Synthesis of Penta-*N*-Protected Homocaldopentamine and Its Selective Acylation

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The synthesis of the penta-*N*-protected polyamine homocaldopentamine {PA 4333, **1**, *tert*-butyl *N*-[9-allyl-16-azido-13-(2,2,2-trichloro-*tert*-butoxycarbonyl)-5-(trimethylsilylethylsulfonyl)-5,9,13-triazahexadec-1-yl]carbamate}, containing five independent amino-protecting groups is described. These five protecting groups used—allyl, azido, *tert*-butoxycarbonyl (BOC), 2,2,2-trichloro-*tert*-butoxycarbonyl (TCBOC), and trimethylsilylethylsulfonyl (SES)—were removed selectively. The acylation with *p*-methoxycinnamoyl chloride at each nitrogen of the pentaamine was determined.

Introduction

Polyamines are present throughout nature in various bacteria, plants, animals, and other organisms.[1−4] It has been recognized that, because of their positive charged character under physiological ionic and pH conditions, naturally occurring polyamines are generally involved in biochemical processes such as DNA, RNA, and protein syntheses.[5,6] A few years ago, there have been many reports about polyamines isolated from the venom of spiders. These venoms are rich sources of novel neurotoxins, which are important as tools for studying neurophysiology and as potential lead structures for insecticides and pharmaceuticals.[7,8] Particularly, toxins of low molecular weight have been reported to be highly effective potentiators (at low concentration) and antagonists (at high concentration) of ionotropic glutamate receptors in central nervous systems.[9,10] Because of the limitations on isolation and structural elucidation of compounds set by the scarcity of the natural toxins, versatile synthetic approaches to these polyamine toxins and their analogues have proven useful in studies on pharmacology and physiology of important biological systems.[11]

In our studies of acylpolyamines,[12,13] we are investigating the chemistry of toxins such as HO 395 and HO 416b, which arise from the same family of spiders (Agelenidae) (Figure 1). They contain the same polyamine backbone, homocaldopentamine (PA 4333), but different carboxylic acids bonded as amides to the actual polyamine. For a more flexible synthetic approach to these compounds and their analogues, we now utilized a nonlinear synthetic method as reported in our previous paper. In that article,[14] we discussed the synthesis of a penta-*N*-protected thermopentamine (PA 3433) by the reaction of the spermidine reagent with the building block.

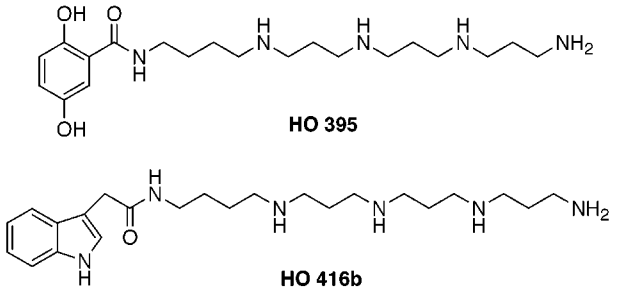

Figure 1.

In this paper, we report on the synthesis of a homocaldopentamine with five independent amino-protecting groups and their regioselective deprotection and as well on their refunctionalization with *p*-methoxycinnamoyl chloride. These protecting groups include allyl, azido, *tert*-butoxycarbonyl (BOC), 2,2,2-trichloro-*tert*-butoxycarbonyl (TCBOC), and trimethylsilylethylsulfonyl (SES).

Results and Discussion

We planned to synthesize the polyamine **1** by reaction of the spermidine reagent **2** with the building block **3** (Scheme 1). It was determined that removal of allyl, *tert*-butoxycarbonyl (BOC), and trimethylsilylethylsulfonyl groups (SES) from the target compound **1** requires mild treatment with tetrakis(triphenylphosphine)palladium and *N*,*N*′-dimethylbarbituric acid (NDMBA),[15] brief exposure to trifluoroacetic acid, and CsF in DMF,[16] respectively. These conditions and the presence of a *p*-methoxycinnamoyl group as the aromatic acyl moiety elimina-

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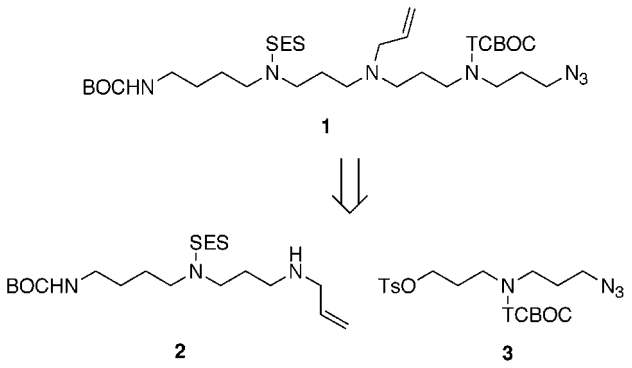
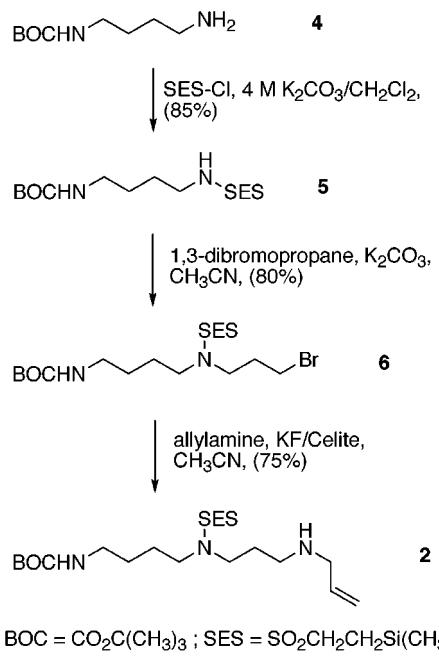
Scheme 1



