Regioselective Deprotection and Acylation of Penta-*N*-Protected Thermopentamine

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The synthesis of the penta-*N*-protected polyamide **1** (*tert*-butyl *N*-{9-allyl-16-azido-13-(trifluoroacetyl)-4-[2-(trimethylsilyl)ethylsulfonyl]-4,9,13-triazahexadecyl]carbamate = *tert*-butyl *N*-{3-{{4-{allyl{3-[(3-azidopropyl)(trifluoroacetyl)aminopropyl}amino}butyl}{[2-(trimethylsilyl)ethyl]sulfonyl}amino}propyl}carbamate) is described, a derivative of thermopentamine (PA 3433) containing five independently removable amino-protecting groups. The selective deprotection of the five protecting groups used, *i.e.*, of allyl, azido, (*tert*-butoxy)carbonyl (Boc), trifluoroacetyl, and [2-(trimethylsilyl)ethyl]sulfonyl (SES), as well as the rapid transamidation reaction of the trifluoroacetyl group yielding secondary amides is discussed. Subsequent acylation with 4-methoxycinnamoyl chloride at each N-atom of the pentamine backbone is achieved. For the acylation of the terminal N-atom the azido group is replaced by a (2,2,2-trichloro-1,1-dimethylethoxy)carbonyl (Tcboc) group.

Introduction. – Natural polyamines – triamines, tetramines, and pentamines – are widely distributed in living organisms and are essential for many important biological systems [1–3]. Recently, there has been an upsurge of research into polyamines from spider venoms. Especially, low molecular weight components in spider venom, such as acylpolyamines, have been known to have important neural functions with postjunctional proteins (the glutamate receptors) [4][5]. Studies on their structure and mode of action are currently being performed, because not all acylpolyamines have the same effects on the same receptors, and very small structural differences can change their pharmacological behavior [6–8].

However, since progress in the isolation and structure determination of the natural acylpolyamines is very limited, and larger amounts of material than normally available by isolation from natural sources are necessary for research, the need for versatile synthetic approaches to acylpolyamines is increasing.

During our studies of polyamines and acylpolyamines [9][10], we have developed great interest in the synthetic approach to acylpolyamine toxins and their analogues like Agel 416 (HO 416a) and Agel 448 which are produced by spiders of the genera *Agelenopsis* and *Hololena* [1] (*Fig.*). These polyamine toxins contain the same polyamine backbone as thermopentamine (PA 3433; = *N*-(3-aminopropyl)-*N'*-{3-[(3-aminopropyl)amino]propyl}butane-1,4-diamine), but different carboxylic acids bonded as amides to the main polyazaalkane chain. These aromatic carboxylic acids are characteristic.

In a previous paper [11], we reported the synthesis of a penta-*N*-protected thermopentamine containing five independently removable amino-protecting groups. These protecting groups were allyl, benzyl, (*tert*-butoxy)carbonyl, (pyridin-2-yl)sulfonyl, and trifluoroacetyl. To reach our aim of preparing acylpolyamines, 4-methoxy-

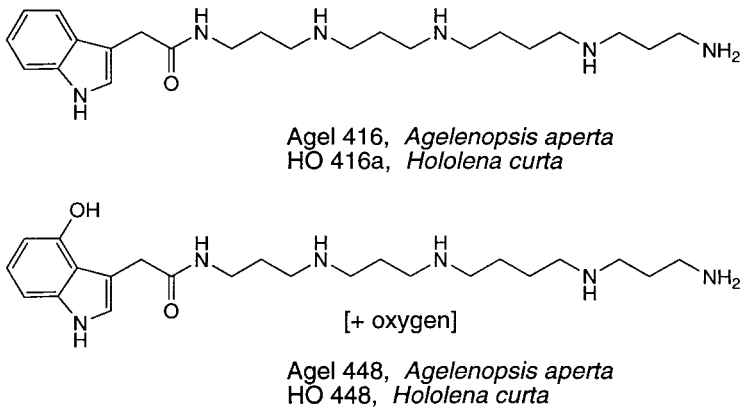


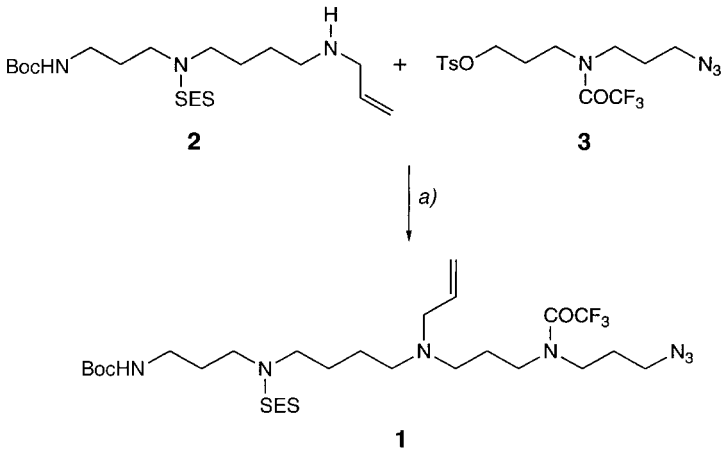
Figure. *Polyamine toxins from the spiders* Agelenopsis aperta *and* Hololena curta

cinnamoyl chloride was used as an acylation reagent. During this procedure, we recognized that some amino-protecting groups of the pentamine should be exchanged to achieve optimal acylation, and that, depending on their disposition in the polyamine backbone, the formation of a primary amine at the terminal N-atom induced the rearrangement of the trifluoroacetyl group by a $N \rightarrow N'$ acyl migration.

Therefore, we now report the synthesis of a penta-*N*-protected thermopentamine with different kinds and dispositions of the *N*-protecting groups. Furthermore, the selective deprotection as well as the acylation of each N-atom were investigated. The constant protecting groups used were allyl, (*tert*-butoxy)carbonyl (Boc), and trifluoroacetyl, whereas azido, (2,2,2-trichloro-1,1-dimethylethoxy)carbonyl (Tcboc), and [2-(trimethylsilyl)ethyl]sulfonyl (SES) were the variable groups. In addition, the transamidations of amino-amides occurring during the formation of some primary amines have been investigated.

Results and Discussion. – After various examinations of proper protecting groups and procedures, we aimed to synthesize the polyamine derivative **1** by the reaction of the spermidine derivate **2** with the building block **3** (*Scheme 1*). It was determined that the removal of the allyl, azido, (*tert*-butoxy)carbonyl (Boc), trifluoroacetyl, and [2-(trimethylsilyl)ethyl]sulfonyl (SES) groups required five different procedures: for allyl removal mild treatment with $[Pd(PPh_3)_4]$ and 1,3-dimethylbarbituric acid (= 1,3-dimethylpyrimidine-2,4-6(1*H*,3*H*,5*H*)-trione; NDMBA) [12], for azido transformation PPh_3/H_2O in THF [13], for Boc removal brief exposure to CF_3COOH, for trifluoroacetyl removal K_2CO_3 in $MeOH/H_2O$, and for SES removal CsF in DMF [14]. These conditions were independent from each other and did not affect the 4-methoxycinnamoyl group as an aromatic acyl moiety. However, when we tried to reduce the azido group to the primary amino group at the terminal position of the polyamine derivative **1**, we always isolated the amino-amide derivative, in which the trifluoroacetyl group had migrated to the terminal N-atom, instead of the amido-amine derivative ($N \rightarrow N'$ acyl migration; see below, *Scheme 4*). Therefore, the complete reduction of the azido group, required to get the primary-amine function at the terminal position, could not be performed with the polyamine derivative **1**.

Scheme 1



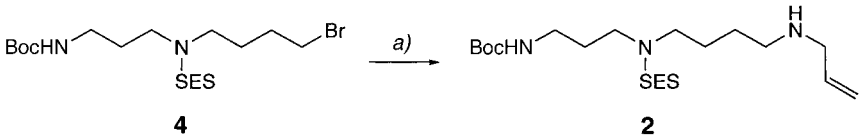
Boc = Me_3COCO, SES = $Me_3SiCH_2CH_2SO_2$

a) NaI, $(i\text{-}Pr)_2EtN$, toluene, 100°, 72 h; 76%.

However, after the investigation of protecting groups which do not induce acyl migration, a satisfying solution was found with the replacement of the trifluoroacetyl by the (2,2,2-trichloro-1,1-dimethylethoxy)carbonyl (Tcboc) group. The latter is cleaved by mild metal reduction employing Zn dust in dilute acid, producing the free amine, 1,1-dichloro-2-methylprop-1-ene, and carbon dioxide. With the Tcboc protecting group on the neighboring N-atom the terminal N-atom could be deprotected without interference by acyl migration and acylated with 4-methoxycinnamoyl chloride.

The spermidine derivate **2** was prepared by using KF/*Celite* in MeCN from allylamine and *tert*-butyl *N*-{3-{(4-bromobutyl){[2-(trimethylsilyl)ethyl]sulfonyl}amino}propyl}carbamate (**4**) [15] which was synthesized in two steps from N^1-Boc-protected propane-1,3-diamine, [2-(trimethylsilyl)ethyl]sulfonyl chloride (SES-Cl), and 1,4-dibromobutane (*Scheme 2*).

