Synthesis of Novel Nucleo-β-Amino Acids and Nucleobase-Functionalized β-Peptides

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Four novel β-amino acids bearing the canonical nucleobases guanine, cytosine, adenine, and thymine in the side chain, are synthesized starting from Boc-L-aspartic acid 4-benzyl ester. The syntheses are accomplished in six steps by the nucleophilic substitution of (*S*)-β-(*tert*-butoxycarbonylamino)-δ-bromopentanoic acid benzyl ester with the corresponding nucleobase derivative as the key step. The guaninyl and cytosinyl β-amino acids were built into β-peptides that were studied by temperature-dependent CD and UV spectroscopy.

Introduction

There is a growing interest in β-amino acids as building blocks for natural products and pharmaceutical agents.[1] Furthermore, oligomers composed of β-amino acids (β-peptides) are an attractive class of compounds for drug design: oligomers (''foldamers'') with low molecular weights fold into well-ordered secondary structures (helix, sheet, and turn)[2] and show a remarkable stability towards enzymatic degradation.[3] The proper choice of β-amino acid side-chains leads to β-peptides with interesting biological properties.[4] Side-chain functionalities can be introduced, for example, to fine-tune solubility[5] and lipophilicity[6] or to promote secondary structure stability.[7]

β-Peptides with proteinogenic and cyclic nonproteinogenic side chains usually fold into helical or sheet-like secondary structures. The incorporation of nucleobases into the side chains enables β-peptide structures to be influenced through base pairing and aromatic π-interactions. Recently, oligomers have been reported that are composed of six nucleo-β^3-amino acid building blocks,[8] like β-amino acid **1**, in which the nucleobases are connected to β-homoalanine at the γ-position (Figure 1).[9] It was shown that these β-homoalanyl peptide nucleic acids (β-homoalanyl PNA) form stable pairing complexes with a β-sheet-like backbone conformation in aqueous media.[9]

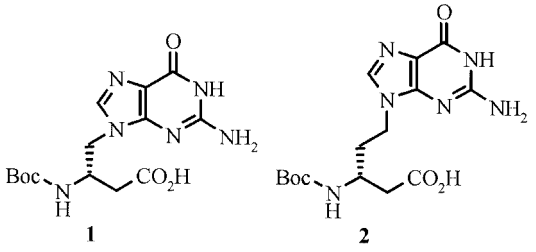

Figure 1. Structures of nucleo-β^3-amino acids **1** and **2**

Here, we report the first step towards an analogous organization of β-peptide helices through nucleobase pairing. The syntheses of novel protected nucleo-β^3-amino acids like **2** with an ethylene linker between the nucleobase and the β-amino acid backbone is described. The length of the linker was chosen to minimize the nucleobase-peptide backbone interactions and to allow specific nucleobase interactions. Finally, the β-amino acid monomers were incorporated into β-peptides by solid-phase peptide synthesis, and first structural investigations were performed with these oligomers.

Results and Discussion

Several methods for the stereoselective preparation of β-amino acids have been published.[10] However, many methods are not transferable to the preparation of nucleo-β-am-