Scheme 2

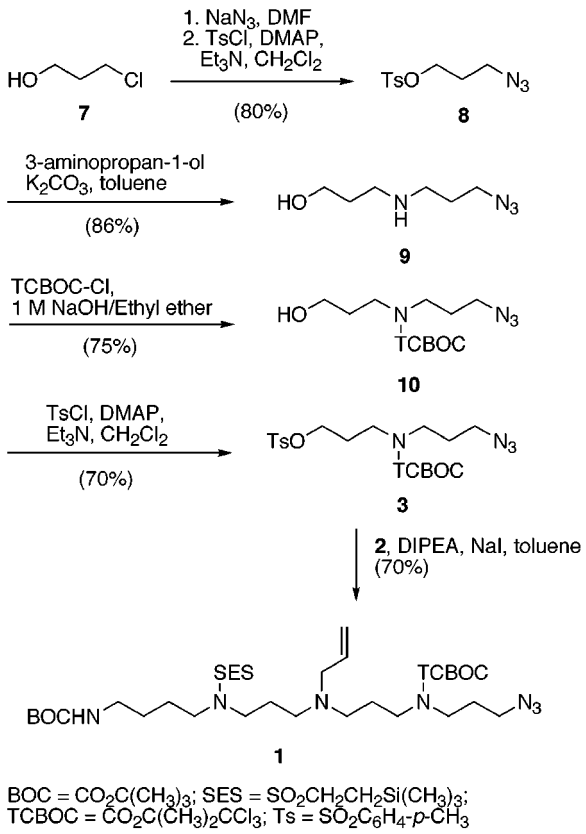


ted a large number of amino-protecting groups as candidates for two independent protecting groups on building block **3**. Finally, the 2,2,2-trichloro-*tert*-butoxycarbonyl (TCBOC) group and azido group solved this crucial problem. They can be cleaved by treatment with Zn dust in dilute acid[17] and mild treatment with triphenylphosphine in THF in the presence of water.[18,19] These mild conditions do not effect the allyl and cinnamoyl groups.

The preparation of the spermidine reagent **2** begins with *N*-BOC-1,4-diaminobutane (**4**), prepared according to the literature[20] (Scheme 2). Trimethylsilylethylsulfonyl chloride (SES-Cl)[16] was added to a solution of **4** in the presence of aqueous potassium carbonate in dichloromethane at 0 °C for 5 h to afford (trimethylsilyl)-ethanesulfonamide derivative **5**. The treatment of the latter with 1,3-dibromopropane in the presence of potassium carbonate in refluxing acetonitrile for 24 h provided the bromide **6** which was converted to the spermidine reagent **2** by using allylamine in a suspended solution of KF/Celite in acetonitrile.

O-Tosyl-3-azidopropan-1-ol (**8**), the starting material for the second building block, was prepared from the

Scheme 3



commercial 3-chloropropan-1-ol (**7**) and sodium azide in DMF for 1 day, followed by successive treatment with *p*-toluenesulfonyl chloride, (dimethylamino)pyridine (DMAP), and triethylamine as bases in dichloromethane (Scheme 3). Using a Dean−Stark apparatus, **8** was added to 3-aminopropan-1-ol in the presence of potassium carbonate in refluxing toluene to afford **9**. The amino alcohol **9** was acylated with 2,2,2-trichloro-*tert*-butoxycarbonyl chloride (TCBOC-Cl) in the presence of aqueous sodium hydroxide in diethyl ether to provide **10**. The *O*-tosylation of **10** with *p*-toluenesulfonyl chloride, DMAP, and triethylamine in dichloromethane gave the building block **3**.

Finally, the coupling of these two compounds, **2** and **3**, with diisopropylethylamine and sodium iodide in toluene at 100 °C for 3 days provided the target homocaldopentamine **1** in 70% yield.

We next deprotected and refunctionalized each nitrogen of the polyamine to demonstrate the independence of the protecting groups and the versatility of the new reagent. After the removal of each protecting group, the resulting tetrafunctionalized pentaamine was acylated with *p*-methoxycinnamoyl chloride, simply prepared with *p*-methoxycinnamic acid and oxalyl dichloride, as depicted in Scheme 4.