Scheme 2



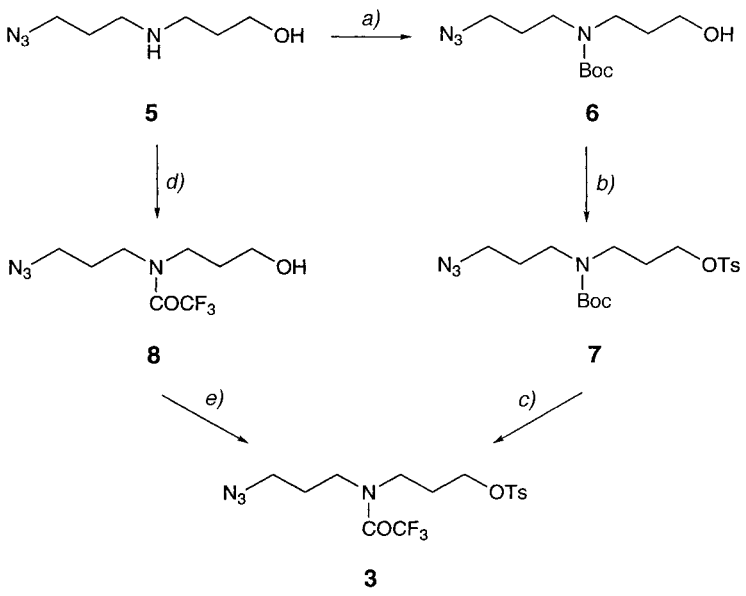
Boc = Me_3COCO SES = $Me_3SiCH_2CH_2SO_2$

a) Allylamine, KF/*Celite*, MeCN, 50°, 72 h; 86%.

The second starting compound **3** was prepared by two different pathways, *via* the hydroxyamides **6** or **8**, from 3-[(3-azidopropyl)amino]propan-1-ol (**5**) [16] which was synthesized in turn from commercial 3-chloropropan-1-ol in two steps. Amino alcohol **5** was acylated with di(*tert*-butyl) dicarbonate and Et_3N in CH_2Cl_2 to provide

hydroxyamide **6** (*Scheme 3*). *O*-Tosylation of **6** with *p*-toluenesulfonyl chloride, 4-(dimethylamino)pyridine (DMAP), and Et_3N in CH_2Cl_2 gave the sulfonate **7**. Then, the exchange of the Boc group in the sulfonate **7** by the trifluoroacetyl group on exposure to CF_3COOH for 30 min, followed by acylation with $(CF_3CO)_2O$ and Et_3N in CH_2Cl_2, resulted in the building block **3**. Alternatively, hydroxy amide **8** was synthesized from the amino alcohol **5** by selective acylation at the N-atom ($(CF_3CO)_2O$ in MeOH and a few drops of 25% aqueous NH_3 solution [17], or *S*-ethyl trifluorothioacetate in MeOH [18]) and tosylated to give **3**. Even though the pathway *via* **8** needed one step less than *via* **6**, the latter process was more convenient because hydroxy amide **8** was not so stable and the overall yield of **3** from **5** *via* **8** lower.

Scheme 3

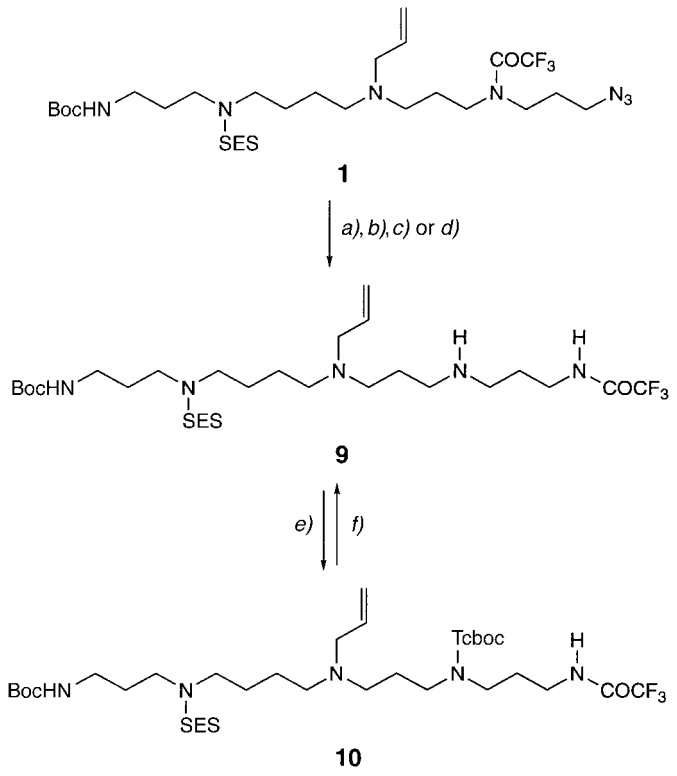


Boc = Me_3COCO, Ts = 4-$MeC_6H_4SO_2$

a) $(Boc)_2O$, Et_3N, CH_2Cl_2, 0°, 1 h, r.t., 28 h; 85%. *b*) TsCl, NDMAP, Et_3N, CH_2Cl_2, r.t., 24 h; 80%. *c*) CF_3COOH, 30 min, $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, 0°, 1 h, r.t.; 13 h; 85%. *d*) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, r.t., 2 h, MeOH, a few drops 25% aq. NH_3 soln., 15 min; 62%; or CF_3COSEt, MeOH, r.t., 72 h; 60%. *e*) TsCl, NDMAP, Et_3N, CH_2Cl_2, r.t., 18 h; 70%.

Finally, the coupling of the building blocks **2** and **3**, in the presence of diisopropylethylamine and NaI in toluene at 100°, provided the target thermopentamine derivative **1** (*Scheme 1*). For the acylation with 4-methoxycinnamoyl chloride at the terminal N-atom, the trifluoroacetyl-protected polyamine **1** was modified to the Tcboc-protected compound **10** (*Scheme 4*). Thus, the azido group of **1** was reduced by PPh_3 in THF in the presence of water yielding the terminal amide **9** which was reacted with 2,2,2-trichloro-1,1-dimethylethyl carbonochloridate (Tcboc-Cl) in the presence of aqueous NaOH in Et_2O at 0° to afford the penta-*N*-protected thermopentamine **10**.

Scheme 4



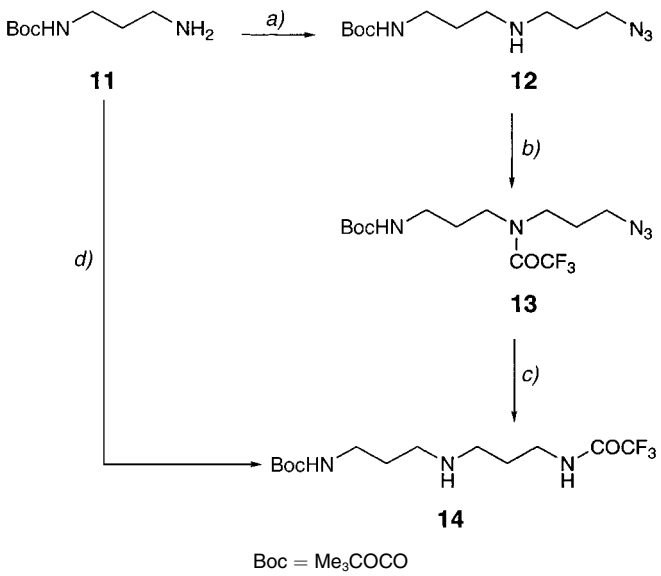
Boc = Me_3COCO, SES = $Me_3SiCH_2CH_2SO_2$, Tcboc = $Cl_3CC(Me)_2OCO$

a) PPh_3, H_2O, THF, r.t., 48 h; 90%. *b*) $SnCl_2$, MeOH, r.t., 72 h; 60%. *c*) H_2, *Lindlar* catalyst, EtOH, r.t., 24 h; 50%. *d*) $HSCH_2CH_2SH$, Et_3N, MeOH, r.t., 24 h; 55%. *e*) Tcboc-Cl, 1M NaOH/Et_2O, 0°, 30 min; 80%. *f*) Zn dust, AcOH, r.t., 20 h; 65%.

We next determined whether the migration of the trifluoroacetyl group to the terminal N-atom (**1** → **9**) was a general reaction. At first, we tried to reduce the azido group of the polyamine derivative **1** by other methods than by PPh_3/H_2O in THF, *i.e.*, with $SnCl_2$ in MeOH, H_2/*Lindlar* catalyst in EtOH, and $HSCH_2CH_2SH/Et_3N$ in MeOH (*Scheme 4*), and indeed, we always obtained the same product, *i.e.*, amino-amide **9**. Therefore, we synthesized model compounds to confirm the migration of the CF_3CO group (*Scheme 5*).

