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Synthesis and Selective Deprotection of the Penta-*N*-Protected Polyamine 1,16-Diamino-4,8,13-triazahexadecane

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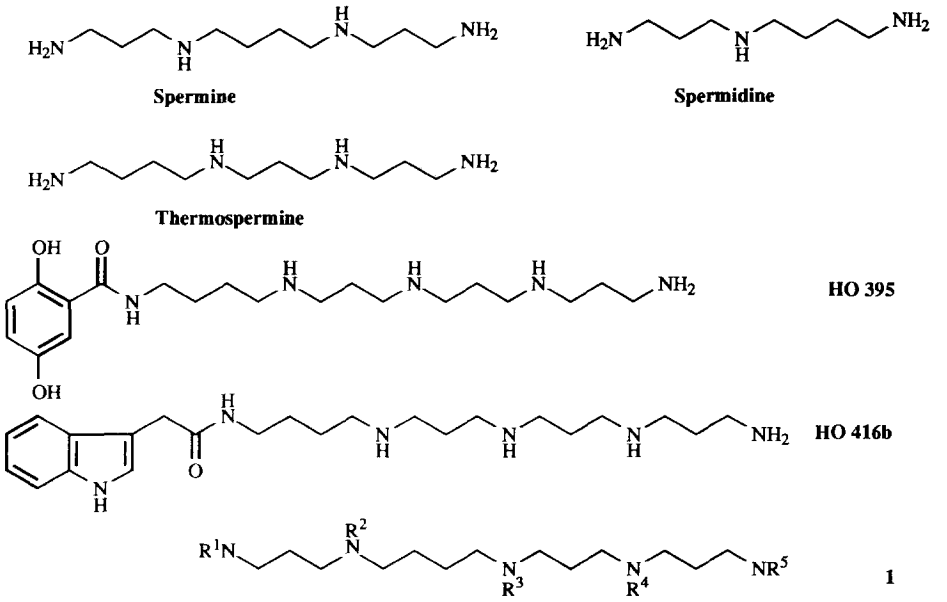
Abstract: The synthesis of the penta-*N*-protected polyamine thermopentamine {PA 3343, **1a**, *tert*-butyl *N*-[4-benzyl-16-diallylamino-13-(pyridine-2-sulfonyl)-9-trifluoroacetyl-4,9,13-triazahexadec-1-yl]-carbamate}, containing five different *N*-protecting groups is described. These protecting groups include *tert*-butoxycarbonyl, benzyl, trifluoroacetyl, diallyl, and pyridine-2-sulfonyl. In spite of the syntheses of specific polyamine derivatives the selective removal of each of these groups has been investigated.

INTRODUCTION

In recent years[1] a great deal of attention has been focused on the polyamine venom components of spiders and wasps. It was shown that these low-molecular-weight toxins are highly effective potentiators (at low concentration) and antagonists (at high concentration) of ionotropic glutamate receptors in mammalian central nervous systems.[2] The separation and purification as well as structural elucidation of natural toxins is, to date, still the major problem to the development of these neuroscience investigations. Chemically synthesized spider or wasp toxins and their analogs have been used in the characterization of natural toxins and the exitatory amino acid receptors. During the course of our investigation about acyl-polyamines,[3] we were interested in the chemistry of toxins like **HO 395** and **HO 416b** (Scheme 1) which arise from the same family of spiders (Agelenidae) and contain the same polyamine backbone, homocaldopentamine (PA 3334)[1]. The general structure of Agelenidae toxins is a polyamine backbone monoacylated by an (aromatic) carboxylic acid. Looking for a versatile synthetic approach to these compounds and their analogons, we aimed to synthesize the penta-*N*-protected polyamine thermopentamine (**1**, PA 3343) derivative, containing five independently removable *N*-protecting groups,[4] which should allow the regioselective introduction of an acyl moiety.

METHODS AND RESULTS

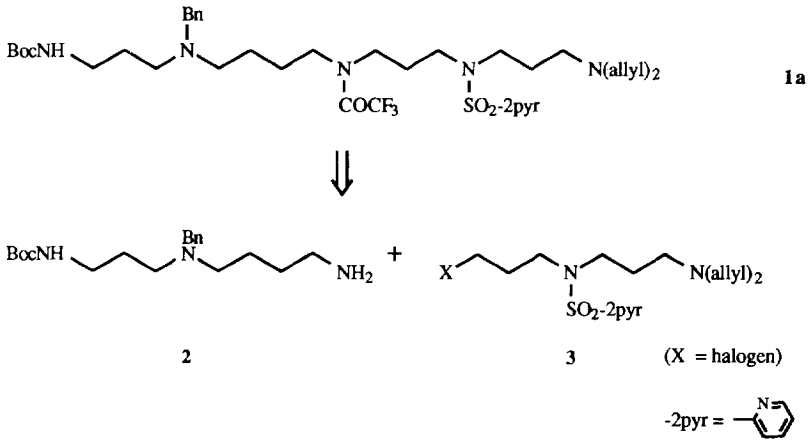
The selective protection of polyamines is a rather laborious and uneconomic task,[5] we proposed to investigate a non linear approach for the construction of the target compound **1** (Scheme 2). We planned to prepare **1** by reaction of the spermidine reagent **2**[6] with the building block **3** following by trifluoroacetylation of the resulting polyamine. Introduction of the labile *N*-trifluoroacetyl moiety at the last step of the synthesis allow