Exposure of the polyamine **1** to trifluoroacetic acid in dichloromethane for 0.5 h removed the BOC group and, after a basic workup, afforded the primary amine **11**. A trimethylsilylethylsulfonyl (SES) group can be cleaved with CsF in DMF or with tetrabutylammonium fluoride (TBAF) in acetonitrile.[16] The latter cleavage procedure often gives difficulty in separating tetrabutylammonium salts from some amines. Therefore, the compound **1** was treated with CsF in DMF which gave the polyamine **13**. Because of the high hygroscopicity of CsF, the yield of

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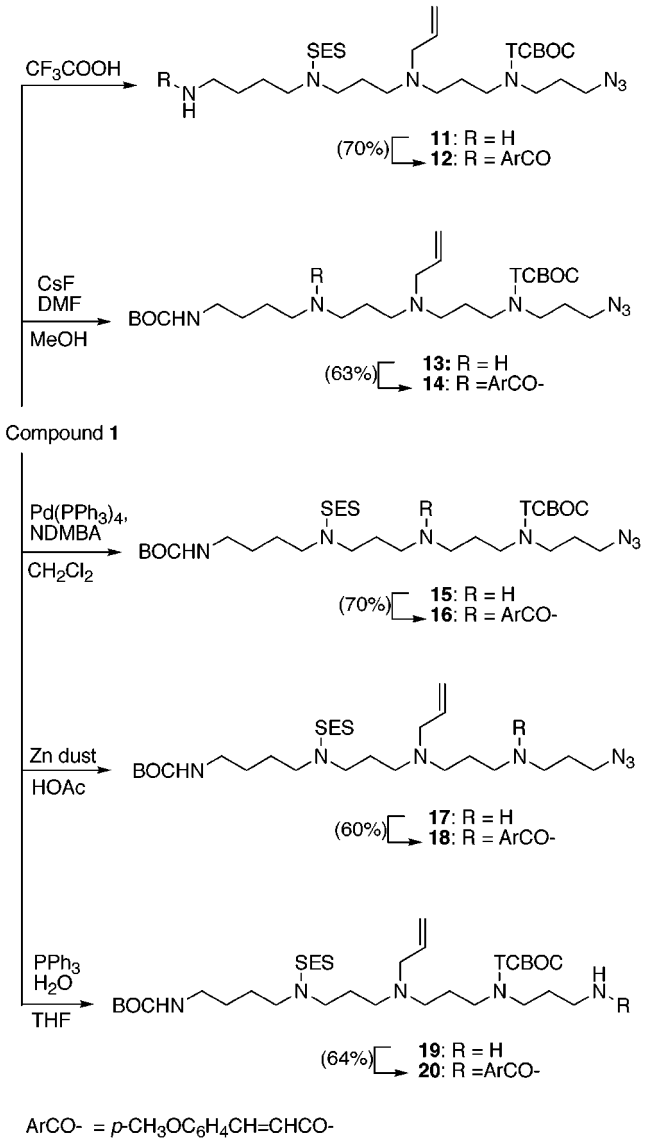
Scheme 4



13 was very dependent upon the dryness of the reaction mixture. The pentaamine **1** was deallylated by heating (35 °C) in dichloromethane in the presence of *N*,*N*′-dimethylbarbituric acid (NDMBA) as an allyl group scavenger, and tetrakis(triphenylphosphine)palladium as a catalyst, to be converted to the polyamine **15**.

The 2,2,2-Trichloro-*tert*-butoxycarbonyl (TCBOC) group is reported as an acid- and base-resistant amino-protecting group of aliphatic linear polyamines[17] or amino acids.[21] The removal of the TCBOC group from **1** was done with freshly activated Zn dust[21] in acetic acid at room temperature, to provide the tetraprotected compound **17**. Considering possible side effects by acid, the reaction was performed in refluxing methanol instead of acetic acid. But the same result was obtained from both methods. The fifth functional group of the polyamine **1**, the azido group, was reduced to the primary amine **19** by mild treatment with triphenylphosphine in the presence of water in THF.

In conclusion, the penta-*N*-protected homocaldopentamine (PA 4333, **1**) was synthesized in good yields from *N*-BOC-1,4-diaminobutane and 3-chloropropan-1-ol. The stepwise deprotection and refunctionalization of each nitrogen of the polyamine backbone was performed regioselectively.

Experimental Section

General Methods. All reactions involving air-sensitive reagents were performed under nitrogen or argon. Solvents and reagents were purchased from Fluka. *N*-BOC-1,4-diaminobutane,[20] KF/Celite,[22] and trimethylsilylethylsulfonyl chloride[16] were prepared according to the literature. THF was freshly distilled from benzophenone/sodium prior to use. Merck precoated silica gel 60 F-254 plates were used for TLC. Column chromatographies were performed using silica gel (Merck 60, 230−400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. All chemical shifts were recorded as values (ppm) relative to internal tetramethylsilane. Mass spectra (MS) were obtained using chemical ionization (CI) with NH_3 as reactant gas and electrospray ionization (ESI).