N^1-Boc-protected propane-1,3-diamine **11** [15] was reacted with 3-azidopropyl *p*-toluenesulfonate [16] and KF/*Celite* in MeCN to provide *tert*-butyl *N*-{[(3-azidopropyl)amino]propyl}carbamate (**12**). The secondary-amine derivative **12** was acylated with $(CF_3CO)_2O$ and Et_3N in CH_2Cl_2 to give amide **13**. This compound was used for the reduction of its azido group with PPh_3/H_2O in THF which resulted in the amino-amide **14**. On the other hand, N^1-Boc-protected propane-1,3-diamine **11** was reacted with *N*-(3-bromopropyl)-2,2,2-trifluoroacetamide and KF/*Celite* in MeCN, and the identical amino-amide was obtained.

Scheme 5

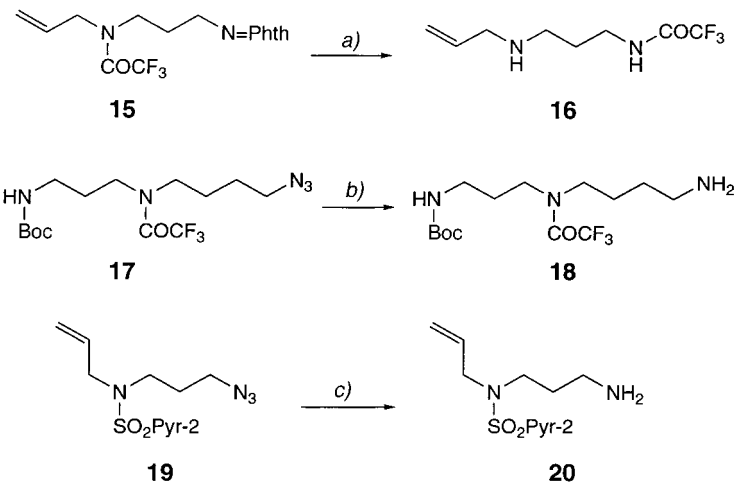


a) 3-Azidopropyl *p*-toluenesulfonate, KF/*Celite*, MeCN, 50°, 3 d; 70%. *b*) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, 0°, 1.5 h, r.t., 14 h; 70%. *c*) PPh_3, H_2O, THF, r.t., 48 h; 76%. *d*) *N*-(3-Bromopropyl)-2,2,2-trifluoroacetamide, KF/*Celite*, MeCN, 50°, 3 d; 53%.

There are many reports about transamidation reactions of macrocyclic lactams [19–22] and of open chain amino-amides [23][24]. It is known that these transamidations occur by attack of the uncharged ω-amino group at the carbonyl group of the amide *via* a cyclic transition state, and the migration occurs most rapidly when the amide is *N*-substituted with a 3-aminopropyl residue [23]. In many reports, it was stated that the transamidation reaction needed strong bases or acids as catalysts, such as the KAPA reagent (propane-1,3-diamine/potassium (3-aminopropyl)amide) [25], KF/DMF/[18]crown-6 [26], $KN(SiMe_3)_2$/THF [21], TsOH/xylene, HCl/Ph_2O [27]. However, in the case of the transamidation of the trifluoroacetyl group, the reaction occurred, already under mild conditions, *i.e.*, simultaneously with the reduction of the azido to the primary amino group (see above). We also observed such a trifluoroacetyl migration on removal of the phthalimido group as in the reaction of **15** to **16** (*Scheme 6*). This reaction suggests that the primary amine is nucleophilic enough to attack the amide carbonyl group under these conditions and that the reaction is faster, when the amide group is flanked with an electron-withdrawing group, like CF_3, instead of an alkyl group.

We also examined if other groups than trifluoroacetyl would undergo a similar $N \rightarrow N'$ migration. As shown in *Scheme 6*, an allyl or a (pyridin-2-yl)sulfonyl group did not migrate at all (**15** → **16**, **19** → **20**). Moreover, the transamidation did not occur under the conditions mentioned above in the case of the *N*-(4-aminobutyl)-substituted amide **17** which yielded **18**. The reason might be that the energetically less favorable seven-

Scheme 6



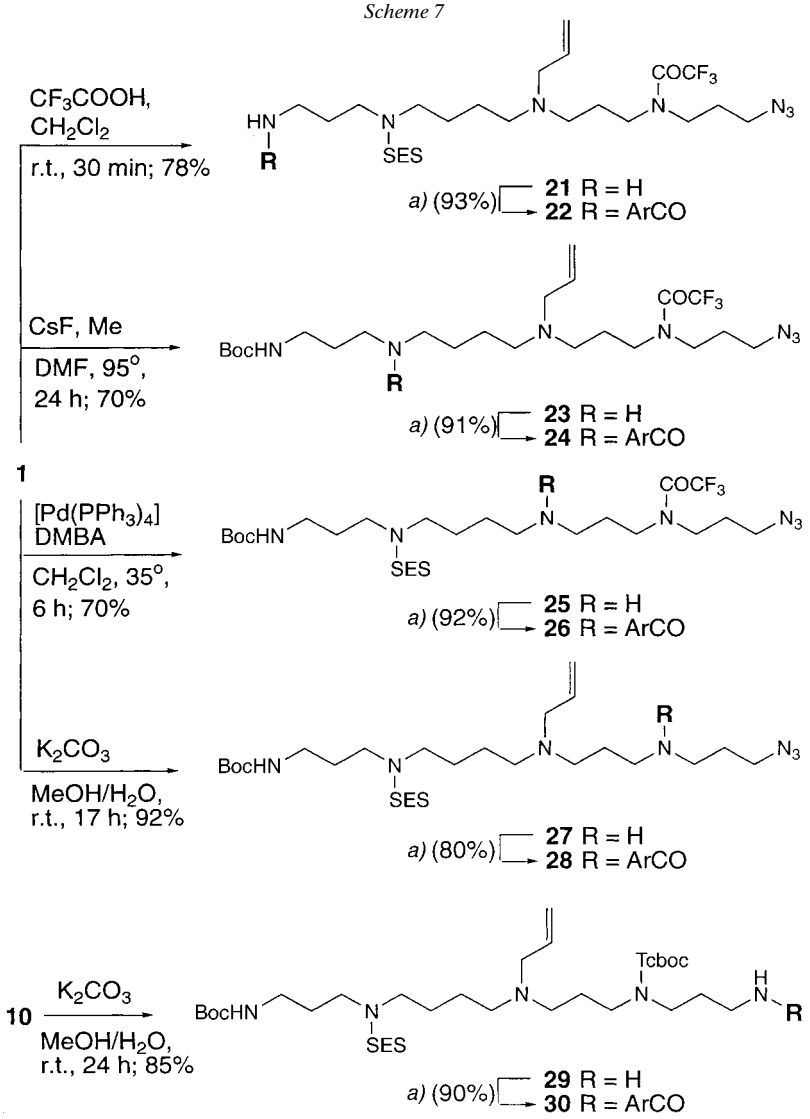
Boc = Me_3COCO, Pyr-2 = pyridin-2-yl

a) $N_2H_4 \cdot H_2O$, EtOH, reflux, 1.5 h; 70%. *b*) PPh_3, H_2O, THF, r.t., 48 h; 70%. *c*) PPh_3, H_2O, THF, r.t., 35 h; 89%.

membered-ring transition state required more vigorous conditions for transamidation than the six-membered-ring transition state (see above).

Finally, we successively deprotected each N-atom of the polyamine derivative **1** and the terminal trifluoroacetyl-protected N-atom of **10** to demonstrate the independence of the protecting groups, and thus the versatility of the chosen approach. The resulting tetra-*N*-protected pentaamine precursors **21**, **23**, **25**, **27**, and **29** (from **10**) were acylated to **22**, **24**, **26**, **28**, and **30**, respectively, with 4-methoxycinnamoyl chloride, the latter being simply obtained from 4-methoxycinnamic acid and oxalyl dichloride (*Scheme 7*). Thus, exposure of **1** to CF_3COOH in CH_2Cl_2 for 30 min removed the Boc group and, after basic workup, afforded the primary-amine derivative **21**. Treatment of **1** with CsF in DMF cleaved the [2-(trimethylsilyl)ethyl]sulfonyl (SES) group to give **23**. Even though the yield of **23** was very dependent upon the dryness of the reaction mixture (CsF is highly hygroscopic), this SES group is quite stable under acidic and basic conditions, and can be cleaved in good yields [14]. The polyamine derivative **1** was deallylated to **25** using 1,3-dimethylbarbituric acid (NDMBA) as an allyl-group scavenger and [$Pd(PPh_3)_4$] as a catalyst [12], and reaction of **1** with K_2CO_3 in MeOH/H_2O 3:1 removed the trifluoroacetyl group ($\rightarrow$ **27**). The Tcboc group of **10** was cleaved by using freshly activated Zn dust [28] in AcOH at room temperature yielding **9** (see *Scheme 4*); it is noteworthy that the allyl group was not affected under these conditions. Finally, for the deprotection of the terminal N-atom, the polyamine derivative **10** was treated with K_2CO_3 in MeOH/H_2O to provide the desired primary-amine derivative **29** without migration of the Tcboc group to the terminal N-atom (*Scheme 7*).

Scheme 7



ArCO = 4-MeOC$_6$H$_4$CH=CHCO, Boc = Me$_3$COCO, SES = Me$_3$SiCH$_2$CH$_2$SO$_2$, Tcboc = Cl$_3$CC(Me)$_2$OCO

a) 4-Methoxycinnamoyl chloride, Et_3N, AcOEt, $-10°$, 30 min, r.t., 16–18 h.

