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Facile Synthetic Route to Selectively Protected Spermidine Homologues

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Facile Synthetic Route to Selectively Protected Spermidine Homologues

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Abstract: Several selectively protected spermidine homologues were synthesized via cyanoethylation reaction of monoprotected diamines, subsequent protection of their secondary amino group, hydrolysis of nitrile to primary amide function, and final Hofmann degradation of amides to amines with the aid of iodosobenzene diacetate (PIDA). The protected spermidine homologues may be directly used in the synthesis of polyamine amides or may be further functionalized.

Keywords: Hofmann degradation, Michael addition, polyamines, protecting groups

Biogenic polyamines are widely distributed in a variety of biologically active compounds and play key roles in a number of biological processes. A few reviews on the chemistry and biological properties of polyamines and their conjugates, including synthetic approaches to polyamine chemistry, have been published over the past decade.[1,2] Although many efforts have also been made in the design of new methods for the synthesis of polyamines and their conjugates on the solid phase,[3–6] there is still need for the synthesis of orthogonally protected polyamines that may be subsequently used in the synthesis of polyamine amides. In continuation of our studies on

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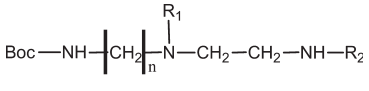
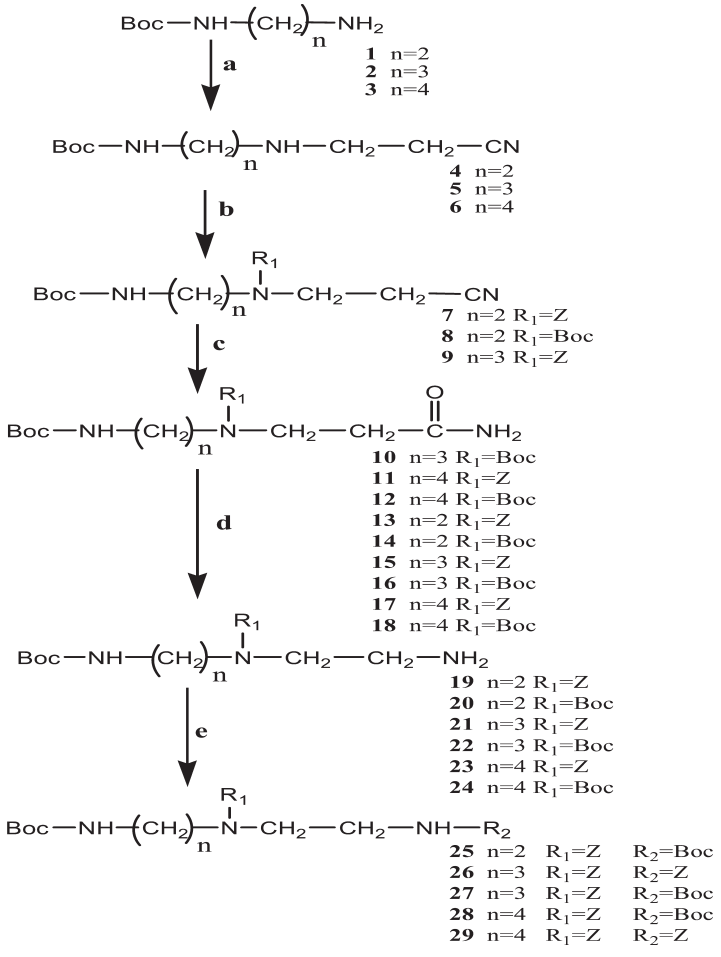
edeine antibiotic and their analogues with interesting immunomodulatory properties,[7,8] for further synthesis we needed not only a selectively protected novel amino acid[9] to be built into edeine analogues but also modified polyamine homologues. Therefore, we present here a convenient method for the preparation of a series of spermidine homologues, selectively protected at different amino groups, so that functional group manipulation may be performed at the other sites on polyamine molecule (Fig. 1). Therefore, application of the most popular amino protecting groups [i.e., *tert*-butoxycarbonyl (Boc) and benzyloxycarbonyl (Z)] allowed us to obtain selectively protected spermidine homologues in such a way that any of the amino group present in the spermidine homologue molecule may be used for amide linkage formation.

