* to SO_2), 131.9 (s, 2 arom. C of Phth), 131.4 (d, arom. CH *o* to NO_2), 124.2 (d, arom. CH *o* to SO_2), 123.7 (d, 2 arom. C*C*H of Phth), 117.9 (t, *C*H$_2$=CH), 65.7 (t, CH$_2$=CH*C*H$_2$), 58.1 [t, NsN*C*H$_2$(CH$_2$)$_3$NPhth], 57.1 [t, NOH(CH$_2$)$_2$*C*H$_2$], 48.2 [t, PhthN(CH$_2$)$_2$*C*H$_2$NOH], 44.7 [t, NOH*C*H$_2$(CH$_2$)$_2$NNs], 40.3 (t, AllocNHCH$_2$), 34.8 (t, PhthNCH$_2$), 27.2 (t, AllocNHCH$_2$*C*H$_2$), 26.0 (t, AllocNHCH$_2$CH$_2$*C*H$_2$), 23.7 (t, PhthNCH$_2$*C*H$_2$), 22.9 (t, NOHCH$_2$*C*H$_2$CH$_2$NNs) ppm. ESI-MS: *m*/*z* (%) = 618.2 (100) $[M + H]^+$. HRMS: calcd. for $C_{28}H_{36}N_5O_9S_1$ 664.2234; found 618.2232.

Supporting Information (see also the footnote on the first page of this article): NMR spectra of the final products.

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