***tert*-Butyl *N*-[*N*′-(Trimethylsilylethylsulfonyl)-4-aminobut-1-yl]carbamate (5)**. To a vibromixed solution of *N*-BOC-1,4-diaminobutane (**4**, 3.12 g, 16.60 mmol) in a mixture of 4 M solution of K_2CO_3 (60 mL) and dichloromethane (60 mL) at 0 °C was added over 2 h a solution of (trimethylsilyl)-ethanesulfonyl chloride (6.66 g, 33.19 mmol) in dichloromethane (60 mL). The reaction mixture was allowed to stir for 5 h at 0 °C. The aqueous layer was extracted three times with dichloromethane. The organic layer was combined and dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (2:1 hexane/ethyl acetate) gave **5** as white solid (4.96 g, 85%): Mp (hexane) 92−94 °C; IR ν_{max} ($CHCl_3$) 3455 (NH), 3400 (NH), 1710 (C═O), 1365 (SO_2), 1250 (CO), 1165 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.51 (br s, 1H), 4.26 (br s, 1H), 3.13−3.05 (m, 4H), 2.90−2.84 (m, 2H), 1.65−1.51 (m, 4H), 1.38 (s, 9H), 0.99−0.93 (m, 2H), 0.00 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 50.78, 45.00, 44.99, 40.00, 30.41 (CH_3), 29.62, 29.30, 12.65, 0.00 (CH_3) ppm; ESIMS *m*/*z* 375.1 [M + Na]$^+$.

***tert*-Butyl *N*-[*N*′-(3-Bromopropyl)-*N*′-(trimethylsilylethylsulfonyl)-4-aminobut-1-yl]carbamate (6).** To a solution of **5** (3 g, 8.52 mmol) in acetonitrile (60 mL) were added anhydrous K_2CO_3 (3.77 g, 27.26 mmol) and 1,3-dibromopropane (17 mL, 0.17 mol). The reaction mixture was heated at reflux for 24 h. Then, it was filtered and washed with acetonitrile and the solvent was evaporated. The residue was given to flash chromatography (2.5:1 hexane/ethyl acetate) to provide **6** as a colorless oil (3.22 g, 80%): IR ν_{max} ($CHCl_3$) 3450 (NH), 1715 (C═O), 1370 (SO_2), 1250 (CO), 1165 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.50 (br s, 1H), 3.38 (t, J = 6.34 Hz, 2H), 3.29 (t, J = 7.19 Hz, 2H), 3.17 (t, J = 7.46 Hz, 2H), 3.08 (q, J = 5.42 Hz, 2H), 2.86−2.80 (m, 2H), 1.61−1.56 (m, 4H), 1.45 (quint, J = 6.93 Hz, 2H), 1.39 (s, 9H), 0.97−0.91 (m, 2H), 0.00 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 157.97, 50.20, 49.78, 48.70, 34.33 (CH_2Br), 32.19, 30.37 (CH_3), 29.27, 28.24, 12.28, 0.00 (CH_3) ppm; CIMS *m*/*z* 490.4 (59, [M + NH_4]$^+$), 410.4 (100).

***tert*-Butyl *N*-[8-(*N*′-Allylamino)-5-(trimethylsilylethylsulfonyl)-5-azaoct-1-yl]carbamate (2).** To a solution of **6** (455 mg, 0.96 mmol) in acetonitrile (60 mL) were added KF/Celite (2.67 g, 23.04 mmol) and allylamine (0.22 mL, 2.88 mmol). The suspended solution was heated at 45 °C. After 48 h, it was cooled to room temperature and filtered. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (30:1:0.1 dichloromethane/methanol/25% ammonia water) to give the colorless oil **2** (258 mg, 75%): IR ν_{max} ($CHCl_3$) 3450 (NH), 1710 (C═O), 1370 (SO_2), 1250 (CO), 1165 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.91−5.79 (m, 1H), 5.17−5.04 (m, 2H), 4.58 (br s, 1H), 3.26−3.14 (m, 6H), 3.09 (q, J = 6.45 Hz, 2H), 2.84−2.78 (m, 2H), 2.61 (t, J = 6.79 Hz, 2H), 1.76−1.43 (m, 7H), 1.39 (s, 9H), 0.98−0.92 (m, 2H), 0.00 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 157.98, 138.40 (CH═CH_2), 118.21 (CH_2═CH), 81.16, 54.38, 49.77, 48.07, 41.97,

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31.43, 30.38 (CH_3), 29.27, 28.34, 12.29, 0.00 (CH_3) ppm; CIMS *m*/*z* 450.5 $[M + H]^+$.

3-Azidopropyl 1-*p*-Toluenesulfonate (8). Sodium azide (11.66 g, 0.18 mol) was added to a solution of 3-chloropropan-1-ol (**7**, 5 mL, 59.76 mmol) in DMF (40 mL). The reaction mixture was heated at 60 °C for 24 h. Then it was diluted four times with water and extracted with diethyl ether three times. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude compound (6 g, 99%) was used in to the next step without purification.