The Michael addition reaction of the mono Boc-protected 1,2-ethanediamine, 1,3-propanediamine, or 1,4-butanediamine to acrylonitrile in methanolic solution afforded cyanoetylamines **4**, **5**, and **6** in high yields (Scheme 1). Secondary amino function in these nitriles was protected with the use of benzyloxycarbonyl or *tert*-butoxycarbonyl protecting groups in a classical manner. Then, the protected nitriles **7**, **8**, and **9** were subjected to a hydrolysis reaction in a methanolic ammonia solution and hydrogen peroxide at room temperature for a prolonged time. Raising the temperature gave rise to undesired reaction products containing unmasked amino function. Thus, the obtained partially protected primary amides, **10**–**15**, underwent the Hofmann rearrangement with the use of iodosobenzene diacetate in a N,N-dimethylformamide (DMF)/water (1:1, v/v) solution in the presence of a catalytic amount of pyridine at 20°C. The rearrangement reaction proceeded in good yield, affording protected spermidine homologues **16**–**21** in good yield. Then the partially protected triamine derivatives were further reacted with benzyloxycarbonyl chloride/di-*tert*-butyl dicarbonate to obtain fully protected spermidine homologues **22**–**27** with differentially protected primary and secondary amino groups. Additionally, the orthogonally and fully protected spermidine homologues may be further functionalized after deprotection of their primary or secondary amino groups, thus forming the suitable protected synthetic synthons.



n= 2, 3, 4
R1= Z, R2 = Z
R1 = Z, R2= Boc
R1 = Boc or Z, R2 = H

Figure 1. Chemical structures of protected spermidine homologues.



Scheme 1.

EXPERIMENTAL

Melting points were measured on a Boetius heating block and are uncorrected. ^{1}H NMR spectra were recorded at 200 MHz with a Gemini Varian spectrometer. Elemental analyses were performed on a Carlo Erba CHNS-O-EA 1108 analyzer. All reagents and solvents were of reagent grade. Thin-layer chromatography (TLC) was performed on silica-gel 60 precoated plates. Spots were visualized with ninhydrin or cerium reagents.

Mono-protected polyamines (i.e., Boc-1,2-ethanediamine, Boc-1,3-propanediamine, and Boc-1,4-butanediamine) were synthesized following the reported procedures.[10] Aminonitriles **4**–**6** and protected aminonitriles **9** and **11** were prepared as previously described.[11]

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General Procedure for the Preparation of Fully Protected Aminonitriles

Partially protected aminonitile with a free secondary amino group (50 mmol) and triethylamine (50 mmol, 7 mL) were dissolved in THF (100 mL) and cooled to 5°C. Then, benzyl chloroformate (50 mmol) was added over 30 min with vigorous stirring. The reaction was kept overnight at room temperature. The solvent was evaporated; the residue was dissolved in water and extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with 1 M $KHSO_4$ and water, dried over $MgSO_4$, and evaporated to give the protected aminonitrile. In the case of Boc protection, aminonitrile (50 mmol) was dissolved in THF (100 mL), and di-tert-butyl dicarbonate (50 mmol) was adedd with stirring over 15 min at room temperature. The reaction was kept at room temperature overnight and evaporated; the residue extracted with ethyl acetate and evaporated to dryness to yield the final, fully protected compound.

Data

Benzyl 2-cyanoethyl-{2-[(*tert*-butoxycarbonyl)amino]ethyl}carbamate (7). Yield: 88%. ^{1}H NMR ($CDCl_3$): $\delta = 1.45$ [s, 9H, $C(CH_3)_3$], 2.6 (m, 2H, CH_2-CN), 3.25 (m, 2H, NH-CH_2), 3.45 (t, 2H, CH_2-N, $J = 6.8$ Hz), 3.55 (t, 2H, N-CH_2, $J = 6.8$ Hz), 5.5 (s, 2H, Ph-CH_2-O), 5.6 (br. signal, 1H, CO-N*H*), 7.35 (m, 5H, *Ph*, CH_2-O). Anal. calcd. for $C_{18}H_{25}N_3O_4$ (347.41): C, 62.23; H, 7.25; N, 12.10. Found: C, 62.15; H, 7.12; N, 12.33.