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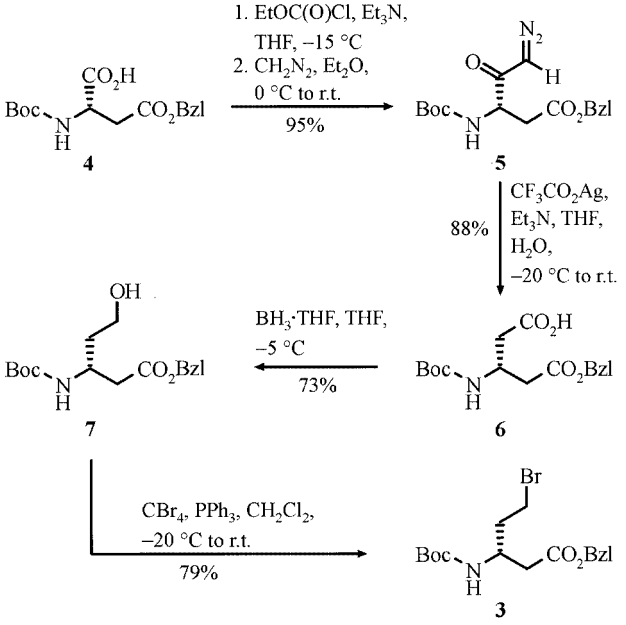
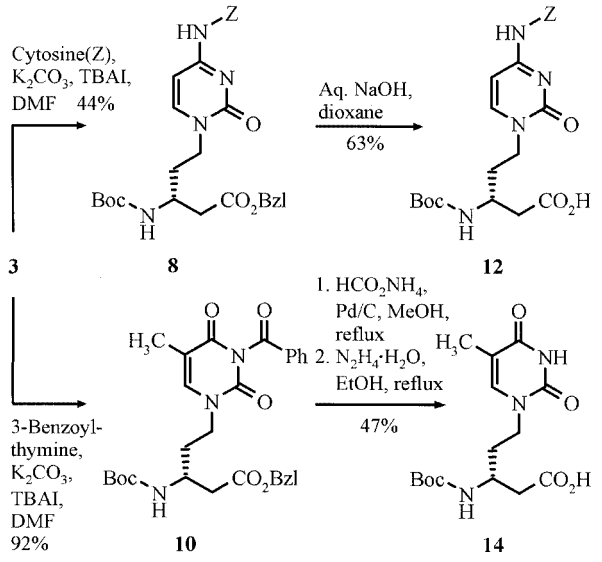
ino acids because of the competition of N^9/N^7 purine or N^1/N^3 pyrimidine regioisomer formation, the low nucleophilicity of the nucleobases and their poor solubility in common organic solvents. In addition, the Arndt−Eistert homologation of aromatic α-amino acids is expected to proceed with racemization.[11]

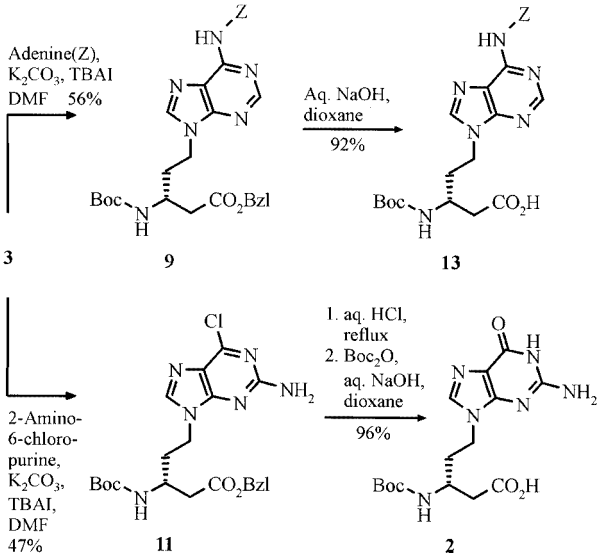
Hence, we decided to link the nucleobase or its precursor to the desired β-amino acid moiety. The linkage of the nucleobases to the amino acid side-chain is usually accomplished by nucleophilic substitution of a halide or alkylsulfonate or — under milder conditions — by employing a Mitsunobu reaction. Since the latter strategy often requires laborious chromatography bromide **3** was used as the key intermediate for the alkylation of all nucleobase precursors. This compound was synthesized from commercially available Boc-L-aspartic acid 4-benzyl ester (**4**; Scheme 1). First, the amino-acid backbone was extended by one carbon atom through an Arndt−Eistert homologation. This involved the preparation of the diazo ketone **5** as described by Seebach et al.[12] and its Wolff rearrangement, according to a literature procedure,[13] to give carboxylic acid **6**. Reduction with borane in THF yielded alcohol **7**, which was then converted into the desired bromide **3** by treatment with PPh_3/CBr_4. Bromide **3** was reacted with 1.5−3.3 equivalents of the nucleobase or its precursor at room temperature in DMF in the presence of K_2CO_3 and tetrabutylammonium iodide (TBAI) to give the products **8**−**11** in 44−92% yield (Schemes 2 and 3). The yields correspond with the range of solubility and reactivity of the nucleobase moieties. For example, 3-benzoyl-protected thymine[14] is much more soluble in polar aprotic solvents and possesses a higher reactivity towards alkylation than the moderately soluble N^4-(benzyloxycarbonyl)cytosine [cytosine(Z)].[15] The benzoyl protecting group in the N^3-position of thymine excludes N^3-alkylation and improves the solubility. Z-protected cytosine and adenine[15b] were used to prevent chain extension at the exocyclic amino groups during later β-peptide synthesis. 2-Amino-6-chloropurine, a synthon for guanine,[16] gave almost exclusively the N^9-alkylated regioisomer. It is noteworthy that all alkylations with bromide **3** proceeded much more cleanly than those carried out for the preparation of nucleo-β^3-amino acids of type **1**.[9] BocHNCH-(CH_2CH_2Br)CH_2CO_2Bzl (**3**) with a two-carbon linker is quite stable under the conditions of nucleophilic substitution, whereas BocHNCH(CH_2X)CH_2CO_2Bzl (X = Br, OH, OMs) with a shorter side chain showed a tendency to decompose by formation of aziridines or 2-oxazolidones under the conditions of Mitsunobu-type reactions (X = OH) or nucleophilic substitutions (X = Br, OMs), respectively.[17]