To the solution of the crude compound (6 g) in dichloromethane (60 mL) were added DMAP (1.45 g, 11.88 mmol) and Et_3N (12.42 mL, 89.12 mmol). And then a solution of *p*-toluenesulfonyl chloride (17 g, 89.12 mmol) in dichloromethane (30 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and warmed to room temperature. After 12 h of stirring, it was diluted with dichloromethane (100 mL) and washed with saturated aqueous $NaHCO_3$, 10% aqueous HCl, and 10% brine continuously. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The purification by flash column chromatography (3:1 hexane/ethyl acetate) gave **8** as a colorless oil (12 g, 80%): IR ν_{max} ($CHCl_3$) 2100 (N_3), 1370 (SO_2), 1190 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.80 (d, J = 8.33 Hz, 2H), 7.36 (d, J = 8.22 Hz, 2H), 4.11 (t, J = 5.99 Hz, 2H), 3.38 (t, J = 6.49 Hz, 2H), 2.45 (s, 3H), 1.89 (quint, J = 6.24 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 145.05, 132.82, 132.28, 129.95, 129.89, 128.07, 127.92, 67.03 (CH_2O), 60.39, 56.16, 47.31 (CH_2N_3), 28.48, 21.65, 14.21 ppm; CIMS *m*/*z* 273.3 (32, $[M + NH_4]^+$), 204.2 (100).

***N*-(3-Azidopropyl)-3-aminopropan-1-ol (9).** To a refluxing solution of 3-aminopropan-1-ol (7.4 mL, 96.08 mmol) and anhydrous K_2CO_3 (9.47 g, 68.63 mmol) in toluene (150 mL) was added dropwise a solution of **8** (7 g, 27.45 mmol) in toluene (40 mL) over 50 min. The solution was refluxed for 24 h using a Dean−Stark apparatus. It was cooled to room temperature and filtered. The filtrate was concentrated in vacuo and given to flash column chromatography (10:1:0.1 dichloromethane/methanol/25% ammonia water) to provide **9** as a colorless oil (3.73 g, 86%): IR ν_{max} ($CHCl_3$) 3610 (OH), 3300 (NH), 2100 (N_3), 1070 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.81 (t, J = 5.36 Hz, 2H), 3.36 (t, J = 6.67 Hz, 2H), 2.88 (t, J = 5.77 Hz, 2H), 2.72 (t, J = 6.87 Hz, 4H), 1.81−1.69 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$): δ 64.26 (CH_2O), 49.96, 49.53, 47.01 (CH_2N_3), 30.83, 29.15 ppm; CIMS *m*/*z* 159.2 $[M + H]^+$.

2,2,2-Trichloro-*tert*-butyl *N*-[3-Azido-*N*-(3-hydroxypropyl)-prop-1-yl]carbamate (10). To a solution of **9** (1 g, 6.32 mmol) in a mixture of 1 M solution of NaOH (30 mL) and diethyl ether (30 mL) was added dropwise over 1 h a solution of 2,2,2-trichloro-*tert*-butoxycarbonyl chloride (2.43 g, 10.11 mmol) in diethyl ether (25 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and separated. The water phase was extracted with diethyl ether twice. During the separation and extraction, the reaction mixture should be kept cold. The organic phases were combined, dried over Na_2SO_4, and concentrated in vacuo. The purification by flash column chromatography (1:1 hexane/ethyl acetate) afforded **10** as a colorless oil (1.71 g, 75%): IR ν_{max} ($CHCl_3$) 3610 (OH), 2100 (N_3), 1740 (C=O), 1250 (CO), 1060 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.59 (t, J = 5.55 Hz, 2H), 3.44−3.28 (m, 6H), 2.70 (br s, 1H), 1.95−1.86 (m, 8H), 1.78−1.70 (quint, J = 5.85 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 154.97, 106.67, 89.56, 60.40 (CH_2O), 60.18, 58.53, 49.09 (CH_2N_3), 45.14, 43.66, 31.78, 30.60, 28.13, 27.59, 21.63, 21.04 (CH_3), 14.21 ppm; CIMS *m*/*z* 360.9 $[M + H]^+$.