***tert*-Butyl 2-cyanoethyl-{2-[(*tert*-butoxycarbonyl)amino]ethyl}carbamate (8).** Yield: 56%. Mp 70–71°C. ^{1}H NMR ($CDCl_3$): $\delta = 1.45$–1.50 [s, 18H, $2C(CH_3)_3$], 2.65 (m, 2H, CH_2-CN), 3.25 (m, 2H, NH-CH_2), 3.4 (t, 2H, CH_2-N, $J = 7.5$ Hz), 3.5 (t, 2H, N-CH_2, $J = 7.5$ Hz), 5.6 (br. signal, 1H, CO-N*H*). Anal. calcd. for $C_{15}H_{27}N_3O_4$ (313.39): C, 57.49; H, 8.68; N, 13.41. Found: C, 57.22; H, 8.45; N, 13.22.

***tert*-Butyl 2-cyanoethyl-{3-[(*tert*-butoxycarbonyl)amino]propyl}carbamate (10).** Yield: 64%. ^{1}H NMR ($CDCl_3$): $\delta = 1.45$-1.50 [s, 18H, $2C(CH_3)_3$], 1.7 (m, 2H, CH_2-CH_2-CH_2), 2.6 (m, 2H, CH_2-CN), 3.15 (m, 2H, NH-CH_2), 3.35 (t, 2H, CH_2-N, $J = 7.5$ Hz)), 3.5 (t, 2H, N-CH_2, $J = 7.5$ Hz), 5.5 (br. signal, 1H, CO-N*H*). Anal. calcd. for $C_{16}H_{29}N_3O_4$ (327.42): C, 58.69; H, 8.93; N, 12.83. Found: C, 58.42; H, 8.67; N, 12.78.

***tert*-Butyl 2-cyanoethyl-{4-[(*tert*-butoxycarbonyl)amino]butyl}carbamate (12).** Yield: 75%. ^{1}H NMR ($CDCl_3$): $\delta = 1.45$–1.50 [s, 18H, $2C(CH_3)_3$], 1.7 (m, 2H, CH_2-CH_2-CH_2-CH_2), 2.6 (m, 2H, CH_2-CN), 3.15 (m, 2H, NH-CH_2), 3.3 (t, 2H, CH_2-N, $J = 7.1$ Hz), 3.45 (t, 2H, N-CH_2, $J = 7.1$ Hz), 5.5

(br. signal, 1H, CO-N*H*). Anal. calcd. for $C_{17}H_{31}N_3O_4$ (341.44): C, 59.80; H, 9.15; N, 12.31. Found: C, 59.68; H, 9.05; N,12.21.

General Procedure for the Preparation of Primary Amides from Aminonitriles

To a stirred solution of protected aminonitrile (10 mmmol) in 25% methanolic ammonia (40 mL) and 25% aqueous ammonia (40 mL), 50% hydrogen peroxide (2 mL) was added and the reaction mixture was left at room temperature for 48 h. The solvents were evaporated to yield crude yellow oil. Column chromatography on silica gel and elution with $CHCl_3$–acetone (2/1, v/v) afforded amide as an oil.

Data

3-{Benzyloxycarbonyl-[2-(*tert*-butoxycarbonylamino)ethyl]amino} propionamide (13). Yield: 76%. ^{1}H NMR ($CDCl_3$): $\delta = 1.4$ [s, 9H, $2C(CH_3)_3$], 2.5 (m, 2H, CH_2-C*H*$_2$-CO), 3.25 (m, 2H, CH_2-C*H*$_2$-N), 3.4 (m, 2H, N-C*H*$_2$-CH_2), 3.6 (m, 2H, N-C*H*$_2$-CH_2), 4.8 (br. signal, 1H, CO-N*H*-CH_2), 5.1 (s, 2H, Ph-C*H*$_2$-O), 5.6 and 6.1 (br. signals, 2H, CO-N*H*$_2$), 7.35 (m, 5H, *Ph*,CH_2-O). Anal. calcd. for $C_{18}H_{27}N_3O_5$ (365.42): C, 59.16; H, 7.45; N, 11.50. Found: C, 58.85; H, 7.41; N, 11.42.

3-{*tert*-Butoxycarbonyl-[2-(*tert*-butoxycarbonylamino)ethyl]amino}propionamide (14). Yield: 88%.%. ^{1}H NMR ($CDCl_3$): $\delta = 1.4$ [s, 18H, $2C(CH_3)_3$], 2.5 (m, 2H, CH_2-C*H*$_2$-CO), 3.20 (m, 2H, C*H*$_2$-CH_2-N), 3.35 (m, 2H, NH-CH_2-C*H*$_2$), 3.55 (m, 2H, N-C*H*$_2$-CH_2), 4.6 (br. signal, 1H, CO-N*H*-CH_2), 5.6 and 6.25 (br. signals, 2H, CO-N*H*$_2$). Anal. calcd. for $C_{15}H_{29}N_3O_5$ (331.41): C, 54.36; H, 8.82; N, 12.68. Found: C, 54.23; H, 8.76; N, 12.55.