R^1, R^2, R^3, R^4 and R^5 : *N*-protecting group

Scheme 1

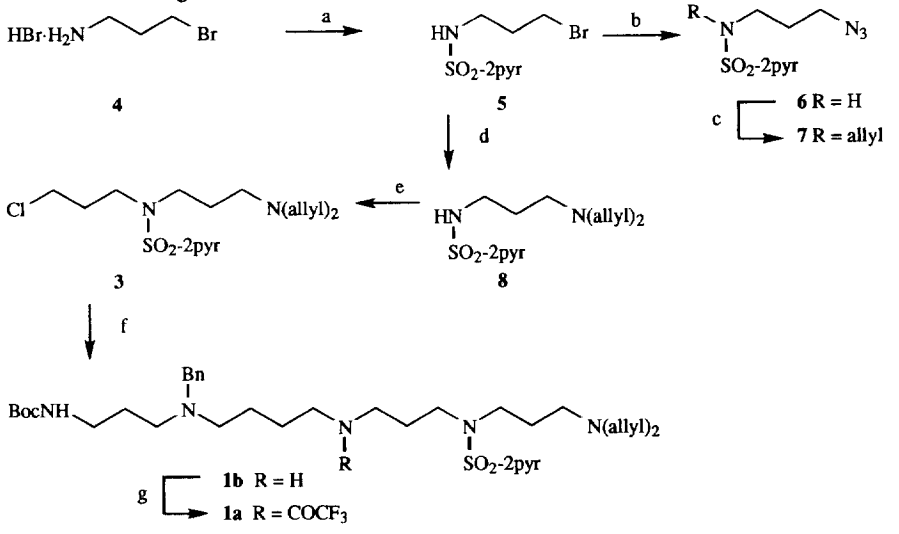
the use of basic conditions during the isolation of the intermediates. A crucial problem is, of course, the definition of the two remaining *N*-protecting groups of **3**. We have chosen the pyridine-2-sulfonyl group which we have already described as a very convenient amino protecting group.[7] The removal of *tert*-butoxycarbonyl, benzyl, trifluoracetyl, and pyridine-2-sulfonyl groups require treatment with trifluoacetic acid, α-chloroethylchloroformate,[8] potassium carbonate, and SmI_2[7] respectively. These reaction conditions eliminate a large number of *N*-protecting groups as candidates for the fifth different protecting group of **1**. The 2,2,2-trichloro-(*tert*-butoxycarbonyl) group (TCBOC) has already been used by Bergeron[6a] as the fourth orthogonal



Scheme 2

group (Boc, Bn, $COCF_3$, TCBOC). However, the deprotection conditions required in this case might not be compatible with the presence of a cinnamoyl group as the aromatic acyl moiety. Therefore we chose to use the diallyl group which can be deprotected under non-reducing conditions.[9] In this paper we report a practical synthesis of the polyamine **1a** *via* **2** and **3** as well as studies about the deprotection of its five different *N*-protecting groups.

Treatment of the commercial 3-bromopropylamine hydrobromide **4** with pyridine-2-sulfonyl chloride[10] in the presence of aqueous potassium carbonate gave the pyridine-2-sulfonamide derivative **5** (Scheme 3). Compound **5** was first converted to the azide **6** with sodium azide in order to use the azido group as a masked amino group.[11-13] Alkylation of the anion of pyridine-2-sulfonamide **6** (NaH, DMF) with allyl bromide gave **7.** However, attempts to deprotect selectively the pyridine-2-sulfonyl group in **7** by treatment with SmI_2 at room temperature failed. Under these conditions, the competitive reduction of the azido to the amino group was observed and occurred faster.[14] This approach was then given up and compound **5** was treated with diallylamine in the presence diisopropylethylamine at 80°C in toluene to give the diallylamino derivative **8.** Successive treatment of the latter with sodium hydride and 1-bromo-3-chloropropane in dimethylformamide afforded the desired building block **3**.