In conclusion, the penta-*N*-protected polyamine derivatives **1** and **10** were synthesized easily and in good yields from N^1-Boc-protected propane-1,3-diamines and 3-chloropropan-1-ol. The selective deprotection and subsequent acylation with 4-methoxycinnamoyl chloride of each N-atom of the polyamine backbone was performed. The two polyamine derivatives can be used as intermediates for further investigation of acyl-substituted polyamines. In addition, the transamidation reaction

of the CF_3CO group was observed already under very mild conditions, when the CF_3CO group is situated at the N-atom carrying a 3-aminopropyl residue.

We are grateful for financal support of *Swiss National Science Foundation* and to the analytical department of our institute for measuring the spectra.

Experimental Part

General. All reactions were carried out under N_2 or Ar. *tert*-Butyl *N*-{3-{(4-bromobutyl){[2-trimethylsilyl)ethyl]sulfonyl}amino}propyl}carbamate (**4**) [15], 3-[(3-azidopropyl)amino]propan-1-ol (**5**) [16], *tert*-butyl *N*-(3-aminopropyl)carbamate (**11**) [15], 3-azidopropyl *p*-toluenesulfonate [16], *N*-allyl-*N*-(3-azidopropyl)pyridine-2-sulfonamide (**19**) [11], and KF/*Celite* [29] were prepared according to the literature. THF was freshly distilled from benzophenone/Na prior to use. TLC: *Merck* aluminium sheets coated with silica gel *60* F_{254}. Column chromatography (FC): silica gel *60* (230–400 mesh, *Merck*). IR Spectra ($CHCl_3$): *Perkin-Elmer-IR-297* spectrometer; in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: in $CDCl_3$ at 300 and 75 MHz, resp.; *Bruker-AC-300* spectrometer; chemical shifts δ in ppm rel. to internal Me_4Si, J in Hz. Mass spectra: *Finnigan SSQ 700* or *Finnigan MAT 90*; chemical ionization (CI) utilizing NH_3 as reactant gas and electrospray ionization (ESI).

tert-*Butyl* N-*{3-{[4-(Allylamino)butyl]{[2-(trimethylsilyl)ethyl]sulfonyl}amino}propyl}carbamate* (**2**). To a soln. of **4** (1 g, 2.11 mmol) in MeCN (100 ml), KF/*Celite* (6.28 g, 54.16 mmol) was added at r.t., followed by allylamine (0.51 ml, 6.77 mmol). The suspension was heated at 50° for 70 h, and then filtered. The filtrate was evaporated and the residue purified by FC (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 20:1:0.1): **2** (813 mg, 86%). Colorless oil. IR: 3450 (NH), 1705 (C=O), 1370 (SO_2), 1250 (CO), 1165 (SO_2). ^{1}H-NMR: 5.91–5.78 (*m*, 1 H); 5.16–5.07 (*m*, 2 H); 4.95 (br. *s*, 1 H); 3.24–3.13 (*m*, 8 H); 2.85–2.80 (*m*, 2 H); 2.60 (*t*, J = 6.9, 2 H); 1.71–1.46 (*m*, 7 H); 1.38 (*s*, 9 H); 0.98–0.92 (*m*, 2 H); 0.00 (*s*, 9 H). ^{13}C-NMR: 158.08; 118.25; 54.28; 50.58; 50.06; 49.79; 47.45; 31.24; 30.41 (Me); 29.05; 28.93; 12.31; 0.00 (Me). CI-MS: 450.2 ($[M+H]^+$).

tert-*Butyl* N-*(3-Azidoproyl)*-N-*(3-hydroypropyl)carbamate* (**6**). A soln. of di-*tert*-butyl dicarbonate (5.52 g, 25.30 mmol) in CH_2Cl_2 (50 ml) was added dropwise over 1 h at 0° to a soln. of **5** (2 g, 12.65 mmol) and Et_3N (2.65 ml, 18.98 mmol) in CH_2Cl_2 (100 ml). The mixture was stirred at 0° for 1 h and at r.t. for 28 h, then diluted with CH_2Cl_2, washed with 3% aq. HCl, sat. $NaHCO_3$, and 10% NaCl soln., dried (Na_2SO_4), and evaporated. FC (hexane/AcOEt 1:1), gave **6** (2.77 g, 85%). Colorless oil. IR: 3620 (OH), 2100 (N_3), 1680 (C=O), 1250 (CO), 1160 (CO). ^{1}H-NMR: 3.61–3.51 (*m*, 2 H); 3.41–3.21 (*m*, 7 H); 1.82 (*quint.*, J = 7.0, 2 H); 1.75–1.63 (*m*, 2 H); 1.47 (*s*, 9 H). ^{13}C-NMR: 169.52 (C=O); 80.44; 58.33 (CH_2OH); 49.02; 44.55; 42.94; 30.62; 28.39 (Me); 27.94. CI-MS: 259.3 ($[M+H]^+$).

*3-{(3-Azidopropyl)[(*tert-*butoxy)carbonyl]amino}propyl 4-Methylbenzenesulfonate* (**7**). To a soln. of **6** (2.5 g, 9.69 mmol), Et_3N (2.03 ml, 14.54 mmol), and DMPA (1.18 g, 9.69 mmol) in CH_2Cl_2 (200 ml), a soln. of *p*-toluenesulfonyl chloride (2.78 g, 14.54 mmol) in CH_2Cl_2 (100 ml) was added dropwise at 0° over 1.5 h. The mixture was stirred for an additional hour at 0° and overnight at r.t., then diluted with CH_2Cl_2, washed with 3% aq. HCl, sat. $NaHCO_3$, and 10% NaCl soln., dried (Na_2SO_4), and evaporated. FC (hexane/AcOEt 2:1) gave **7** (3.19 g, 80%). Colorless oil. IR: 2100 (N_3), 1680 (C=O), 1365 (SO_2), 1175 (SO_2). ^{1}H-NMR: 7.79 (*d*, J = 8.3, 2 H); 7.35 (*d*, J = 8.1, 2 H); 4.04 (*t*, J = 6.3, 2 H); 3.28 (*t*, J = 6.7, 2 H); 3.20 (*q*, J = 6.5, 4 H); 2.45 (*s*, 3 H); 1.95–1.86 (*m*, 2 H); 1.76 (*quint.*, J = 7.0, 2 H); 1.43 (*s*, 9 H). ^{13}C-NMR: 174.10; 168.95; 144.98; 139.25; 133.02; 132.58; 129.91; 127.94; 80.01; 49.01; 45.10; 44.10; 28.38 (Me); 21.64 (Me). CI-MS: 430.3 (14, $[M+NH_4]^+$), 369.3 (100).

3-[(3-Azidopropyl)(trifluoroacetyl)amino]propyl 4-Methylbenzenesulfonate (**3**). a) *From* **7**: CF_3COOH (10 ml, 0.13 mol) was added to a soln. of **7** (2.7 g, 6.55 mmol) in CH_2Cl_2 (50 ml). After 30 min stirring at r.t., the solvent and excess CF_3COOH were evaporated. The residue was dissolved in CH_2Cl_2 (200 ml) and cooled to 0°. Et_3N (2.74 ml, 19.65 mmol) and $(CF_3CO)_2$ (1.82 ml, 13.10 mmol) in CH_2Cl_2 (100 ml) were added dropwise successively. The mixture was stirred at 0° for 1 h and at r.t. for 14 h. Then, it was diluted with CH_2Cl_2, washed with 3% aq. HCl, sat. $NaHCO_3$, and 10% NaCl soln., dried (Na_2SO_4), and evaporated. FC provided **3** (2.27 g, 85%). Colorless oil.

b) *From* **8**: To a soln. of **8** (150 mg, 0.59 mmol), Et_3N (0.16 ml, 1.18 mmol), and DMAP (22 mg, 0.18 mmol) in CH_2Cl_2 (20 ml), a soln. of TsCl (169 mg, 0.89 mmol) in CH_2Cl_2 (10 ml) was added dropwise at 0°. The mixture was stirred at 0° for 30 min and at r.t. for 16 h, then diluted with CH_2Cl_2 (30 ml), washed with 10% aq. HCl and 10% NaCl soln., dried (Na_2SO_4), and evaporated. The residue was purified by FC (hexane/AcOEt 3:1): **3** (168 mg, 70%). Colorless oil. IR: 2100 (N_3), 1690 (C=O), 1365 (SO_2), 1175 (SO_2). ^{1}H-NMR: 7.79 (*d*, J = 8.3, 2 H); 7.38 (*d*, J = 1.9, 1 H); 7.35 (*d*, J = 1.9, 1 H); 4.07 (*q*, J = 5.8, 2 H); 3.44 (*quint.*, J = 7.0, 4 H); 3.35 (*q*,

$J = 6.4$, 2 H); 2.46 (*s*, 3 H); 2.04–1.96 (*m*, 2 H); 1.90–1.81 (*m*, 2 H). ^{13}C-NMR: 168.95, 130.01; 127.93; 67.69 (CH_2O); 48.85; 48.52; 45.11; 44.94; 28.25; 26.57; 26.34; 21.67 (Me). CI-MS: 426.2 ($[M+NH_4]^+$).