3-{Benzyloxycarbonyl-[3-(*tert*-butoxycarbonylamino)propyl]amino}propionamide (15). Yield: 54%. ^{1}H NMR ($CDCl_3$): $\delta = 1.4$ [s, 18H, $2C(CH_3)_3$], 1.7 (m, 2H, CH_2-C*H*$_2$-CH_2), 2.5 (m, 2H, CH_2-C*H*$_2$-CO), 3.0 (m, 2H, NH-C*H*$_2$-CH_2), 3.3 (m, 2H, CH_2-C*H*$_2$-N), 3.55 (m, 2H, N-C*H*$_2$-CH_2), 4.6 (br. signal, 1H, CO-N*H*-CH_2), 5.1 (s, 2H, Ph-C*H*$_2$-O), 5.6 and 6.25 (br. signals, 2H, CO-N*H*$_2$), 7.35 (m, 5H, *Ph*, CH_2-O). Anal. calcd. for $C_{19}H_{29}N_3O_5$ (379.45): C, 60.14; H, 7.70; N, 11.07. Found: C, 60.02; H, 7.65; N, 10.95.

3-{*tert*-Butoxycarbonyl-[3-(*tert*-butoxycarbonylamino)propyl]amino}propionamide (16). Yield: 53%. ^{1}H NMR ($CDCl_3$): $\delta = 1.4$ [s, 18H, $2C(CH_3)_3$], 1.7 (m, 2H, CH_2-C*H*$_2$-CH_2), 2.5 (m, 2H, CH_2-C*H*$_2$-CO), 3.0 (m, 2H, NH-C*H*$_2$-CH_2), 3.3 (m, 2H, CH_2-C*H*$_2$-N), 3.55 (m, 2H, N-C*H*$_2$-CH_2), 4.6 (br. signal, 1H, CO-N*H*-CH_2), 5.6 and 6.25 (br. signals, 2H, CO-N*H*$_2$). Anal. calcd. for $C_{16}H_{31}N_3O_5$ (345.43): C, 55.63; H, 9.05; N, 12.16. Found: C, 55.51; H, 8.97; N, 12.04.

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3-{Benzyloxycarbonyl-[4-(*tert*-butoxycarbonylamino)butyl]amino}propionamide (17). Yield: 93%.^{1}H NMR ($CDCl_3$): $\delta = 1.4$ [s, 9H, $C(CH_3)_3$], 1.5–1.7 (m, 4H, CH_2-C*H*$_2$-C*H*$_2$-CH_2), 2.5 (m, 2H, CH_2-C*H*$_2$-CO), 3.0 (m, 2H, NH-C*H*$_2$-CH_2), 3.3 (m, 2H, CH_2-C*H*$_2$-N), 3.55 (m,2H, N-C*H*$_2$-CH_2), 4.7 (br. signal, 1H, CO-N*H*-CH_2), 5.1 (s, 2H, Ph-CH_2-O), 5.8 and 6.6 (br. signals, 2H, CO-N*H*$_2$), 7.35 (m, 5H, *Ph*,CH_2-O). Anal. calcd. for $C_{20}H_{31}N_3O_5$ (393.47): C, 61.05; H, 7.94; N, 10.68. Found: C, 61.06; H, 7.85; N, 10.47.

3-{*tert*-Butoxycarbonyl-[4-(*tert*-butoxycarbonylamino)butyl]amino}propionamide (18). Yield: 95%. ^{1}H NMR ($CDCl_3$): $\delta = 1.4$ [s, 18H, $2C(CH_3)_3$], 1.5–1.8 (m, 4H, CH_2-C*H*$_2$-C*H*$_2$-CH_2), 2.5 (m, 2H, CH_2-CH_2-CO), 3.05 (m,2H, NH-C*H*$_2$-CH_2), 3.3 (m, 2H, CH_2-C*H*$_2$-N), 3.55 (m, 2H, N-C*H*$_2$-CH_2), 4.7 (br. signal, 1H, CO-N*H*-CH_2), 5.9 and 6.65 (br. signals, 2H, CO-N*H*$_2$). Anal. calcd. for $C_{17}H_{33}N_3O_5$ (359.46): C, 56.80; H, 9.25; N, 11.68. Found: C, 56.68; H, 9.12; N, 11.55.