Scheme 1. Preparation of bromide **3** starting from Boc-L-aspartic acid 4-benzyl ester (**4**); for preparation of diazo ketone **5** see ref.[12]



Scheme 2. Synthesis of the pyrimidinyl-nucleo-β^3-amino acids **12** and **14** from bromide **3**



Scheme 3. Synthesis of the purinyl-nucleo-β^3-amino acids **13** and **2** from bromide **3**

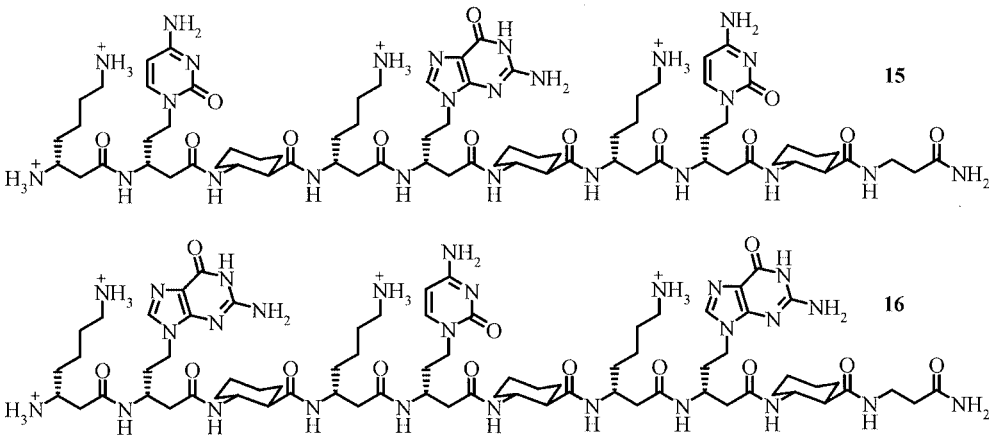


Figure 2. Complementary oligomers **15** and **16** prepared by solid-phase peptide synthesis (SPPS)

Finally, the free nucleo-β^3-amino acids **12** and **13** with cytosine(Z) and adenine(Z) in the side chains were obtained by saponification of the benzyl esters **8** and **9** with aqueous NaOH. The thyminyl-β^3-amino acid benzyl ester **10** was saponified by catalytic hydrogenation on Pd/C, and the N^3-atom was deprotected by treatment with N_2H_4 in ethanol. The guaninyl-β^3-amino acid **2** was afforded in excellent yield by treating **11** with refluxing HCl, followed by protection with Boc_2O.

The oligomers H-(β-HLys-ApaC-ACHC-β-HLys-ApaG-ACHC-β-HLys-ApaC-ACHC-β-HGly)-NH_2 (**15**) and H-(β-HLys-ApaG-ACHC-β-HLys-ApaC-ACHC-β-HLys-ApaG-ACHC-β-HGly)-NH_2 (**16**, Figure 2) were designed in order to explore self-assembly of β-peptides containing nucleo-β^3-amino acid residues.[18] (*R*)-β-Amino-δ-(guanin-9-yl)pentanoic acid (ApaG) and (*R*)-β-amino-δ-(cytosin-1-yl)pentanoic acid (ApaC) were chosen as base-pair recognition units because they should prefer the formation of very stable triply hydrogen bonded guanine-cytosine Watson−Crick base pairs, whereas a doubly hydrogen bonded adenine-thymine base pair is expected to lead to less-stable pairing complexes. ApaG and ApaC were incorporated into a β-peptide scaffold comprised of (1*R*,2*R*)-2-aminocyclohexanecarboxylic acid (ACHC) and β-(*R*)-homolysine (H-β-HLys-OH).[19] β-Peptides built from ACHC and β-HLys have been shown to adopt a 14-helical conformation in aqueous solution.[5a] The 14-helix has approximately three residues per turn; therefore, the spacing among nucleo-β^3-amino acid residues in oligomers **15** and **16** should lead to alignment of the bases along one side of the 14-helical conformations adopted by these oligomers.