N-*(3-Azidopropyl)-2,2,2-trifluoro*-N-*(3-hydroxypropyl)acetamide* (**8**). To a soln. of **5** (200 mg, 1.26 mmol) and Et_3N (0.39 ml, 2.77 mmol) in CH_2Cl_2 (20 ml), a soln. of $(CF_3CO)_2O$ (0.44 ml, 3.15 mmol) in CH_2Cl_2 (10 ml) was added dropwise within 40 min at 0°. Then the mixture was warmed to r.t., stirred for 2 h, and then evaporated. The residue was dissolved in MeOH (40 ml) containing a few drops of 25% aq. NH_3 soln. and stirred for 15 min. N_2 Gas was passed through the soln. for 1 h. After evaporation, the residue was purified by FC (hexane/AcOEt 1:1): **8** (200 mg, 62%). Colorless oil. IR: 3610 (OH), 2100 (N_3), 1690 (C=O), 1250 (CO), 1155 (CO). ^{1}H-NMR: 3.63–3.55 (*m*, 4 H); 3.49 (*t*, $J = 7.5$, 2 H); 3.38 (*q*, $J = 6.2$, 2 H); 1.93–1.72 (*m*, 5 H). ^{13}C-NMR: 59.73; 58.85; 48.97; 48.60; 45.29; 45.06; 43.73; 31.68; 29.80; 28.20; 26.41. CI-MS: 272.3 ($[M+NH_4]^+$).

tert-*Butyl* N-*{9-Allyl-16-azido-13-(trifluoroacetyl)-4-[2-(trimethylsilyl)ethylsulfonyl]-4,9,13-triazahexadecyl}carbamate* (=tert-*Butyl* N-*{3-{[4-{Allyl[3-[(3-azidopropyl)(trifluoroacetyl)amino]propyl}amino}butyl]{[2-(trimethylsilyl)ethyl]sulfonyl}amino}propyl}carbamate*; **1**). A stirred soln. of **2** (600 mg, 1.34 mmol), **3** (454 mg, 1.11 mmol), $(i\text{-}Pr)_2EtN$ (0.35 ml, 2.01 mmol), and NaI (183 mg, 1.22 mmol) in toluene (60 ml) was heated at 100° for 3 d, then cooled to r.t., and filtered. The filtrate was washed with H_2O (1×) and the aq. layer extracted with CH_2Cl_2. The combined org. layers were dried (Na_2SO_4) and evaporated. FC (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 70:1:0.1) provided **1**(576 mg, 76%). Colorless oil. IR: 3450 (NH), 2100 (N_3), 1710 (C=O), 1370 (SO_2), 1250 (CO), 1160 (SO_2). ^{1}H-NMR: 5.81–5.69 (*m*, 1 H); 5.18–5.07 (*m*, 2 H); 4.92 (br. *s*, 1 H); 3.48–3.29 (*m*, 6 H); 3.23–3.11 (*m*, 6 H); 3.03–2.97 (*m*, 2 H); 2.85–2.79 (*m*, 2 H); 2.40–2.31 (*m*, 4 H); 1.89–1.46 (*m*, 10 H); 1.39 (*s*, 9 H); 0.99–0.94 (*m*, 2 H); 0.00 (*s*, 9 H). ^{13}C-NMR: 58.89; 55.31; 52.65; 50.94; 50.23; 49.72; 47.56; 46.96; 31.37; 30.42; 29.03 (Me); 28.39; 26.28; 0.00 (Me). CI-MS: 686.5 ($[M+H]^+$).

tert-*Butyl* N-*{9-Allyl-16-(trifluoroacetamido)-4-[2-(trimethylsilyl)ethylsulfonyl]-4,9,13-triazahexadecyl}-carbamate* (=tert-*Butyl* N-*{9-Allyl-19,19,19-trifluoro-18-oxo-4-{[2-(trimethylsilyl)ethyl]sulfonyl}-4,9,13,17-tetraazanonadecyl}carbamate*; **9**). a) *From* **1**: To a soln. of **1** (150 mg, 0.22 mmol) in distilled THF (15 ml), PPh_3 (86 mg, 0.33 mmol) and H_2O (6 µl) were added at r.t. After 3 days, the mixture was evaporated and the residue submitted to FC (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 20:1:0.1): **9** (129 mg, 90%). Colorless oil.

b) *From* **10**: To a soln. of **10** (35 mg, 0.04 mmol) in AcOH (3 ml) activated Zn powder [19] (16 mg, 0.25 mmol) was added in portions within 1 h. The mixture was stirred at r.t. for 20 h and then filtered. The filtrate was diluted with H_2O, basified with 10% aq. NaOH soln., and extracted wtih CH_2Cl_2 (3×). The org. layer was evaporated and purified by FC (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 12:1:0.1): **9** (18 mg, 70%). Colorless oil. IR: 3440 (NH), 3200 (NH), 1710 (C=O), 1365 (SO_2), 1170 (SO_2). ^{1}H-NMR: 9.55 (br. *s*, 1 H); 5.81–5.69 (*m*, 1 H); 5.14–5.06 (*m*, 2 H); 4.95 (br. *s*, 1 H); 3.42 (*t*, $J = 6.0$, 2 H); 3.23–3.12 (*m*, 6 H); 2.99 (*d*, $J = 6.4$, 2 H); 2.85–2.75 (*m*, 4 H); 2.60 (*t*, $J = 6.7$, 2 H); 2.41, 2.36 (*dt*, $J = 6.9$, 7.3, 4 H); 2.01 (br. *s*, 1 H); 1.71–1.41 (*m*, 10 H); 1.38 (*s*, 9 H); 0.97–0.91 (*m*, 2 H); 0.00 (*s*, 9 H). ^{13}C-NMR: 137.51 (*C*H=CH$_2$); 119.49 (*C*H$_2$=CHCH$_2$N); 59.02; 55.24; 54.27; 51.23; 50.69; 50.30; 49.72; 47.58; 42.79; 31.38; 30.42 (Me); 29.07; 28.79; 28.49; 26.36; 12.31; 0.00 (Me). ESI-MS: 660.4 ($[M+H]^+$).

tert-*Butyl* N-*{9-Allyl-13-[(2,2,2-trichloro-1,1-dimethylethoxy)carbonyl]-16-(trifluoroacetamido)-4-[2-(trimethylsilyl)ethylsulfonyl]-4,9,13-triazahexadecyl}carbamate* (=tert-*Butyl* N-*{9-Allyl-19,19,19-trifluoro-18-oxo-13-[(2,2,2-trichloro-1,1-dimethylethoxy)carbonyl]-4-{[2-(trimethylsilyl)ethyl]sulfonyl}-4,9,13,17-tetraazanonadecyl}carbamate*; **10**). A soln. of 2,2,2-trichloro-1,1-dimethylethyl carbonochloridate (Tcboc-Cl; 105 mg, 0.44 mmol) in dry Et_2O (15 ml) was added dropwise over 30 min to a vibro-mixed soln. of **9** (120 mg, 0.18 mmol) in 0.2N NaOH/Et_2O 1:1 (20 ml) at 0°. After another 30 min stirring at 0°, the H_2O layer was extracted with Et_2O (2×; during workup, the mixture should be kept cold). The combined org. layer was dried (Na_2SO_4) and evaporated. FC (CH_2Cl_2/MeOH 25:1) gave **10** (125 mg, 80%). Colorless oil. IR: 3440 (NH), 1700 (C=O), 1365 (SO_2), 1160 (SO_2). ^{1}H-NMR: 7.90 (br. *s*, 1 H); 5.81–5.68 (*m*, 1 H); 5.16–5.05 (*m*, 2 H); 4.91 (br. *s*, 1 H); 3.36–3.10 (*m*, 12 H); 3.02–2.98 (*m*, 2 H); 2.85–2.79 (*m*, 2 H); 2.43–2.31 (*m*, 4 H); 1.86 (*s*, 6 H); 1.78–1.48 (*m*, 10 H); 1.38 (*s*, 9 H); 0.97–0.91 (*m*, 2 H); 0.00 (*s*, 9 H). ^{13}C-NMR: 172.50 (C=O); 72.59; 59.01; 55.17; 52.94; 50.30; 49.68; 47.94; 47.62; 45.78; 38.14; 31.63; 30.40 (Me); 29.12; 23.60 (Me); 12.29; 0.00 (Me). ESI-MS: 862.4 ($[M+H]^+$).

tert-*Butyl* N-*{3-[(3-Azidopropyl)amino]propyl}carbamate* (**12**). To a soln. of **11** (500 mg, 2.87 mmol) in MeCN, KF/*Celite* (2.34 g, 20.09 mmol) was added at r.t., followed by 3-azidopropyl *p*-toluenesulfonate (732 mg, 2.87 mmol) [16]. The suspension was heated at 50° for 3 days and then filtered. The filtrate was evaporated and the residue purified by FC (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 15:1:0.1): **12** (515 mg, 70%). Colorless oil. IR: 3450 (NH), 2100 (N_3), 1700 (C=O). ^{1}H-NMR: 5.25 (br. *s*, 1 H); 3.41–3.37 (*m*, 2 H); 3.28–3.17 (*m*, 2 H); 2.71–2.62 (*m*, 4 H); 1.81–1.62 (*m*, 4 H); 1.44 (*s*, 9 H); 1.37 (br. *s*, 1 H). ^{13}C-NMR: 156.17; 78.98; 49.55; 47.72; 46.90; 39.21; 29.88; 29.30; 28.45 (Me). CI-MS: 258.1 ($[M+H]^+$).