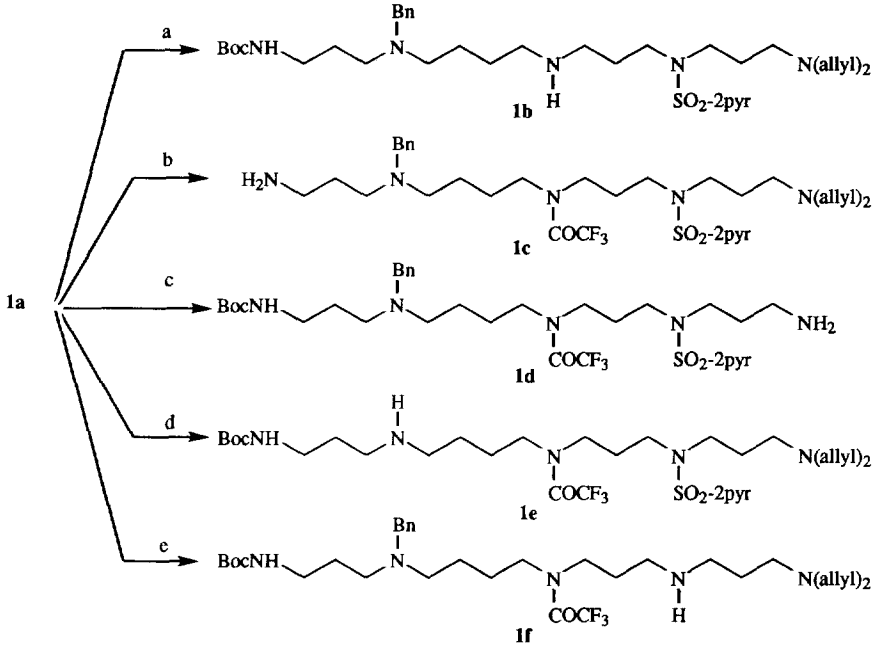


a) 2-pyrSO_2Cl, K_2CO_3, H_2O, CH_2Cl_2, 0°C, 1 h, 98%; b) NaN_3, DMF, rt, 18 h, 90%; c) NaH, DMF, rt, 1 h 30 then allylBr, rt, 2 h, 98%; d) $(allyl)_2NH$, DIPEA, toluene, 80°C, 2 h 30, 90%; e) NaH, DMF, rt, 2 h then $Br(CH_2)_3Cl$, rt, 2 h, 97%; f) **2** , NaI, DIPEA, toluene, 80°C, 30 h, 66% or **2** , NaI, KF / Celite, CH_3CN, 60°C, 96 h then 70°C, 72 h, 65%; g) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, -20°C, 1 h, 85%.

Scheme 3

tert-Butyl *N*-(8-amino-4-benzyl-4-azaoct-1-yl)-carbamate (**2**) can be prepared according to literature[6,15] in five steps from commercially available starting materials such as acrylonitrile and benzylamine[6] or in three steps from *N*-Boc-1,3-diaminopropane[16] and *N*-(4-bromobutyl)phthalimide.[15] Coupling of these two building blocks **2** and **3** using KF/Celite®,[7,17] or diisopropylethylamine (DIPEA) in presence of catalytic amounts of sodium iodide gave the desired polyamine **1b**. Finally, treatment of the polyamine **1b** with trifluoroacetic anhydride and triethylamine at -20°C afforded the polyamine target **1a**.

Independent deprotection of each *N*-protecting group in **1a** was then investigated (Scheme 4). Treatment of **1a** with an excess of potassium carbonate in aqueous methanol at room temperature gave cleanly the tetra-*N*-protected spermine derivative **1b** in 80% yield. Exposure of **1a** to trifluoroacetic acid in tetrahydrofuran for 2.5 h removed the *tert*-butoxycarbonyl group and afforded the primary amine **1c** as hydrochloride.



a) K_2CO_3, MeOH aq., rt, 24 h, 80%; b) CF_3CO_2H, CH_2Cl_2, rt, 2 h 30, 88%; c) $Pd(Ph_3)_4$, NDMBA, CH_2Cl_2, 35°C, 1 h 30, 98%; d) $ClCOCHClCH_3$, CH_2Cl_2, -10°C, 12 h then MeOH, Et_3N, reflux, 12 h, 46%; e) SmI_2, THF, rt, 12 h, 60%.

Scheme 4

Garro-Helion et al.[9] have described recently that palladium(0) catalyzes the mild and selective deallylation of allylic amines in the presence of *N,N'*-dimethylbarbituric acid (NDMBA) as an allyl group scavenger. According to this method, treatment of *N,N*-diallyl compound **1a** with tetrakis(triphenylphosphine)-palladium and NDMBA in dichloromethane at 35°C afforded the polyamine **1d**.

It is known that α-chloroethyl chloroformate induces a selective cleavage of *N*-benzyl groups.[8] Therefore, it was anticipated that debenzylation of **1a** using this reagent could leave the diallyl function intact.[18] The polyamine **1a** was then treated with 1 equiv. of α-chloroethyl chloroformate in dichloromethane for 12 h at -10°C and the resulting mixture was hydrolyzed upon refluxing in methanol and triethylamine for 12 h. The expected polyamine **1e** has been isolated in 46% only. This reaction product was accompanied by numerous not-separated by-products. Nevertheless, analysis of this mixture by mass spectrometry and NMR revealed the presence of mono-deallylated compounds, starting material **1a** and traces of primary amine **1c**. The removal of the *tert*-butoxycarbonyl group in **1a** could be explained by the presence, in the reaction mixture, of residual acid chloride resulting from the partial hydrolysis of α-chloroethyl chloroformate during the first step of the reaction. When the reaction of **1a** with α-chloroethyl chloroformate was performed at room temperature or under reflux in dichloromethane until complete consumption of starting material, the proportion of by-products after

hydrolysis increased whereas the isolated yields of **1e** decreased. Presumably, debenzylation of **1a** might proceed slowly because of the steric hindrance resulting from the presence of the *tert*-butoxycarbonyl and trifluoroacetyl neighbouring moieties.

Finally, removal of the pyridine-2-sulfonyl group in **1a** to **1f** was performed by treatment of **1a** with SmI_2 (6 equiv.) in tetrahydrofuran at room temperature[7].

In conclusion, the penta-*N*-protected polyamine derivative **1a** has been synthesised in good yield, in five steps from 3-bromopropylamine hydrobromide and the spermidine reagent **2**. The following *N*-protecting group: *tert*-butoxycarbonyl, trifluoroacetyl, diallyl and pyridine-2-sulfonyl in **1a** are orthogonal.[4] The removal of benzyl group in **1a** interferes to a certain extend with deprotection of the diallyl moiety. The application of polyamine **1**, as a versatile precursor of Agelenidae toxins, is currently under investigation in our laboratory.