2,2,2-Trichloro-*tert*-butyl *N*-{3-Azido-*N*-[3-(*p*-tolylsulfonyloxy)-propyl]-prop-1-yl}carbamate (3). A solution of *p*-toluenesulfonyl chloride (950 mg, 4.98 mmol) in dichloromethane (70 mL) was added dropwise over 1 h to a solution of **10** (1.2 g, 3.32 mmol), Et_3N (0.7 mL, 4.98 mmol), and DMAP (487 mg, 3.98 mmol) in dichloromethane (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 24 h. Then, it was diluted with dichloromethane, washed with 10% aqueous HCl and 10% brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (hexane/ethyl acetate 2.5:1) to provide **3** as a colorless oil (1.19 g, 70%): IR ν_{max} ($CHCl_3$) 2100 (N_3), 1740 (C=O), 1360 (SO_2), 1210 (CO), 1170 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.79 (d, J = 8.29 Hz, 2H), 7.36 (d, J = 8.07 Hz, 2H), 4.06 (t, J = 5.27 Hz, 2H), 3.31−3.23 (m, 6H), 2.46 (s, 3H), 1.98−1.81 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$) δ 153.59, 144.99, 129.93, 127.95, 106.70, 88.80, 68.00 (CH_2O), 49.04 (CH_2N_3), 45.50, 44.66, 28.22, 27.57, 21.65 (CH_3), 21.60 ppm; CIMS *m*/*z* 532.0 $[M + NH_4]^+$.

***tert*-Butyl *N*-[9-Allyl-16-azido-13-(2,2,2-trichloro-*tert*-butoxycarbonyl)-5-(trimethylsilylethylsulfonyl)-5,9,13-triazahexadec-1-yl]carbamate (1).** A stirred solution of **2** (358 mg, 0.80 mmol), **3** (493 mg, 0.96 mmol), diisopropylethylamine (0.2 mL, 1.20 mmol), and sodium iodide (187 mg, 1.22 mmol) in toluene (60 mL) was heated at 100 °C for 72 h. It was cooled to room temperature and filtered. The filtrate was washed with water once, and the water layer was extracted with dichloromethane twice. The organic layer was combined, dried over Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography (30:1 dichloromethane/methanol) to provide the polyamine **1** as a colorless oil (441 mg, 70%): IR ν_{max} ($CHCl_3$) 3440 (NH), 2100 (N_3), 1700 (C=O), 1370 (SO_2), 1160 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.81−5.70 (m, 1H), 5.15−5.06 (m, 2H), 4.55 (br.s, 1H), 3.31−3.23 (m, 4H), 3.21−3.13 (m, 6H), 3.10−3.08 (m, 2H), 3.06−3.01 (m, 2H), 2.83−2.77 (m, 2H), 2.37−2.30 (m, 4H), 1.87 (s, 6H), 1.85−1.80 (m, 2H), 1.75−1.62 (m, 4H), 1.58−1.42 (m, 4H), 1.39 (s, 9H), 0.97−0.91 (m, 2H), 0.00 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 157.96, 137.20 ($CH=CH_2$), 130.25, 130.00, 127.25, 119.37 ($CH_2=CH$), 90.51, 58.90, 55.38, 53.12, 52.95, 51.08, 49.84, 49.75, 48.30, 47.10, 30.39 (CH_3), 29.27, 28.97, 28.38, 23.62 (CH_3), 12.31, 0.00 (CH_3) ppm; ESIMS *m*/*z* 792.4 $[M + H]^+$.

General Procedure for the Acylation of Tetra-*N*-Protected Pentamines. A solution of *p*-methoxycinnamoyl chloride (1.1 equiv of polyamines) in absolute ethyl acetate (5 mL) was added dropwise over 5 min to a solution of polyamine (0.06−0.08 mmol) and Et_3N (1.5 equiv of polyamines) in absolute ethyl acetate (10 mL) at −10 °C. The reaction mixture was allowed to stir at −10 °C for 30 min and at room temperature for 16−18 h. It was filtered and then concentrated in vacuo. Flash chromatography of the residue (20:1−30:1 dichloromethane/methanol) provided acylpolyamines as a colorless oil.

2,2,2-Trichloro-*tert*-butyl *N*-{4-Allyl-*N*-(3-azidopropyl)-12-[3-(*p*-methoxyphenyl)prop-2-enoylamino]-8-(trimethylsilylethylsulfonyl)-4,8-diazadodec-1-yl}carbamate (12). Removal of BOC Group from 1 (11). A solution of **1** (50 mg, 0.06 mmol) in dichloromethane (3 mL) was added at once to a solution of trifluoroacetic acid (0.23 mL, 3.04 mmol) in dichloromethane (10 mL) under argon at room temperature. The reaction mixture was stirred for 40 min and then the solvent and the excess of trifluoroacetic acid were evaporated under reduced pressure. The residue was dissolved in dichloromethane, washed with saturated aqueous Na_2CO_3 once, dried over Na_2SO_4, and concentrated in vacuo, to lead to the primary amine **11** as a colorless oil (40 mg).