tert-*Butyl* N-*{3-[(3-Azidopropyl)(trifluoroacetyl)amino]propyl}carbamate* (**13**). A soln. of $(CF_3CO)_2O$ (0.22 ml, 1.56 mmol) in CH_2Cl_2 (20 ml) was added dropwise to a soln. of **12** (200 mg, 0.78 mmol) and Et_3N (0.16 ml, 1.17 mmol) in CH_2Cl_2 (20 ml) at 0°. The mixture was subsequently stirred at 0° for 1.5 h and warmed to r.t. After 14 h and dilution with CH_2Cl_2 (20 ml) the mixture was extracted with 10% aq. HCl (1×), sat. Na_2CO_3 (1×), and sat. NaCl soln. (1×), the org. layer dried (Na_2SO_4) and evaporated. FC (hexane/AcOEt 3:1) provided **13** (192 mg, 70%). Colorless oil. IR: 3440 (NH), 2100 (N_3), 1710 (C=O), 1690 (C=O). ^{1}H-NMR: 4.92 (br. *s*, 1 H); 4.61 (br. *s*, 1 H); 3.50–3.34 (*m*, 6 H); 3.20–3.09 (*m*, 2 H); 1.92–1.75 (*m*, 4 H); 1.44 (*s*, 9 H). ^{13}C-NMR: 156.25; 61.91; 48.93; 48.58; 29.83; 28.41 (Me); 27.49; 26.41. CI-MS: 371.1 (20, $[M+NH_4]^+$), 315 (100).

tert-*Butyl* N-*{3-{[3-[(Trifluoroacetyl)amino]propyl}amino}propyl}carbamate* (**14**). *From* **13**: To a soln. of **13** (50 mg, 0.14 mmol) in THF (10 ml), PPh_3 (56 mg, 0.21 mmol) and H_2O (8 µl, 0.21 mmol) were added. After 2 d stirring at r.t., the soln. was filtered and evaporated and the residue purified by FC (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 12:1:0.1): **14** (35 mg, 76%). Colorless oil.

From **11**: To a suspension of **11** (100 mg, 0.58 mmol) and KF/*Celite* (467 mg, 4.02 mmol) in MeCN (30 ml), *N*-(3-bromoprop-1-yl)-2,2,2-trifluoroacetamide (134 mg, 0.58 mmol; prepared from 3-bromopropylamine hydrobromide, $(CF_3CO)_2O$, and Et_3N) was added. The mixture was heated at 50° for 3 d, then cooled to r.t., filtered, and evaporated. FC (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 12:1:0.1) provided **14** (99 mg, 53%). Colorless oil. IR: 3440 (NH), 1710 (C=O). ^{1}H-NMR: 9.35 (br. *s*, 1 H); 4.73 (br. *s*, 1 H); 3.48 (*t*, *J* = 5.9, 2 H); 3.19 (*q*, *J* = 6.4, 2 H); 2.81 (*t*, *J* = 5.6, 2 H); 2.64 (*t*, *J* = 6.7, 2 H); 1.76–1.60 (*m*, 4 H); 1.44 (*s*, 9 H). ^{13}C-NMR: 156.32; 48.99; 46.64; 40.59; 38.12; 30.25; 28.38 (Me); 26.75. CI-MS: 328.1 ($[M+H]^+$).

N-*Allyl*-N-*(3-phthalimidopropyl)-2,2,2-trifluoroacetamide* (**15**). Allylamine (0.6 ml, 7.46 mmol) was added to a suspension of *N*-(3-bromopropyl)phthalimide (1 g, 3.73 mmol) and KF/*Celite* (6.92 g, 59.6 mmol) in MeCN (40 ml). After 30 h stirring at 50°, the soln. was filtered and evaporated. FC (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 40:1:0.1) gave *N*-[3-(allylamino)propyl]phthalimide as a colorless oil (615 mg, 65%). To a soln. of the latter (244 mg, 1 mmol) in CH_2Cl_2 (10 ml), a soln. of $(CF_3CO)_2O$ (0.2 ml, 1.5 mmol) in CH_2Cl_2 (2 ml), and Et_3N (0.2 ml, 1.5 mmol) were added at 0°. After 2 h stirring at 0°, the soln. was warmed to r.t., diluted with CH_2Cl_2 (10 ml), and extracted with 3% aq. HCl soln. (1×) and H_2O (1×). The org. layer was dried (Na_2SO_4) and evaporated. FC (hexane/AcOEt 3:1) provided **15** (298 mg, 88%). Colorless oil. ^{1}H-NMR: 7.89–7.84 (*m*, 2 H); 7.76–7.71 (*m*, 2 H); 5.81–5.69 (*m*, 1 H); 5.27–5.13 (*m*, 2 H); 4.08–4.02 (*m*, 2 H); 3.71 (*t*, *J* = 7.0, 2 H); 3.49–3.42 (*m*, 2 H); 2.08–1.98 (*m*, 2 H). ^{13}C-NMR: 134.08; 131.94; 123.41; 123.33; 119.34; 35.48; 26.05.

N-*{3-(Allylamino)propyl]-2,2,2-trifluoroacetamide* (**16**). To a soln. of **15** (100 mg, 0.29 mmol) in EtOH (20 ml), $N_2H_4 \cdot H_2O$ (0.12 ml, 2.47 mmol) was added dropwise at r.t. The mixture was refluxed for 1.5 h, cooled to r.t., filtered, and evaporated. The residue was dissolved in CH_2Cl_2 (30 ml) and the soln. washed with brine (2×) and dried (Na_2SO_4). Evaporation gave **16** (43 mg, 70%). Colorless oil. ^{1}H-NMR: 9.35 (br. *s*, 1 H); 5.91–5.80 (*m*, 1 H); 5.30–5.12 (*m*, 2 H); 3.51–3.47 (*m*, 2 H); 3.27–3.24 (*m*, 2 H); 2.90–2.84 (*m*, 2 H); 1.78–1.70 (*m*, 2 H); 1.58 (br. *s*, 1 H). ^{13}C-NMR: 116.49; 70.48; 51.95; 48.56; 40.81; 29.59; 26.49.

tert-*Butyl* N-*{3-[(4-Azidobutyl)(trifluoroacetyl)amino]propyl}carbamate* (**17**). To a soln. of **11** (3.5 g, 20.10 mmol) in CH_2Cl_2 (100 ml), a soln. of $(CF_3CO)_2O$ (4.2 ml, 30.15 mmol) in CH_2Cl_2 (25 ml) and Et_3N (4.4 ml, 30.15 mmol) were added at 0°. The mixture was stirred at 0° for 1 h and at r.t. for 15 h, then diluted with CH_2Cl_2 (50 ml), washed with 3% aq. HCl soln. (2×) 5% aq. $NaHCO_3$ soln. (2×), and H_2O (1×), dried (Na_2SO_4), and evaporated. FC (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 15:1:0.1) provided tert-*butyl* N-*{3-[(trifluoroacetyl)amino]propyl}carbamate* as a colorless oil (3.12 g, 58%). To a suspension of NaH (60% in oil; 89 mg, 2.22 mmol) in DMF (3 ml), a soln. of this carbamate (500 mg, 1.85 mmol) in DMF (8 ml) was added dropwise at r.t. After 1 h (no more gas emission), 1,4-dibromobutane (0.33 ml, 2.78 mmol) was added dropwise at r.t. The soln. was stirred for additional 3 h, and CO_2 gas was passed through the soln. for 30 min to remove H_2. The solvent was removed under high vacuum and the residue dissolved in Et_2O (30 ml). The soln. was washed with H_2O (1×) and brine (1×), dried (Na_2SO_4), and evaporated. Chromatography (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 60:1:0.1), gave tert-*butyl* N-*{3-[(4-bromobutyl)(trifluoroacetyl)amino]propyl}carbamate* as a colorless oil (210 mg, 28%). NaN_3 (35 mg, 0.54 mmol) was added to a soln. of this carbamate (100 mg, 0.25 mmol) in DMF (3 ml) at r.t. After 24 h stirring, the soln. was diluted with H_2O (10 ml) and extracted with Et_2O (3×) and the extract dried (Na_2SO_4) and evaporated: **17** (90 mg, quant.). Colorless oil. IR: 3440 (NH), 2100 (N_3), 1710 (C=O), 1690 (C=O). ^{1}H-NMR: 4.91 (br. *s*, 1 H); 3.50–3.30 (*m*, 6 H); 3.19–3.10 (*m*, 2 H); 1.85–1.56 (*m*, 6 H); 1.43 (*s*, 9 H). ^{13}C-NMR: 162.45 (C=O); 50.74; 46.93; 46.29; 45.12; 44.05; 29.61; 28.22 (Me); 27.35; 25.89; 24.07. ESI-MS: 390 ($[M+Na]^+$).