General Procedure for the Preparation of Amines from Primary Amides

A solution of primary amide (5 mmol), DMF (10 mL), water (10 mL), and iodosobenzene diacetate (7.5 mmol) was stirred at temperature colder than 20°C. After 15 min, pyridine (0.2 mL) was added and stirring was continued overnight. Then, the solvents were evaporated, the residue was dissolved in a cold solution of 1 M $KHSO_4$. The aqueous solution was extracted with ethyl acetate, the organic extracts were discarded, and the aqueous layer was alkalized with 4 M NaOH solution. The alkaline solution was extracted with ethyl ether; the organic layer was washed with brine, dried over $MgSO_4$, and evaporated to yield the protected spermidine homologues.

Data

N-Benzyloxycarbonyl-N-[2-(*tert*-butoxycarbonylaminoethyl)-ethane-1,2-diamine (19). Yield: 64%. Colorless oil. ^{1}H NMR ($CDCl_3$): $\delta = 1.4$ [s, 9H, $C(CH_3)_3$], 1.6–1.7 (m, 2H, CH_2-C*H*$_2$-CH_2), 1.9–2.0 (br. signal, 2H, NH_2), 2.85 (m,2H, CH_2-C*H*$_2$-NH_2), 3.35 (m, 6H, HN-C*H*$_2$-C*H*$_2$-N-C*H*$_2$-CH_2), 5.1 (s, 2H, Ph-C*H*$_2$), 5.2 (br. signal, 1H, CO-N*H*-CH_2), 7.35 (m, 5H, *Ph*-CH_2). Anal. calcd. for $C_{17}H_{27}N_3O_4$ (337.41): C, 60.52; H, 8.07; N, 12.45. Found: C, 60.33; H, 7.82; N, 12.21.

N-*tert*-Butoxycarbonyl-N-[2-(*tert*-butoxycarbonylaminoethyl)-ethane-1,2-diamine (20). Yield: 67%. Colorless oil. ^{1}H NMR ($CDCl_3$): $\delta = 1.4$ [s, 18H, $2C(CH_3)_3$], 2.0 (m, 2H, NH_2), 2.85 (m, 2H, CH_2-C*H*$_2$-NH_2), 3.3 (m, 6H, HN-C*H*$_2$-C*H*$_2$-N-C*H*$_2$-CH_2), 5.4 (br. signal, 1H, CO-N*H*-CH_2).

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Anal. calcd. for $C_{14}H_{29}N_3O_4$ (303.40): C, 55.42; H, 9.63; N, 13.85. Found: C, 55.14; H, 9.47; N, 13.70.

N-(2-Aminoethyl)-N-benzyloxycarbonyl-N′-tert-butoxycarbonyl-propane-1,3-diamine (21). Yield: 64%. Yellowish oil. ^{1}H NMR ($CDCl_3$): $\delta = 1.45$ [s, 9H, $C(CH_3)_3$], 1.6–1.7 (m, 2H, CH_2-C*H*$_2$-CH_2), 1.9–2.0 (m, 2H, NH_2), 2.8–3.1 (br. signal, 4H, CH_2-C*H*$_2$-NH_2 and HN-C*H*$_2$-CH_2), 3.2–3.5 (m, 4H, CH_2-C*H*$_2$-N-C*H*$_2$-CH_2),5.1(s,2H, Ph-C*H*$_2$), 5.2 (br. signal, 1H, CO-N*H*-CH_2), 7.359 m, 5H, *Ph*-CH_2). Anal. calcd. for $C_{18}H_{29}N_3O_4$ (351.44): C, 61.52; H, 8.32; N, 11.96. Found: C, 61.46; H, 8.06; N, 11.55.

N-(2-Aminoethyl)-N,N′-bis-tert-butoxycarbonyl-propane-1,3-diamine (22). Yield: 70%. Colorless oil. ^{1}H NMR ($CDCl_3$): $\delta = 1.45$ [s, 18H, $2C(CH_3)_3$], 1.6–1.7 (q, 2H, CH_2-C*H*$_2$-CH_2), 1.9 (m, 2H, NH_2), 2.8 (m, 2H, CH_2-C*H*$_2$-NH_2), 3.1 (q, 2H, HN-C*H*$_2$-CH_2),3.25 (m, 4H, CH_2-C*H*$_2$-N-C*H*$_2$), 4.95 (br. signal, 1H, CO-N*H*-CH_2). Anal. calcd. for $C_{15}H_{31}N_3O_4$ (317.42): C, 56.76; H, 9.84; N, 13.24; Found: C, 56.47; H, 9.72; N, 13.34.