EXPERIMENTAL

Reagents were purchased from Fluka. Samarium diiodide was prepared according to the method of Kagan et al.[19] Potassium fluoride/Celite was prepared according to Ando's method.[17] Pyridine-2-sulfonyl chloride was synthesized by a previously described methodology.[10] THF was freshly distilled from benzophenone/sodium prior to use. TLC was performed on Merck aluminium sheets coated with *silica gel 60* F_{254}. Column chromatographies were performed with *silica gel 60* (230-400 mesh, Merck). ^1H NMR spectra and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, on a Bruker AC 300 n.m.r. spectrometer. All chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane. Infrared (IR) spectra were recorded on a Perkin-Elmer IR-297 spectrometer. Mass spectra were obtained using a Finnigan SSQ 700 or Finnigan MAT 90; Chemical ionization (CI) utilizing NH_3 as reactant gas and electron impact (EI) operated with 70 eV. Melting points were determined on a Mettler FP-5 instrument.

Starting material available by literature method: ***N*^{1}-(*tert*-Butoxycarbonyl)-*N*^{4}-benzylspermidin (2).**[6]

N-*(3-Bromopropyl)-pyridine-2-sulfonamide* (5). To a vibromixed solution of 3-bromopropylamine hydrobromide (**4**, 3.67 g, 16.43 mmol) in a (1:1) mixture of 4 M K_2CO_3 (30 mL) and dichloromethane (30 mL) at 0°C, was added over 10 min a solution of pyridine-2-sulfonyl chloride (3.50 g, 19.7 mmol) in dichloromethane (5 mL). After 1 h at 0°C, the emulsion was decanted and the aqueous layer was extracted twice with chloroform. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (silica gel, ethyl acetate/hexane 1:1) gave **5** as a yellow oil (4.59 g, 98%). IR (neat) 3270 (NH), 1365 (SO_2), 1170 (SO_2) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.01 (*p*, *J* = 6.25 Hz, 2 H, CH_2CH_2Br), 3.19 (*q*, *J* = 6.25 Hz, 2 H, CH_2NH), 3.47 (*t*, *J* = 6.25 Hz, 2 H, CH_2Br), 5.63 (*t*, *J* = 6.25 Hz, 1 H, NH), 7.51-7.59 (*m*, 1 H), 7.91-8.09 (*m*, 2 H), 8.75 (*d*, *J* = 4.4 Hz, 1 H) ppm; δ_C (75 MHz, $CDCl_3$) 30.15 (CH_2CH_2Br), 32.63 (CH_2Br), 41.83 (CH_2NH), 122.41, 126.83, 138.24, 150.08, 157.31 ppm; *m/z* (CI) 280 $[M+H]^+$; Anal. calc. for $C_8H_{11}BrN_2O_2S$ (279.162): C 34.42, H 3.97, N 10.03; found C 33.93, H 4.04, N 9.74.

N-*(3-Azidopropyl)-pyridine-2-sulfonamide* (6). To a stirred solution of **5** (0.518 g, 1.93 mmol) in dry DMF (4 mL) was added solid sodium azide (0.276 g, 4.25 mmol) under argon at room temperature. After 18 h, the solvent was evaporated under vacuum. The residual oil was taken up in ether. The ether solution was washed successively with water and brine and dried (Na_2SO_4). After evaporation, the residual oil was purified

by flash chromatography (silica gel, ethyl acetate/hexane 1:1) to afford 0.419 g of **6** as a colorless oil (90%). IR (neat) 3270 (NH), 2100 (N_3), 1360 (SO_2), 1175 (SO_2) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.77 (*p*, *J* = 6.25 Hz, 2 H, $CH_2CH_2N_3$), 3.15 (*t*, *J* = 6.25 Hz, 2 H, CH_2NH), 3.87 (*t*,*J* = 6.25 Hz, 2 H, CH_2N_3), 6.18 (br *s*, 1 H, NH), 7.51-7.57 (*m*, 1 H), 7.92-8.06 (*m*, 2 H), 8.17.8.67 (*m*, 1 H) ppm; δ_C (75 MHz, $CDCl_3$) 29.11 ($CH_2CH_2N_3$), 40.91 (CH_2NH), 48.61 (CH_2N_3), 122.39, 126.84, 138.27, 150.04, 157.38 ppm; m/z (CI) 242 $[M+H]^+$; Anal. calc. for $C_8H_{11}N_5O_2S$ (241.273): C 39.83, H 4.60, N 29.03; found C 40.02, H 4.72, N 29.28.

N-*Allyl*-N-*(3-azidopropyl)-pyridine-2-sulfonamide* (7). To a stirred solution of **6** (142 mg, 0.588 mmol) in DMF (4 mL) was added NaH (30 mg of a 60% dispersion in mineral oil, 0.706 mmol), under argon, at room temperature. After 1.5 h, allyl bromide (0.528 mL, 5.88 mmol) was added, and the mixture was stirred for 2 h at room temperature. It was concentrated *in vacuo*. The residual oil was purified by flash chromatography (silica gel, ethyl acetate/hexane 3:7) to provide 164 mg of **7** (98%) as a yellow oil. IR (neat) 2100 (N_3), 1350 (SO_2), 1175 (SO_2) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.78 (*p*, *J* = 6.5 Hz, 2 H, $CH_2CH_2N_3$), 3.26-3.32 (*m*, 4 H, CH_2N_3 and CH_2CH_2N), 3.91 (*d*, *J* = 7.0 Hz, 2 H, NCH_2), 5.06-5.20 (*m*, 2 H, $CH{=}CH_2$), 5.57-5.73 (*m*, 1 H, $CH{=}CH_2$), 7.39-7.46 (*m*, 1 H), 7.79-7.96 (*m*, 2 H), 8.60-8.67 (*m*, 1 H) ppm; δ_C (75 MHz, $CDCl_3$) 28.19 ($CH_2CH_2N_3$), 45.77 (CH_2CH_2NH), 48.70 (CH_2N_3), 52.05 (CH_2N), 119.04 ($CH{=}CH_2$), 122.54, 126.55, 133.32 ($CH{=}CH_2$), 137.92, 150.03, 158.01 ppm; m/z (CI) 282 $[M+H]^+$; Anal. calc. for $C_{11}H_{15}N_5O_2S$ (281.338): C 46.96, H 5.37, N 24.89; found C 46.80, H 5.40, N 24.74.