Acylation of 11 (12). According to the general procedure of the acylation, the reaction of **11** (40 mg) with *p*-methoxycinnamoyl chloride (13 mg, 0.07 mmol) and Et_3N (0.01 mL, 0.10 mmol) afforded the acylpolyamine **12** (37 mg, 70%): IR ν_{max} ($CHCl_3$) 3420 (NH), 2100 (N_3), 1730 (C=O), 1510 (C=O), 1375 (SO_2), 1175 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.57 (d, J = 15.59 Hz, 1H), 7.45 (d, J = 8.72 Hz, 2H), 6.88 (d, J = 8.76 Hz, 2H), 6.38−6.20 (m, 1H), 6.00−5.70 (m, 2H), 5.25−5.08 (m, 2H), 3.82 (s, 3H), 3.47−3.38 (m, 2H), 3.35−3.20 (m, 10H), 3.11−3.03 (m, 2H), 2.89−2.83 (m, 2H), 2.49−2.40 (m, 4H), 1.92 (s, 6H), 1.90−1.59 (m, 10H), 1.11−0.98 (m, 2H), 0.00 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.46 (C=O), 139.98 ($CH=CH_2$), 129.32, 114.26, 107.55, 55.36 (CH_3), 49.12, 46.56, 39.03, 26.12, 21.68 (CH_3), 10.36, 0.00 (CH_3) ppm; ESIMS *m*/*z* 852.5 $[M + H]^+$.

***tert*-Butyl *N*-{9-Allyl-16-azido-5-[3-(*p*-methoxyphenyl)-prop-2-enoyl]-13-(2,2,2-trichloro-*tert*-butoxycarbonyl)-5,9,13-triazahexadec-1-yl}carbamate (14). Removal of SES Group from 1 (13).** CsF (46 mg, 0.30 mmol) was added at once to the reaction flask filled with argon. A solution of **1** (60 mg, 0.08 mmol) in DMF (4 mL) was added dropwise at room temperature, and then it was heated to 95 °C. After 24

h, the reaction mixture was cooled to room temperature, and absolute methanol (4 mL) was added to stir for 1 h. The completion of the reaction was checked by TLC (10:1:0.1 dichloromethane/methanol/ 25% ammonia water). The solvent was evaporated under reduced pressure and in vacuo. Without further purification, the crude compound **13** (50 mg) was next acylated.

Acylation of 13 (14). According to the general procedure of the acylation, the reaction of the crude **13** (50 mg) with *p*-methoxycinnamoyl chloride (16 mg, 0.08 mmol) and Et_3N (0.02 mL, 0.14 mmol) afforded the acylpolyamine **14** (38 mg, 63%): IR ν_{max} ($CHCl_3$) 3440 (NH), 2100 (N_3), 1740 (C═O), 1510 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.66 (d, J = 15.30 Hz, 1H), 7.50−7.43 (m, 2H), 6.89 (d, J = 8.50 Hz, 2H), 6.80−6.53 (m, 1H), 5.88−5.79 (m, 1H), 5.21−5.12 (m, 2H), 4.65 (br s, 1H), 3.84 (s, 3H), 3.49−3.39 (m, 4H), 3.35−3.08 (m, 10H), 2.51−2.41 (m, 4H), 1.91 (s, 6H), 1.86−1.49 (m, 10H), 1.42 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 129.40, 114.25, 55.36 (CH_3), 49.11, 28.43 (CH_3), 21.66 (CH_3) ppm; ESIMS m/z 788.3 $[M + H]^+$.

***tert*-Butyl *N*-{16-Azido-9-[3-(*p*-methoxyphenyl)prop-2-enoyl]-13-(2,2,2-trichloro-*tert*-butoxycarbonyl)-5-(trimethylsilylethylsulfonyl)-5,9,13-triazahexadec-1-yl}carbamate (16). Removal of Allyl Group from 1 (15).** A well-degassed solution of **1** (50 mg, 0.06 mmol) in dichloromethane (5 mL) was added dropwise to the flask containing tetrakis(triphenylphosphine)palladium (2 mg, 0.002 mmol) and *N*,*N*′-dimethylbarbituric acid (34 mg, 0.22 mmol) under argon. The reaction mixture was stirred at 35 °C for 7 h. It was diluted with dichloromethane (20 mL), washed with saturated aqueous $NaHCO_3$ once, dried over Na_2SO_4, and concentrated in vacuo. After the flash column chromatography (30:1:0.1 dichloromethane/methanol/25% ammonia water), the polyamine **15** was obtained as a colorless oil (35 mg, 75%).

Acylation of 15 (16). According to the general procedure of the acylation, the reaction of **15** (35 mg) with *p*-methoxycinnamoyl chloride (11 mg, 0.06 mmol) and Et_3N (0.01 mL, 0.08 mmol) afforded the acylpolyamine **16** (40 mg, 70%): IR ν_{max} ($CHCl_3$) 3450 (NH), 2100 (N_3), 1705 (C═O), 1510 (C═O), 1370 (SO_2), 1240 (CO), 1160 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.66 (d, J = 15.27 Hz, 1H), 7.49 (d, J = 8.30 Hz, 2H), 6.90 (d, J = 8.60 Hz, 2H), 6.78−6.62 (m, 1H), 4.68 (br s, 1H), 3.83 (s, 3H), 3.51−3.41 (m, 4H), 3.38−3.09 (m, 12H), 2.90−2.82 (m, 2H), 1.91−1.41 (m, 25H), 1.02−0.97 (m, 2H), 0.00 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$): δ 129.52, 114.29, 55.38 (CH_3), 48.23, 28.44 (CH_3), 21.68 (CH_3), 10.32, 0.00 (CH_3) ppm; ESIMS m/z 934.5 $[M + Na]^+$.