General Procedure 1 (GP 1): Reduction of the Azido Group. PPh_3 (1.2 equiv.) and H_2O (3 equiv.) were added to a soln. of the azide in THF at r.t. After 48–72 h, the solvent was evaporated, the residue dissolved in

Et_2O, the soln. filtered and evaporated, and the residue purified by FC (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 10:1:0.1 → 15:1:0.1).

tert-*Butyl* N-*{3-[(4-Aminobutyl)(trifluoroacetyl)amino]propyl}carbamate* (**18**). According to *GP 1* **17** (80 mg, 0.22 mmol) gave **18** (50 mg, 68%). Colorless oil. IR: 3440 (NH_2), 3370 (NH), 1690 (C=O), 1510 (C=O). ^{1}H-NMR: 4.95 (br. *s*, 1 H); 3.45–3.08 (*m*, 6 H); 2.84–2.80 (*m*, 2 H); 2.25 (br. *s*, 2 H); 1.85–1.55 (*m*, 6 H); 1.44 (*s*, 9 H). ^{13}C-NMR: 170.58 (C=O); 44.95; 28.24 (Me). CI-MS: 342.4 (88, $[M+H]^+$), 246.4 (100).

N-*Allyl*-N-*(3-aminopropyl)pyridine-2-sulfonamide* (**20**). According to *GP 1*, *N*-allyl-*N*-(3-azidopropyl)-pyridine-2-sulfonamide (**19**) [11] (43 mg, 0.15 mmol) afforded **20** (34 mg, 89%). Colorless oil. IR: 3380 (NH_2), 1340 (SO_2), 1170 (SO_2). ^{1}H-NMR: 8.69 (*d*, *J* = 4.6, 1 H); 7.98–7.86 (*m*, 2 H); 7.49–7.45 (*m*, 1 H); 5.78–5.65 (*m*, 1 H); 5.22–5.10 (*m*, 2 H); 3.98 (*d*, *J* = 6.6, 2 H); 3.40 (*t*, *J* = 7.0, 2 H); 2.75 (*t*, *J* = 6.7, 2 H); 1.69 (*quint.*, *J* = 6.9, 2 H); 1.58 (*s*, 2 H). ^{13}C-NMR: 158.19; 149.89; 137.74 (*C*H=CH_2); 133.37; 126.32; 122.34; 118.56 (CH_2=CHCH_2N); 51.30; 45.56; 38.78; 31.66. ESI-MS: 256.0 ($[M+H]^+$).

General Procedure 2 (GP 2): Acylation of Tetra-N-*Protected Pentamines.* A soln. of 4-methoxycinnamoyl chloride (1.1 equiv. rel. to polyamine) in abs. AcOEt (5 ml) was added dropwise over 5 min to a soln. of polyamine (0.05–0.1 mmol) and Et_3N (1.5 equiv. rel. to polyamine) in abs. AcOEt (10 ml) at −10°. The mixture was stirred at −10° for 30 min and at r.t. for 16–18 h, then filtered, and evaporated. FC (CH_2Cl_2/MeOH 20:1 → 30:1) provided the acylpolyamine as colorless oil.

N-*{9-Allyl-16-azido-13-(trifluoroacetyl)-4-[2-(trimethylsilyl)ethylsulfonyl]-4,9,13-triazahexadecyl}-3-(4-methoxyphenyl)prop-2-enamide* (= N-*{3-{[4-{Allyl[3-[(3-azidopropyl)(trifluoroacetyl)amino]propyl}amino}butyl]{[2-(trimethylsilyl)ethyl]sulfonyl}amino}propyl}-3-(4-methoxyphenyl)prop-2-enamide*; **22**). a) *Removal of Boc Group from* **1**: A soln. of **1** (150 mg, 0.22 mmol) in CH_2Cl_2 (15 ml) was added at once to a soln. of CF_3COOH (0.67 ml, 8.76 mmol) in CH_2Cl_2 (10 ml) under Ar at r.t. The mixture was stirred for 1 h and the solvent and excess of CF_3COOH were evaporated. The residue was dissolved in CH_2Cl_2, washed with sat. Na_2CO_3 soln. (1×), dried (Na_2SO_4), and evaporated to give N-*{4-allyl-12-amino-9-[2-(trimethylsilyl)ethylsulfonyl]-4,9-diazadodecyl}*-N-*(3-azidopropyl)-2,2,2-trifluoroacetamide* (= N-*{3-{allyl{4-[(3-aminopropyl)-{[2-(trimethylsilyl)ethyl]sulfonyl}amino}butyl}amino}propyl}*-N-*(3-azidopropyl)-2,2,2-trifluoroacetamide*; **21**) as a colorless oil (100 mg, 78%).

b) *Acylation of* **21**: According to *GP 2*, with **21** (58 mg, 0.1 mmol): **22** (68 mg, 93%). IR: 3430 (NH), 2100 (N_3), 1690 (C=O), 1670 (C=O), 1325 (SO_2), 1170 (SO_2). ^{1}H-NMR: 7.50 (*d*, *J* = 15.6, 1 H); 7.39 (*d*, *J* = 8.7, 2 H); 6.83 (*d*, *J* = 8.6, 2 H); 6.46, 6.37 (*dt*, *J* = 5.1, 5.1, 1 H); 6.31, 6.26 (*dd*, *J* = 3.2, 3.2, 1 H); 5.78–5.69 (*m*, 1 H); 5.14–5.09 (*m*, 2 H); 3.77 (*s*, 3 H); 3.44–3.13 (*m*, 12 H); 3.05–2.98 (*m*, 2 H); 2.87–2.81 (*m*, 2 H); 2.42–2.37 (*m*, 4 H); 1.86–1.39 (*m*, 10 H); 0.98–0.92 (*m*, 2 H); 0.00 (*s*, 9 H). ^{13}C-NMR: 172.25 (C=O); 168.35; 142.45; 131.33; 129.65; 120.72; 116.21; 58.86; 57.33 (MeO); 55.28; 52.67; 50.93; 50.33; 49.63; 48.62; 47.72; 46.96; 37.71; 30.33; 29.14; 28.39; 12.31; 0.00 (Me). ESI-MS: 746.5 ($[M+H]^+$).

tert-*Butyl* N-*{9-Allyl-16-azido-4-[3-(4-methoxyphenyl)prop-2-enoyl]-13-(trifluoroacetyl)-4,9,13-triazahexadecyl}carbamate* (= tert-*Butyl* N-*{3-{[4-{Allyl[3-[(3-azidopropyl)(trifluoroacetyl)amino]propyl}amino}butyl][3-(4-methoxyphenyl)prop-2-enoyl]amino}propyl}carbamate*; **24**). a) *Removal of the SES Group from* **1**: CsF (89 mg, 0.58 mmol) was put at once into an Ar-filled flask. A soln. of **1** (100 mg, 0.15 mmol) in DMF (4 ml) was added dropwise at r.t. The mixture was then heated to 95° for 24 h. After cooling to r.t., abs. MeOH (4 ml) was added and the mixture stirred for 1 h and then evaporated. FC (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 15:1:0.1) gave tert-*butyl* N-*{9-allyl-16-azido-13-(trifluoroacetyl)-4,9,13-triazahexadecyl}carbamate* (= tert-*butyl* N-*{3-{[4-{allyl[3-[(3-azidopropyl)(trifluoroacetyl)amino]propyl}amino}butyl}amino}propyl}carbamate*; **23**) as a colorless oil (53 mg, 70%).

b) *Acylation of* **23**: According to *GP 2*, with **23** (27 mg, 0.05 mmol): **24** (32 mg, 91%). IR: 3440 (NH), 2100 (N_3), 1690 (C=O), 1640 (C=O), 1230 (CO). ^{1}H-NMR: 7.67 (*d*, *J* = 15.2, 1 H); 7.50–7.44 (*m*, 2 H); 6.90 (*d*, *J* = 8.7, 2 H); 6.72, 6.67 (*dd*, *J* = 3.4, 3.4, 1 H); 5.88–5.75 (*m*, 1 H); 5.52 (br. *s*, 1 H); 5.23–5.11 (*m*, 2 H); 3.84 (*s*, 3 H); 3.52–3.31 (*m*, 10 H); 3.20–3.05 (*m*, 4 H); 2.50–2.40 (*m*, 4 H); 1.86–1.47 (*m*, 10 H); 1.44 (*s*, 9 H). ^{13}C-NMR: 169.63 (C=O); 129.29; 114.17; 107.55; 56.25; 55.26 (MeO); 48.20; 45.15; 43.50; 28.49 (Me); 28.38; 26.29. ESI-MS: 682.3 ($[M+H]^+$).

tert-*Butyl* N-*{16-Azido-9-[3-(4-methoxyphenyl)prop-2-enoyl]-13-(trifluoroacetyl)-4-[2-(trimethylsilyl)ethylsulfonyl]-4,9,13-triazahexadecyl}carbamate* (= tert-*Butyl* N-*{3-{[4-{[3-[(3-Azidopropyl)(trifluoroacetyl)amino]propyl}[3-(4-methoxyphenyl)prop-2-enoyl]amino}butyl]{[2-(trimethylsilyl)ethyl]sulfonyl}amino}propyl}carbamate*; **26**). a) *Removal of Allyl Group from* **1**: A well-degassed soln. of **1** (100 mg, 0.15 mmol) in CH_2Cl_2 (5 ml) was added dropwise to the flask containing $[Pd(PPh_3)_4]$ (3.4 mg, 0.003 mmol), 1,3-dimethylbarbituric acid (DMBA; 80 mg, 0.51 mmol) under Ar. The mixture was stirred at 35° for 6 h, then diluted with CH_2Cl_2 (20 ml), washed with sat. $NaHCO_3$ soln. (1×), dried (Na_2SO_4), and evaporated. FC (CH_2Cl_2/MeOH/25% aq. NH_3 soln.