***3-(Diallylamino)propyl)-pyridine-2-sulfonamide* (8).** A solution of **5** (0.498 g, 1.78 mmol), diisopropylethylamine (0.458 mL, 2.67 mmol) and diallylamine (0.659 mL, 5.35 mmol) in toluene (5 mL) was heated at 80°C for 3 h. The mixture was cooled to room temperature and quenched by adding water. The aqueous layer was extracted twice with chloroform. Purification by flash chromatography (silica gel, ethyl acetate/hexane 7:3) gave **8** as a yellow oil (0.471 g, 90%). IR (neat) 3270 (NH), 1380 (SO_2), 1175 (SO_2) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.65 (*p*, *J* = 6.25 Hz, 2 H, $CH_2CH_2CH_2$), 2.52 (*t*, *J* = 6.25 Hz, 2 H, $CH_2N(allyl)_2$), 3.07 (*d*, *J* = 7.02 Hz, 4 H, $CH_2CH{=}CH_2$), 3.17 (*t*, *J* = 6.25 Hz, 2 H, CH_2NH), 5.10-5.19 (*m*, 5 H, $CH{=}CH_2$ and NH), 5.76-5.92 (*m*, 2 H, $CH{=}CH_2$), 7.45-7.50 (*m*, 1 H), 7.86-8.01 (*m*, 2 H), 8.67-8.71 (*m*, 1 H) pm; δ_C (75 MHz, $CDCl_3$) 24.99 (CH_2CH_2N), 44.07 (CH_2NH), 52.34 ($CH_2N(allyl)_2$), 56.46 ($CH_2CH{=}CH_2$), 118.36 ($CH{=}CH_2$), 122.06, 126.29, 134.46 ($CH{=}CH_2$), 137.77, 149.76, 157.73 ppm; m/z (CI) 296 $[M+H]^+$; Anal. calc. for $C_{14}H_{21}N_3O_2S$ (295.406): C 56.92, H 7.17, N 14.22; found C 56.72, H 7.17, N 14.12.

N-*(Diallylaminopropyl)*-N-*(3-chloro-propyl)-pyridine-2-sulfonamide* (3). To a solution of NaH (98 mg of a 60% dispersion in mineral oil, 2.45 mmol) in DMF (5 mL) was added a solution of **8** (0.604 g, 2.05 mmol) in DMF (9 mL) at room temperature. The solution was stirred for 1.5 h , whereupon 1-bromo-3-chloropropane (282 µL, 2.86 mmol) was added. After stirring for 2 h at room temperature, the solution was quenched by bubbling CO_2 for 10 min. The crude mixture was concentrated *in vacuo* and then dried (Na_2SO_4) for 1 h under high vacuum. Purification by flash chromatography (silica gel, ethyl acetate/hexane 3:2) gave **3** as a yellow oil (0.738 g, 95%). IR (neat) 1380 (SO_2), 1175 (SO_2) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.66 (*p*, *J* = 6.25 Hz, 2 H, $CH_2CH_2CH_2$), 2.04 (*p*, *J* = 6.25 Hz, 2H, $CH_2CH_2CH_2$), 2.36 (*t*, *J* = 6.25 Hz, 2 H, $CH_2N(allyl)_2$),

2.98 (*d*, *J* = 6.50 Hz, 4 H, $CH_2CH{=}CH_2$), 3.29 (*t*, *J* = 6.25 Hz, 2 H, CH_2Cl), 3.47 (*t*, *J* = 6.25 Hz, 2 H, CH_2NSO_2), 3.57 (*t*, *J* = 6.25 Hz, 2 H, CH_2NSO_2), 5.04-5.18 (*m*, 4 H, $CH{=}CH_2$), 5.68-5.85 (*m*, 2 H, $CH{=}CH_2$), 7.41-7.50 (*m*, 1 H), 7.81-7.93 (*m*, 2 H), 8.62-8.69 (*m*, 1 H) ppm; δ_C (75 MHz, $CDCl_3$) 26.42 + 32.30 (2 $CH_2CH_2CH_2$), 42.00 (CH_2Cl), 46.72 (CH_2NSO_2), 47.84 (CH_2NSO_2), 50.21 ($CH_2N(allyl)_2$), 56.66 ($CH_2CH{=}CH_2$), 117.31 ($CH{=}CH_2$), 122.36, 126.35, 135.42 ($CH{=}CH_2$), 137.74, 149.85, 157.96 ppm; m/z (EI) 371 $[M]^+$. Anal. calc. for $C_{17}H_{26}ClN_3O_2S$ (371.933).

tert-*Butyl* N-*[4-Benzyl-16-diallylamino-13-(pyridine-2-sulfonyl)-4,9,13-triazahexadec-1-yl]-carbamate* (1b).

Method A: A solution of **2**, (0.146 g, 1.10 mmol), diisopropylethylamine (80 µL, 0.653 mmol), sodium iodide (20 mg, 0.131 mmol) and **3** (0.162 g, 0.435 mmol) in toluene (2 mL) was heated at 80°C for 30 h under stirring. It was then cooled to room temperature and concentrated *in vacuo*. After dissolution in chloroform, the crude mixture was washed with a saturated solution of sodium thiosulfate (2x), dried (Na_2SO_4), and concentrated under reduced pressure. Purification by flash chromatography (silica gel, chloroform/methanol/ammonia water 25% 90:5:0.5) gave **1b** as a yellow oil (0.194 g, 66%).