Oligomers **15** and **16** were prepared by manual solid-phase peptide synthesis on a 4-methylbenzhydrylamine (MBHA) polystyrene resin loaded with β-homoglycine (H-β-HGly-OH). The Boc-strategy was chosen to prevent aggregation and deprotection problems that might result from secondary structure formation during the synthesis of longer oligomers, especially with Fmoc protection. All amino acids were coupled in DMF with HATU {1-[bis(dimethylamino)methyliumyl]-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-3-oxide hexafluorophosphate} and *N*,*N*-diisopropylethylamine for activation. Because of the sterically demanding ACHC and the expected limited accessibility of the terminal amino group in a compact helix each coupling step was performed twice at 50 °C to ensure chain elongation yields of at least 97%. After cleavage from the solid support with trifluoroacetic acid (TFA)/trifluoromethanesulfonic acid/*m*-cresol/thioanisole/ethanedithiol, 20:2:2:2:1, the oligomers were precipitated with diethyl ether, purified by HPLC, and characterized with electrospray ionization mass spectrometry (ESI-MS).

Temperature-dependent circular dichroism (CD) and UV spectroscopy were used for initial studies of the structural behavior of oligomers **15** and **16**. A positive Cotton effect around 215 nm in the CD spectra of β-peptides has often been correlated with the formation of a right-handed 14-helix.[2,5−7,13,20] The CD spectra of β-peptides **15** and **16** (data not shown) and of an equimolar mixture of both (Figure 3) in 10 mM aq. Na_2HPO_4/H_3PO_4 (pH, 7.0) show a maximum between 210 and 215 nm, which indicates the expected formation of a 14-helix. The Cotton effect at about 270 nm is probably due to a preferred conformational orientation of the nucleobases. Potential pairing of oligomer **15** with the complementary strand **16** was studied by

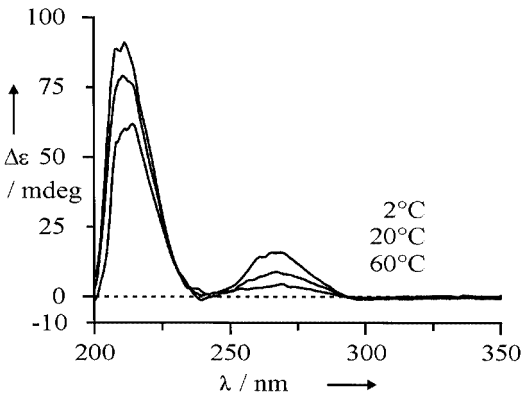


Figure 3. CD spectra of an equimolar mixture of oligomers **15** and **16** (10 μM each, 10 mM aq. Na_2HPO_4/H_3PO_4, pH 7.0)

temperature-dependent UV spectroscopy. As known from DNA chemistry the cooperative destacking of nucleobases due to separation of double strands can be observed as a sigmoidal increase of the absorption.[21] The self-pairing and the 1:1 pairing of β-peptides **15** and **16** were examined. In all three cases, the stabilities were too low (**15**: $T_m < 5$ °C, $A_{rel.} = 3\%$, 26 μM; **16**: $T_m < 5$ °C, $A_{rel.}$ 12%, 23 μM, data not shown; **15** +**16**: $T_m < 5$ °C, $A_{rel.}$ 4%, 10 μM each, Figure 4) to allow us to draw conclusions regarding pairing behavior. Preparation of longer oligomers is in progress.