N-(2-Aminoethyl)-N-benzyloxycarbonyl-N′-tert-butoxycarbonyl-butane-1,4-diamine (23). Yield: 57%. Light yellow oil. ^{1} H NMR ($CDCl_3$): $\delta = 1.4$ [s, 9H, $C(CH_3)_3$], 1.55–1.7 (br. signal, 6H, CH_2-C*H*$_2$-C*H*$_2$-CH_2 and CH_2-N*H*$_2$), 2.9–3.0 (m, 2H, CH_2-C*H*$_2$-NH_2)3.1 (m, 2H, HN-C*H*$_2$-CH_2), 3.3 (m, 4H, CH_2-C*H*$_2$-N-CH_2), 4.6 (br. signal, 1H, CO-N*H*-CH_2), 5.1 (s, 2H, Ph-C*H*$_2$), 7.35 (m, 5H, *Ph*-CH_2). Anal. calcd. for $C_{19}H_{31}N_3O_4$ (365.46): C, 62.44; H, 8.55; N, 11.50. Found: C, 62.05; H, 8.20; N, 11.29.

N-(2-Aminoethyl)-N,N′-bis-tert-butoxycarbonyl-butane-1,4-diamine (24). Yield: 73%. Colorless oil. ^{1}H NMR ($CDCl_3$): $\delta = 1.4$ [s, 18H, $2C(CH_3)_3$], 1.5–1.7 (m, 4H, CH_2-C*H*$_2$-C*H*$_2$-CH_2), 1.9 (br. signal, 2H, NH_2), 2.9 (m, 2H, CH_2-C*H*$_2$-NH_2), 3.1 (m, 2H, HN-C*H*$_2$-CH_2),3.25 (m, 2H, CH_2-CH_2-N-C*H*$_2$), 3.35 (m, 2H, CH_2-C*H*$_2$-N-CH_2), 4.85 (br. signal, 1H, CO-N*H*-CH_2). Anal. calcd. for $C_{16}H_{33}N_3O_4$ (331.4): C, 56.98; H, 10.04; N, 12.68. Found: C, 56.69; H, 10.12; N, 12.39.

General Procedure for the Protection of Spermidine Homologues

A solution of benzyloxycarbonyl chloride (0.34 g, 2 mmol) was added to a cooled solution of protected spermidine homologues **19**, **21**, and **23** (2 mmol) with a free primary amino group and Et_3N (0.35 mL, 2.5 mmol) in THF (20 mL) and stirred overnight. The solvent was evaporated, water was added, and the residue was extracted with EtOAc (3 × 20 mL). The organic phase was dried over $MgSO_4$ and evporated to give the crude product which was chromatographed on silica gel and eluted with $CHCl_3$–acetone (10:1, v/v) to yield the desired product. In the case of Boc protection, spermidine homologues **20**

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and **24** were dissolved in THF (20 mL), and di-tert-butyl dicarbonate (2 mmol) was added with stirring over 15 min at room temperature. The reaction was kept at room temperature overnight and evaporated. The residue was extracted with ethyl acetate and evaporated to dryness to yield the crude product, which was chromatographed on silica gel and eluted with $CHCl_3$–acetone (10:1, v/v) to yield the desired fully protected compound.

Data

***tert*-Butyl {2-[benzyloxycarbonyl-(2-*tert*-butoxycarbonylaminoethyl)-amino]-ethyl}-carbamate (25).** Yield: 79%. Mp 111–112°C. ^{1}H NMR ($CDCl_3$): $\delta = 1.4$ [s, 18H, $2C(CH_3)_3$], 3.25 (m, 4H, CH_2-CH_2-N-CH_2), 3.45 (m, 4H, NH-CH_2-CH_2 and CH_2-CH_2-NH), 4.8 (br. signal, 1H, CO-N*H*-CH_2), 5.0 (br. signal, CH_2-N*H*-CO), 5.1 (s, 2H, Ph-C*H*$_2$), 7.35 (m, 5H, *Ph*-CH_2). Anal. calcd. for $C_{22}H_{35}N_3O_6$ (437.53): C, 60.39; H, 8.06; N, 9.60. Found: C, 60.36; H, 7.98; N, 9.51.