Method B: To a stirred solution of *tert*-butyl *N*-(8-amino-4-benzyl-4-azaoct-1-yl)-carbamate (**2**, 0.317 g, 0.945 mmol), sodium iodide (29 mg, 0.189 mmol) and **3** (0.351 g, 0.945 mmol) in acetonitrile (15 mL) was heated at 60°C for 96 h in the presence of KF/Celite (0.549g, 4.72 mmol). The reaction mixture was then heated at 70°C for 72 h. KF/Celite was removed by filtration. The filtrate was evaporated to dryness. The residual oil was purified by flash chromatography (silica gel, chloroform/methanol/ammonia water 25% 90:5:0.5) to provide 0.411 g of **1b** as a yellow oil (65%). IR (neat) 3480 (NH), 1705 (C=O), 1340 (SO_2), 1170 (SO_2) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.43 (*s*, 9 H, *t*Bu), 1.52-1.70 (*m*, 8 H, $CH_2CH_2CH_2$), 1.82 (*p*, *J* = 6.60 Hz, 2 H, $CH_2CH_2CH_2$), 2.00 (*s*, 1H, NH), 2.36-2.50 (*m*, 6 H, CH_2N), 2.62 (*t*, *J* = 6.60 Hz, 2 H, CH_2N), 2.71 (*t*, *J* = 6.60 Hz, 2 H, CH_2N), 3.01 (*d*, *J* = 6.05 Hz, 4 H, $CH_2CH{=}CH_2$), 3.13 (*q*, *J* = 6.00 Hz, 2 H, $BocNHCH_2$), 3.31 (*t*, *J* = 7.20 Hz, 2 H, CH_2NSO_2), 3.41 (*t*, *J* = 7.20 Hz, 2 H, CH_2NSO_2), 3.52 (*s*, 2 H, NCH_2Ph), 5.09-5.17 (*m*, 4 H, $CH_2{=}CH$), 5.40 (*t*, *J* = 6.00 Hz, 1 H, N*H*Boc), 5.70-5.85 (*m*, 2 H, $CH_2{=}CH$), 7.20-7.35 (*m*, 5 H, Ph), 7.42-7.49 (*m*, 1 H), 7.82-7.98 (*m*, 2 H), 8.66 (*d*, *J* = 4.4 Hz, 1 H) ppm; δ_C (75 MHz, $CDCl_3$) 24.49, 26.43, 26.52, 26.86, 28.14 (CH_3), 28.37, 39.51 ($BocNHCH_2$), 46.26, 46.82, 47.28, 49.33, 50.30, 51.88, 53.37, 56.63, 58.60, 78.59, 117.41 ($CH_2{=}CH$), 122.34, 126.32, 126.89, 128.17, 128.87, 135.32, 137.74, 139.16, 149.85, 155.96 (*C*=O), 157.98 ppm; m/z (CI) 671 $[M+H]^+$; Anal. calc. for $C_{36}H_{58}N_6O_4S$ (670.965): C 64.44, H 8.71 N 12.53; found C 63.84, H 8.54, N 12.12.

tert-*Butyl* *N-[4-Benzyl-16-diallylamino-13-(pyridine-2-sulfonyl)-9-trifluoroacetyl-4,9,13-triazahexadec-1-yl]-carbamate* (1a). To a stirred solution of **1b** (0.572 g, 0.852 mmol) and triethylamine (0.178 mL, 1.28 mmol) in dichloromethane (5 mL) was added dropwise during 20 min to a solution of trifluoroacetic anhydride (142 µL, 1.023 mmol) in dichloromethane (1mL) at -20°C. and stirred at -20°C for another 40 min and then quenched with 5% aqueous $NaHCO_3$ (3 mL). The aqueous layer was extracted with chloroform (3x) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (silica gel, ethyl acetate/methanol 95:5) gave **1a** as a pale yellow oil (0.553 g, 85%). IR ($CHCl_3$) 1705 (C=O), 1685 (C=O), 1345 (SO_2), 1170 (SO_2) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.36 (*s*, 9 H, *t*Bu), 1.40-1.68 (*m*, 8 H, $CH_2CH_2CH_2$),1.83 (*p*, *J* = 7.30 Hz, 2 H, $CH_2CH_2CH_2$), 2.30-2.41 (*m*, 6H,

CH_2N), 2.93-2.98 (*m*, 4 H, $CH_2CH{=}CH_2$), 3.06 (*q*, *J* = 6.60 Hz, 2 H, $BocNHCH_2$), 3.19-3.39 (*m*, 8 H, CH_2NSO_2 and CH_2NCOCF_3), 3.46 (s, 2 H, CH_2Ph), 5.01-5.11 (*m*, 4 H, $CH_2{=}CH$), 5.15-5.20 (br *s*, 1H, NHBoc), 5.66-5.77 (*m*, 2 H, $CH_2{=}CH$), 7.19-7.25 (*m*, 5 H, Ph), 7.37-7.43 (*m*, 1 H), 7.81-7.87 (*m*, 2 H), 8.59 (*d*, *J* = 4.29 Hz, 1 H) ppm; δ_C (75 MHz, $CDCl_3$) 24.02, 24.53, 26.35, 26.54, 28.35 (CH_3), 29.57, 39.43 ($BocNHCH_2$), 44.70, 46.56, 46.88, 47.30, 47.39, 50.25, 52.06, 53.21, 56.60, 56.64, 58.76, 77.80, 117.47 ($CH_2{=}CH$), 122.36, 126.35, 126.95, 128.22, 128.77, 135.22, 137.74, 139.16, 149.85, 155.98 (C=O), 157.98 ppm; m/z (CI) 767 $[M+H]^+$; Anal. calc. for $C_{38}H_{57}F_3N_6O_5S$ (766.974): C 59.51, H 7.49, N 10.96; found C 59.25, H 7.79, N 10.86.