30 : 1 : 0.1) afforded tert-*butyl* N-*{16-azido-13-(trifluoroacetyl)-4-[2-(trimethylsilyl)ethylsulfonyl]-4,9-13-triazahexadecyl}carbamate* (= tert-*butyl* N-*{3-{[4-{[3-[(3-azidopropyl)(trifluoracetyl)amino]propyl}amino}butyl]{[2-(trimethylsilyl)ethyl]sulfonyl}amino}propyl}carbamate*; **25**) as a colorless oil (66 mg, 70%).

b) *Acylation of* **25**: According to *GP 2*, with **25** (30 mg, 0.05 mmol): **26** (34 mg, 92%). IR: 3440 (NH), 2100 (N_3), 1700 (C=O), 1685 (C=O), 1365 (SO_2), 1170 (SO_2). ^{1}H-NMR: 7.64, 7.59 (*dd*, $J = 4.7, 4.6$, 1 H); 7.47–7.40 (*m*, 2 H); 6.88–6.82 (*m*, 2 H); 6.74–6.62 (*m*, 1 H); 4.85 (br. *s*, 1 H); 3.78 (*s*, 3 H); 3.50–3.33 (*m*, 10 H); 3.22–3.11 (*m*, 6 H); 2.85–2.79 (*m*, 2 H); 1.88–1.51 (*m*, 10 H); 1.39 (*s*, 9 H); 0.96–0.90 (*m*, 2 H); 0.00 (*s*, 9 H). ^{13}C-NMR: 171.65 (C=O); 158.86; 145.01; 131.51; 116.39; 57.38 (MeO); 49.69; 48.35; 40.45; 32.35; 30.44 (Me); 12.38; 0.00 (Me). ESI-MS: 806.5 (94, $[M+H]^+$), 706.4 (100).

tert-*Butyl* N-*{9-Allyl-16-azido-13-[3-(4-methoxyphenyl)prop-2-enoyl]-4-[2-(trimethylsilyl)ethylsulfonyl]-4,9,13-triazahexadecyl}carbamate* (= tert-*Butyl* N-*{3-{[4-{Allyl{3-{(3-azidopropyl)[3-(4-methoxyphenyl)prop-2-enoyl]amino}propyl}amino}butyl}{[2-(trimethylsilyl)ethyl]sulfonyl}amino}propyl}carbamate*; **28**). a) *Removal of Trifluoroacetyl Group from* **1**: A soln. of **1** (270 mg, 0.39 mmol) and anh. K_2CO_3 (408 mg, 0.79 mmol) in MeOH/H_2O 3 : 1 was stirred for 17 h at r.t. The mixture was filtered and the filtrate evaporated. FC (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 15 : 1 : 0.1) provided tert-*butyl* N-*{9-allyl-16-azido-4-[2-(trimethylsilyl)ethylsulfonyl]-4,9,13-triazahexadecyl}carbamate* (= tert-*butyl* N-*{3-{[4-{allyl{3-{(3-azidopropyl)[3-[4-methoxyphenyl)prop-2-enoyl]amino}propyl}amino}butyl}{[2-(trimethylsilyl)ethyl]sulfonyl}amino}propyl}carbamate*; **27**) as a colorless oil (210 mg, 92%).

b) *Acylation of* **27**: According to *GP 2*, with **27** (30 mg, 0.05 mmol): **28** (30 mg, 80%). IR: 3440 (NH), 2100 (N_3), 1730 (C=O), 1710 (C=O), 1375 (SO_2), 1180 (SO_2). ^{1}H-NMR: 7.65 (*d*, $J = 15.3$, 1 H); 7.47 (*d*, $J = 8.4$, 2 H); 6.89 (*d*, $J = 8.8$, 2 H); 6.76 (*d*, $J = 15.3$, 1 H); 5.89–5.79 (*m*, 1 H); 5.21–5.10 (*m*, 2 H); 4.92 (br. *s*, 1 H); 3.83 (*s*, 3 H); 3.57–3.32 (*m*, 6 H); 3.28–3.08 (*m*, 6 H); 2.90–2.81 (*m*, 2 H); 2.51–2.42 (*m*, 4 H); 1.94–1.49 (*m*, 10 H); 1.42 (*s*, 9 H); 1.11–0.97 (*m*, 2 H); 0.00 (*s*, 9 H). ^{13}C-NMR: 129.27; 114.20; 107.25; 55.00 (Me); 38.75; 29.85; 28.32 (Me); 11.25; 0.00 (Me). ESI-MS: 750.6 ($[M+H]^+$).

tert-*Butyl* N-*(9-Allyl-16-{[3-(4-methoxyphenyl)prop-2-enoyl]amino}-13-[(2,2,2-trichloro-1,1-dimethylethoxy)-carbonyl]-4-[2-(trimethylsilyl)ethylsulfonyl]-4,9,13-triazahexadecyl}carbamate* (= tert-*Butyl* N-*{9-Allyl-20-(4-methoxyphenyl)-18-oxo-13-[2,2,2-trichloro-1,1-dimethylethoxy)carbonyl]-4-{[2-(trimethylsilyl)ethyl]sulfonyl}-4,9,13,17-tetraazaicos-19-en-1-yl}carbamate*; **30**). a) *Removal of Trifluoroacetyl Group from* **10**: A soln. of **10** (28 mg, 0.03 mmol) and anh. K_2CO_3 (9 mg, 0.07 mmol) in MeOH/H_2O 3 : 1 was stirred for 24 h at r.t. The mixture was filtered and the filtrate evaporated. FC (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 90 : 7 : 0.7) provided tert-*butyl* N-*{9-allyl-16-amino-13-[(2,2,2-trichloro-1,1-dimethylethoxy)carbonyl]-4-[2-(trimethylsilyl)ethylsulfonyl]-4,9,13-triazahexadecyl}carbamate* (= tert-*butyl* N-*{3-{[4-{allyl{3-{(3-aminopropyl)[(2,2,2-trichloro-1,1-dimethylethoxy)carbonyl]amino}propyl}amino}butyl}{[2-(trimethylsilyl)ethyl]sulfonyl}amino}propyl}carbamate*; **29**) (20 mg, 85%). Colorless oil. IR: 3440 (NH_2), 1700 (C=O), 1365 (SO_2), 1155 (SO_2). ^{1}H-NMR: 5.80–5.69 (*m*, 1 H); 5.15–4.95 (*m*, 3 H); 3.31–3.10 (*m*, 10 H); 3.01–2.96 (*m*, 2 H); 2.85–2.79 (*m*, 2 H); 2.40–2.30 (*m*, 4 H); 1.86 (*s*, 6 H); 1.83 (br. *s*, 1 H); 1.74–1.43 (*m*, 10 H); 1.38 (*s*, 9 H); 0.98–0.92 (*m*, 2 H); 0.00 (*s*, 9 H). ^{13}C-NMR: 137.70 (*C*H=CH_2); 119.26 (CH_2=CHCH_2N); 59.02; 55.14; 53.05; 49.78; 47.77; 47.42; 31.25; 30.40 (Me); 29.01; 26.30; 23.63 (Me); 12.30; 0.00 (Me). ESI-MS: 766.5 ($[M+H]^+$).

b) *Acylation of* **29**. According to *GP 2*, with **29** (36 mg, 0.05 mmol): **30** (36 mg, 90%). IR: 3440 (NH), 1700 (C=O), 1665 (C=O), 1380 (SO_2), 1160 (SO_2). ^{1}H-NMR: 7.56 (*d*, $J = 15.6$, 1 H); 7.46 (*d*, $J = 8.7$, 2 H); 6.89 (*d*, $J = 8.8$, 2 H); 6.64 (br. *s*, 1 H); 6.32 (*d*, $J = 15.5$, 1 H); 5.89–5.72 (*m*, 1 H); 5.21–5.08 (*m*, 2 H); 4.95 (br. *s*, 1 H); 3.42–3.13 (*m*, 12 H); 3.10–3.01 (*m*, 2 H); 2.90–2.84 (*m*, 2 H); 2.49–2.38 (*m*, 4 H); 1.93 (*s*, 6 H); 1.82–1.60 (*m*, 10 H); 1.44 (*s*, 9 H); 1.03–0.97 (*m*, 2 H); 0.05 (*s*, 9 H). ^{13}C-NMR: 131.28; 116.27; 71.85; 58.20; 57.32 (MeO); 55.10; 53.00; 50.23; 47.60; 30.44 (Me); 29.20; 23.73; 21.45; 12.38; 0.00 (Me). ESI-MS: 926.6 ($[M+H]^+$).

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