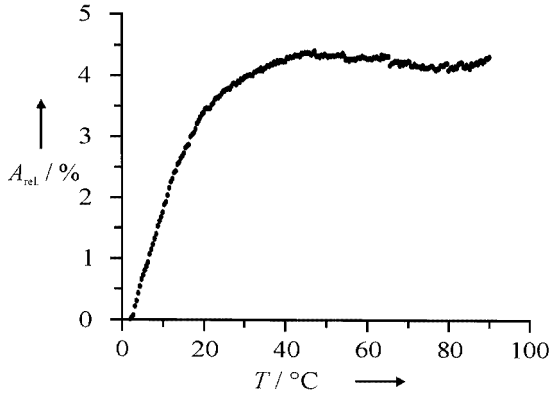


Figure 4. UV melting curve of an equimolar mixture of oligomers **15** and **16** (10 μM each, 10 mm aq. Na_2HPO_4/H_3PO_4, pH 7.0, 270 nm)

Conclusion

The synthesis of novel nucleo-β^3-amino acids with all four canonical nucleobases linked by an ethylene spacer to the β-amino acid backbone has been developed. These compounds should serve as versatile building blocks for PNA analogs, templates for 5′-methacryloylnucleoside polymerisation,[22] and biologically active agents. We incorporated these nucleo-β^3-amino acids into water-soluble β-peptides. Additional investigation of the criteria for specific association of β-peptide helices via nucleobase pairing is underway.

Experimental Section

General Remarks: All reagents were of analytical grade and used as supplied. For preparation of Boc-(*R*,*R*)-ACHC-OH see ref.[23] Boc-β-HLys(*Z*)-OH was prepared from Boc-(*R*)-Lys(*Z*)-OH by Arndt−Eistert homologation.[11,13,24] Boc-L-β-homoaspartic acid 5-benzyl ester (**6**) is available from Fluka. Solvents were of the highest grade available. Melting points were obtained with a Büchi 501 Dr. Tottoli apparatus or a Gallenkamp melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin−Elmer 241 polarimeter. IR spectra were recorded on a Perkin−Elmer 1600 Series FT-IR using KBr pellets or on a Avatar 320 FT-IR with a ′Golden Gate′ Attenuated Total Reflection (ATR) cell attachment. NMR spectra were recorded with Bruker AMX 300, Bruker AC 300, Bruker DPX 300, Varian Unity 300, or Varian Inova 500 instruments. Chemical shifts are referenced to the residual solvent peaks of $CDCl_3$ (^{1}H: δ = 7.24 ppm, ^{13}C: δ = 77.0 ppm), [D_6]DMSO (^{1}H: δ = 2.49 ppm, ^{13}C: δ = 39.5 ppm), or D_2O (^{1}H: δ = 4.77 ppm). The ^{13}C NMR spectra with D_2O as solvent is referenced to MeOH as an internal standard (δ = 49.9 ppm). Multiplicities of ^{13}C NMR peaks were determined with the APT pulse sequence. Mass spectra were recorded with a LCG Finnigan spectrometer or with a Micromass LCT spectrometer. High-resolution mass spectra were recorded with a Varian MAT 731 instrument. Elemental analysis was carried out on a Leco CHN2000 with Heraeus Micro U/D. HPLC of the oligomers was performed on a Pharmacia Äkta basic system with YMC J'sphere ODS-H80, RP-C18, 150 × 10 mm, 4 μm, 80 Å for preparation and 150 × 4.6 mm, 4 μm, 80 Å for analytical samples. The oligomer concentration was calculated by taking the extinction coefficient at 90 °C as being the sum of the extinction coefficients of the nucleo-β^3-amino acids. The CD spectra were recorded with JASCO J-500A Spectropolarimeter with a JASCO ETC-505S/PTC-423S temperature controller. The UV melting curves were measured with a JASCO V-550 UV/Vis Spectrophotometer with a JASCO ETC-505S/ETC-505T temperature controller.