***Removal of Trifluoroacetyl Group from 1a. Formation of* tert-*Butyl N-[4-Benzyl-16-diallylamino-13-(pyridine-2-sulfonyl)-4,9,13-triazahexadec-1-yl]-carbamate* (1b).** A solution of **1a** (100 mg, 0.130 mmol) and K_2CO_3 (36 mg, 0.261 mmol) in a (3:1) mixture methanol/water (3 mL) was stirred for 24 h at room temperature. After removal of the solvent, the crude product was purified by flash chromatography (silica gel, chloroform/methanol/ammonia water 25% 90:10:0.5) to yield 70 mg (80 %) of **1b**.

***Removal of* tert-*Butoxycarbonyl Group from 1a. Formation of* N-*8-Amino-5-benzyl-5-azaoctyl)*-N-*[7-diallylamino-4-(pyridine-2-sulfonyl)-4-azaheptyl]trifluoroacetamide* (1c).** A solution of **1a** (150 mg, 0.196 mmol), and trifluoroacetic acid (134 µL, 1.76 mmol) in dichloromethane (2 mL) was stirred at room temperature for 2.5 h. Excess of trifluoroacetic acid and the solvent were evaporated under reduced pressure. The amine was dissolved in ethanol and converted to its hydrochloride by addition of 4 N HCl until the pH (<2) was reached to yield 121 mg of **1c**·HCl (88%) as a colorless oil. IR ($CHCl_3$) 3400 (NH_2), 1685 (C=O), 1345 (SO_2), 1175 (SO_2) cm^{-1}; δ_H (300 MHz, CD_3OD) 1.69-2.30 (*m*, 10 H, $CH_2CH_2CH_2$), 3.06 (*t*, *J* = 7.5 Hz, 2 H, CH_2N), 3.25-3.58 (*m*, 16 H, CH_2N), 3.86 (*t*, *J* = 7.80 Hz, 4 H, CH_2N), 4.46 (br *s*, 3 H, NH_3^+), 5.63-5.72 (*m*, 4 H, $CH_2{=}CH$), 5.97-6.12 (*m*, 2 H, $CH_2{=}CH$), 7.52-7.72 (*m*, 6 H), 7.99-8.15 (*m*, 2 H), 8.73 (*d*, *J* = 4.47 Hz, 1 H) ppm; δ_C (75 MHz, CD_3OD) 23.07, 24.21, 26.03, 26.51, 27.88, 28.36, 38.92, 47.36, 48.65, 49.96, 51.89, 52.09, 52.26, 54.52, 57.16, 59.55, 125.00, 128.11, 128.33, 129.54, 131.46, 131.55, 132.38, 133.29, 140.89, 152.38, 159.23 ppm; m/z (CI) 667 $[M+H]^+$; Anal. calc. for $C_{33}H_{49}F_3N_6O_3S \cdot HCl + 7\ H_2O$: C 47.79, H 7.78, N 10.13; found C 47.48, H 7.43, N 9.74.

***Removal of the Allyl Groups from* 1a. *Formation* tert-*Butyl N-[16-Amino-4-benzyl-13-(pyridine-2-sulfonyl)-9-trifluoroacetyl-4,9,13-triazahexadec-1-yl]-carbamate* (1d).** To a well-degassed solution of **1a** (146 mg, 0.190 mmol) in dichloromethane (0.5 mL) was added successively tetrakis(triphenylphosphine)palladium (4 mg, 3.81 10^{-3} mmol) and *N*, *N'*-dimethylbarbituric acid (180 mg, 1.14 mmol) under argon. The reaction mixture was stirred at 35°C for 1.5 h. Upon cooling, dichloromethane was added (5 mL) and the reaction mixture was washed with 5% aqueous $NaHCO_3$ (2x), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (silica gel, chloroform/methanol/ammonia water 25% 90:5:0.5) led to 128 mg of **1d** as a colorless oil (98%). IR ($CHCl_3$) 3450 (NH_2), 1710 (C=O), 1685 (C=O), 1345 (SO_2), 1170 (SO_2) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.36 (*s*, 9 H, *t*Bu), 1.40-1.57 (*m*, 8 H, $CH_2CH_2CH_2$), 1.66 (*p*, *J* = 6.70 Hz, 2 H, $CH_2CH_2CH_2$), 1.83 (br *s*, 2 H, NH_2), 2.31-2.45 (*m*, 4 H, NCH_2), 2.68 (*q*, *J* = 6.70 Hz, 2 H, NCH_2), 3.06 (q, *J* = 6.00 Hz, 2 H, $BocNHCH_2$), 3.26-3.36 (*m*, 8 H,

CH_2NSO_2 and CH_2NCOCF_3), 3.45 (*s*, 2 H, CH_2Ph), 5.10 (br *s*, 1 H, N*H*Boc), 7.15-7.28 (*m*, 5 H, Ph), 7.35-7.42 (*m*, 1 H), 7.79-7.92 (*m*, 2 H), 8.59 (*d*, *J* = 4.50 Hz, 1 H) ppm; δ_C (75 MHz, $CDCl_3$) 22.88, 22.93, 25.38, 25.66, 27.18 (CH_3), 30.70, 37.55, 38.26, 43.67, 43.81, 45.63, 45.85, 45.95, 46.06, 46.61, 50.87, 52.04, 57.60, 77.48, 121.27, 125.37, 125.76, 127.05, 127.59, 136.70, 138.12, 148.75, 155.27 (C=O), 156.56 ppm; m/z (CI) 687 $[M+H]^+$; Anal. calc. for $C_{32}H_{49}F_3N_6O_5S$ (686.844): C 55.96, H 7.19, found C 55.81, H 7.38.