***tert*-Butyl *N*-{9-Allyl-16-azido-13-[3-(*p*-methoxyphenyl)-prop-2-enoyl]-5-(trimethylsilylethylsulfonyl)-5,9,13-triazahexadec-1-yl}carbamate (18). Removal of TCBOC Group from 1 (17).** To a solution of **1** (48 mg, 0.06 mmol) in acetic acid (5 mL) was added activated Zn powder[21] (20 mg, 0.32 mmol) in portions over a period of 1 h. The reaction mixture was stirred at room temperature for 24 h. It was filtered, and the precipitate was washed thoroughly with dichloromethane. The filtrate was concentrated and the residue dissolved in diethyl ether. The organic layer was extracted with 10% aqueous NaOH, dried over Na_2SO_4, and concentrated in vacuo. The residue (45 mg) was checked by TLC (10:1:0.1 dichloromethane/methanol/25% ammonia water) and proceeded to the next step.

Acylation of 17 (18). According to the general procedure of the acylation, the reaction of the crude **17** (45 mg) with *p*-methoxycinnamoyl chloride (14 mg, 0.07 mmol) and Et_3N (0.01 mL, 0.10 mmol) afforded the acylated polyamine **18** (26 mg, 60%): IR ν_{max} ($CHCl_3$) 3440 (NH), 2100 (N_3), 1740 (C═O), 1510 (C═O), 1375 (SO_2), 1170 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.66 (d, J = 15.25 Hz, 1H), 7.51−7.45 (m, 2H), 6.90 (d, J = 8.76 Hz, 2H), 6.77 (d, J = 15.32 Hz, 1H), 5.89−5.79 (m, 1H), 5.21−5.10 (m, 2H), 4.92 (br s, 1H), 3.83 (s, 3H), 3.57−3.32 (m, 6H), 3.28−3.08 (m, 6H), 2.90−2.81 (m, 2H), 2.51−2.42 (m, 4H), 1.94−1.49 (m, 10H), 1.42 (s, 9H), 1.11−0.97 (m, 2H), 0.00 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 170.00 (C═O), 129.65, 114.37, 107.25, 55.00 (CH_3), 29.85, 28.32 (CH_3), 11.25, 0.00 (CH_3) ppm; ESIMS m/z 750.6 $[M + H]^+$.

***tert*-Butyl *N*-{9-Allyl-16-[3-(*p*-methoxyphenyl)prop-2-enoylamino]-13-(2,2,2-trichloro-*tert*-butoxycarbonyl)-5-(trimethylsilylethsulfonyl)-5,9,13-triazahexadec-1-yl}carbamate (20). Removal of Azido Group from 1 (19).** Triphenylphosphine (20 mg, 0.08 mmol) was added to a solution of **1** (50 mg, 0.06 mmol) and water (1 μL) in THF. The reaction mixture was stirred at room temperature for 72 h. It was filtered, concentrated in vacuo, and flash chromatographed (90:7:0.7 dichloromethane/methanol/25% ammonia water), to provide the primary amine **19** as a colorless oil (33 mg, 70%).

Acylation of 19 (20). According to the general procedure of the acylation, the reaction of **19** (33 mg, 0.04 mmol) with *p*-methoxycinnamoyl chloride (9 mg, 0.04 mmol) and Et_3N (8 μL, 0.06 mmol) afforded the acylated polyamine **20** (37 mg, 64%): IR ν_{max} ($CHCl_3$) 3440 (NH), 1700 (C═O), 1510 (C═O), 1370 (SO_2), 1170 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.71−7.64 (m, 1H), 7.49−7.44 (m, 2H), 6.89 (d, J = 8.77 Hz, 2H), 6.73 (br s, 1H), 6.34 (d, J = 15.63 Hz, 1H), 5.88−5.73 (m, 1H), 5.21−5.11 (m, 2H), 4.69 (br s, 1H), 3.82 (s, 3H), 3.41−3.30 (m, 4H), 3.28−3.02 (m, 10H), 2.89−2.81 (m, 2H), 2.50−2.40 (m, 4H), 1.94 (s, 6H), 1.82−1.49 (m, 10H), 1.43 (s, 9H), 1.02−0.98 (m, 2H), 0.00 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 172.51 (C═O), 134.14, 134.00, 133.87, 131.29, 130.54, 130.38, 116.18, 57.30 (CH_3), 53.11, 52.93, 49.80, 48.32, 30.40 (CH_3), 29.29, 28.40, 23.66 (CH_3), 12.31, 0.00 (CH_3) ppm; ESIMS m/z 926.6 $[M + H]^+$.

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Supporting Information Available: ^{13}C NMR spectra for three compounds (**1**, **2**, **20**) and ^1H NMR and mass spectral data for all of the compounds prepared (29 pages). This material is contained in libraries on microfiche, immediately follows this article in the microform version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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