***tert*-Butyl {3-[benzyloxycarbonyl-(2-benzyloxycarbonylaminoethyl)-amino]-propyl}-car-bamate (26).** Yield: 80%. Oil. ^{1}H NMR ($CDCl_3$): $\delta = 1.4$ [s, 9H, $C(CH_3)_3$], 1.7 (m, 2H, CH_2-C*H*$_2$-CH_2), 3.1 (m, 2H, CH_2-C*H*$_2$-NH), 3.35 (m, 6H, HN-C*H*$_2$-C*H*$_2$-N-C*H*$_2$-CH_2), 4.6 (br. signal, 1H, -CH_2-CH_2-N*H*-CO), 5.1 (s, 2H, Ph-C*H*$_2$), 5.2(s, 2H, Ph-C*H*$_2$), 7.3–7.5 (br. signal, 10H, 2 × *Ph*-CH_2). Anal. calcd. for $C_{26}H_{35}N_3O_6$ (485.57): C, 64.31; H, 7.27; N, 8.65. Found: C, 64.22; H, 7.09; N, 8.82.

***tert*-Butyl {3-[benzyloxycarbonyl-(2-*tert*-butoxycarbonylaminoethyl)-amino]-propyl}-carbamate (27).** Yield: 78%. Colorless oil. ^{1}H NMR ($CDCl_3$): $\delta = 1.4$ [s, 18H, $2C(CH_3)_3$], 1.7 (m,2H, CH_2-C*H*$_2$-CH_2), 3.1 (m, 2H, CH_2-C*H*$_2$-N), 3.3 (m, 6H, C*H*$_2$-C*H*$_2$-NH-C*H*$_2$), 4.6 (br. signal, 1H, CH_2-CH_2-N*H*-CO), 5.0 (br. signal, 1H, CO-N*H*-CH_2), 5.1 (m, 2H, O-C*H*$_2$-Ph),7.35(m, 5H, *Ph*-CH_2). Anal. calcd. for $C_{23}H_{37}N_3O_6$ (451.56): C, 61.18; H, 8.26; N, 9.31. Found: C, 60.89; H, 8.12; N, 9.22.

***tert*-Butyl {4-[benzyloxycarbonyl-(2-*tert*-butoxycarbonylaminoethyl)-amino]-butyl}-car-bamate (28).** Yield: 62%. Oil. ^{1}H NMR ($CDCl_3$): $\delta = 1.4$ [s, 18H, $2C(CH_3)_3$], 1.55 (m, 4H, CH_2-C*H*$_2$-C*H*$_2$-CH_2), 3.1(m, 2H, NH-C*H*$_2$-CH_2),3.35(m, 6H, CH_2-C*H*$_2$-N-C*H*$_2$-CH_2-NH), 4.6 (br. signal, 1H, CH_2-N*H*-CO), 4.95 (br. signal, 1H, CO-N*H*-CH_2), 5.1 (s, 2H, O-C*H*$_2$-Ph), 7.35 (m, 5H, *Ph*-CH_2). Anal. calcd. for $C_{24}H_{39}N_3O_6$ (465.58): C, 61.91; H, 8.44; N, 9.03. Found: C, 61.75; H, 8.22; N, 8.82.

Benzyl {4-[benzyloxycarbonyl-(2-benzyloxycarbonylaminoethy)-amino]-butyl}-carbamate (29). Yield: 65%. Mp 85–86°C. ^{1}H NMR ($CDCl_3$): $\delta = 1.45$ [s, 9H, $C(CH_3)_3$], 1.6 (m, 4H, CH_2-C*H*$_2$-C*H*$_2$-CH_2), 3.1 (m, 2H,

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CH_2-CH_2-NH), 3.25 (m, 2H, HN-CH_2-CH_2), 3.4 (m, 4H, CH_2-CH_2-N-CH_2), 4.5 (br. signal, 1H, CO-NH-CH_2), 4.9 (br. signal, 1H, CH_2-NH-CO), 5.1 (m, 2H, Ph-CH_2), 7.3–7.5 (br. signal, 10H, 2 × *Ph*-CH_2). Anal. calcd. for $C_{27}H_{37}N_3O_6$ (499.6): C, 64.91; H, 7.46; N, 8.41. Found: C, 64.67; H, 7.47; N, 8.36.

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