***Debenzylation of* 1a. *Formation of* tert-*Butyl N-[16-Diallylamino-13-(pyridine-2-sulfonyl)-9-trifluoracetyl-4,9,13-triazahexadec-1-yl]-carbamate* (1e).** To a stirred solution of **1a** (135 mg, 0.176 mmol) in dichloromethane (2 mL) was added slowly α-chloroethyl chloroformate (20 µL, 0.185 mmol) at -10°C. After stirring for 12 h at -10°C, the mixture was warmed to 0°C for 1 h. After removal of the solvent, the residue was dissolved in methanol (2 mL) and triethylamine (49 µL, 0.352 mmol). It was refluxed for 12 h. Upon cooling, it was quenched with water and the aqueous layer was extracted with chloroform (3x). The combined organic extracts were then dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (silica gel, chloroform/methanol/ ammonia water 25% 90:5:0.5) gave **1e** as a pale yellow oil (55 mg, 46%). IR ($CHCl_3$) 3480 (NH), 1710 (C=O), 1690 (C=O), 1370 (SO_2), 1175 (SO_2) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.26 (*s*, 9 H, tBu), 1.27-1.71 (*m*, 8 H, $CH_2CH_2CH_2$), 1.88 (*p*, *J* = 7.30 Hz, 2 H, $CH_2CH_2CH_2$), 2.17 (br *s*, 1 H, NH), 2.35 (*t*, *J* = 7.00 Hz, 2 H, NCH_2), 2.57-2.73 (*m*, 4 H, NCH_2), 2.95 (*d*, *J* = 6.30 Hz, 4 H, $CH_2CH{=}CH_2$), 3.11-3.45 (*m*, 10 H, NCH_2SO_2, NCH_2COCF_3 and CH_2NHBoc), 5.02-5.10 (*m*, 5 H, NHBoc and $CH{=}CH_2$), 5.66-5.75 (*m*, 2 H, $CH{=}CH_2$), 7.35-7.42 (*m*, 1 H), 7.80-7.98 (*m*, 2 H), 8.60 (*d*, *J* = 4.29 Hz, 1H) ppm; δ_C (75 MHz, $CDCl_3$) 26.58, 28.53, 28.62, 28.82, 30.42 (CH_3), 31.70, 40.93, 46.83, 47.18, 48.70, 48.88, 48.99, 49.46, 49.79, 51.17, 52.37, 58.77, 81.11, 119.47 ($CH_2{=}CH$), 124.48, 128.56, 130.27, 137.51, 139.90, 152.01, 158.21 (C=O), 160.00 ppm; m/z (CI) 677 $[M+H]^+$; Anal. calc. for $C_{31}H_{51}F_3N_6O_5S$ (676.849): C 55.01, H 7.59, N 12.42; found C 54.74, H 7.69, N 12.69.

***Removal of the Pyridine-2-sulfonyl Group from* 1a. *Formation of tert-Butyl N-[4-Benzyl-16-diallylamino-9-trifluoracetyl-4,9,13-triazahexadec-1-yl]-carbamate* (1f).** To a 0.1 M solution of SmI_2 in THF (6 mL, 0.6 mmol) was added dropwise a well-degassed solution of **1a** (80 mg, 0.104 mmol) in THF (1 mL), under argon, at room temperature. After stirring for 12 h, the reaction mixture was diluted with 20 mL chloroform and quenched by the addition of 5 mL of 5% aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer washed well with chloroform (2x). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give an oily residue. Purification by flash chromatography (silica gel, chloroform/methanol/ammonia water 25% 90:10:0.5) gave **1f** as a yellow oil (39 mg, 60%). IR ($CHCl_3$) 3480 (NH), 1710 (C=O), 1685 (C=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.36 (*s*, 9 H, *t*Bu), 1.39-1.90 (*m*,10 H, $CH_2CH_2CH_2$), 2.34-2.95 (*m*,9 H, N*H* and NCH_2), 3.00-3.19 (*m*,6 H, $NCH_2CH{=}CH_2$ and NCH_2), 3.20-3.48 (*m*,8 H, NCH_2), 5.04-5.14 (*m*,5 H, $CH{=}CH_2$ and N*H*Boc), 5.62-5.79 (*m*,2 H, $CH{=}CH_2$), 7.18-7.26 (*m*,5 H, Ph) ppm; δ_C (75 MHz, $CDCl_3$) 21.67, 22.54, 24.52, 25.69 (CH_3), 36.70, 42.98, 43.45, 45.03, 45.31, 48.35, 49.40, 49.55, 51.14, 54.45, 56.36, 78.12, 116.81 ($CH_2{=}CH$), 125.28, 126.31, 127.29, 127.44, 135.32, 154.20, 155.37 (C=O) ppm; m/z (CI) 626 $[M+H]^+$; $C_{33}H_{54}F_3N_5O_3$ (625.825).

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