(*R*)-β-(*tert*-Butoxycarbonylamino)-δ-(guanin-9-yl)pentanoic Acid (2): Benzyl ester **11** (1.83 g, 3.85 mmol) was suspended in 1 M aq. HCl (200 mL). The mixture was heated to reflux for 6 h and then evaporated to dryness under reduced pressure. An analytical sample of the residue (freeze dried from water) contained no organic impurity in addition to the HCl salt of (*R*)-β-amino-δ-(guanin-9-yl)pentanoic acid: ^{1}H NMR (300 MHz, D_2O, 35 °C): δ = 2.38 [dt, $^3J_{H,H}$ = 7 Hz, 7 Hz, 2 H, C(γ)-H], 2.85 [dd, $^2J_{H,H}$ = 18, $^3J_{H,H}$ = 8 Hz, 1 H, C(α)-H], 3.00 [dd, $^2J_{H,H}$ = 18, $^3J_{H,H}$ = 5 Hz, 1 H, C(α)-H], 3.73 [m, 1 H, C(β)-H], 4.44 [t, $^3J_{H,H}$ = 7 Hz, 2 H, C(δ)-H], 8.93 [s, 1 H, C(8)-H] ppm. ^{13}C NMR (75 MHz, D_2O, 35 °C): δ = 32.7 [C(γ)], 36.6 [C(δ)], 42.4 [C(α)], 46.7 [C(β)], 109.0 [C(5)], 138.4 [C(8)], 151.1, 156.0, 156.3, 174.4 (CO_2H) ppm. MS (ESI): *m*/*z* (%) = 267.5 (54) [M + H]$^+$, 555.5 (100) [2 M + Na]$^+$. Di-*tert*-butyl dicarbonate (1.68 g, 7.70 mmol) was added to a suspension of this residue in water/1 M aq. NaOH/dioxane (1:1:1, 100 mL). After stirring for 7 h at room temperature a second portion of di-*tert*-butyl dicarbonate (1.68 g, 7.70 mmol) was added and stirring continued overnight. The resultant solution was washed with diethyl ether, neutralized with 1 M aq. HCl, and concentrated in vacuo. Purification of the residue by chromatography (RP-C18 silica gel, 100% H_2O to H_2O/MeOH, 4:1 gradient) provided, after freeze drying, **2** (1.35 g, 96%) as a colorless solid. M.p. > 300 °C (dec.). R_f = 0.30 (ethyl acetate/MeOH/H_2O/acetic acid, 80:14:6:3). $[\alpha]_D^{20}$ = +6.5 (*c* = 0.92, DMSO). IR (KBr): $\tilde{\nu}$ = 3410, 3134, 2978, 1696, 1574, 1482, 1401, 1367, 1169, 1059, 781, 694 cm^{-1}. ^{1}H NMR (300 MHz, [D_6]DMSO, 35 °C): δ = 1.37 (s, 9 H, *t*Bu), 1.80−1.95 [m, 2 H, C(γ)-H], 2.06−2.22 [m, 2 H, C(α)-H], 3.67−3.74 [m, 1 H, C(β)-H], 3.83−3.95 [m, 2 H, C(δ)-H], 7.06 (3 H, NH_2, NH), 7.63 [s, 1 H, C(8)-H] 12.02 (s, br., 1 H, CO_2H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 35 °C): δ = 28.2 [C(CH_3)$_3$], 35.1 [C(γ)], C(δ) overlapping with residual solvent signal as determined by HMQC, 42.5 [C(α)], 46.0 [C(β)], 77.5 [*C*(CH_3)$_3$], 116.4 [C(5)], 136.9 [C(8)], 151.2, 154.2, 155.0, 157.6, 175.4 (CO_2H) ppm. MS (ESI): *m*/*z* (%) = 389.5 (100) [M + Na]$^+$, 755.5 (86) [2 M + Na]$^+$.

Benzyl (*S*)-β-(*tert*-Butoxycarbonylamino)-δ-bromopentanoate (3): A solution of alcohol **7** (4.30 g, 13.3 mmol) and CBr_4 (8.83 g, 26.6 mmol) in dry CH_2Cl_2 (110 mL) was cooled under nitrogen to −20 °C and a solution of PPh_3 (7.00 g, 26.7 mmol) in dry CH_2Cl_2 (22 mL) was added dropwise over 30 min. The mixture was allowed to warm to room temperature and stirring continued for 15 h. The solvent was removed under reduced pressure and the residue was purified by chromatography (silica gel, ethyl acetate/*n*-hexane, 1:4)

to afford **3** (4.05 g, 79%) as a colorless solid. M.p. 81−83 °C. R_f = 0.19 (*n*-hexane/ethyl acetate, 4:1). IR (solid): $\tilde{\nu}$ = 3365, 2977, 1727, 1678, 1514, 1440, 1274, 1247, 1219, 1161, 1123, 1024, 732, 683 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.43 (s, 9 H, *t*Bu), 1.97−2.07 [m, 1 H, C(γ)-H], 2.07−2.24 [m, 1 H, C(γ)-H], 2.64 [d, $^3J_{H,H}$ = 5 Hz, 2 H, C(α)-H], 3.40 [t, $^3J_{H,H}$ = 7 Hz, 2 H, C(δ)-H], 4.07−4.09 [m, 1 H, C(β)-H], 5.05 (s, br., 1 H, NH), 5.13 (s, 2 H, CH_2Ph), 7.33−7.39 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 28.1 [C(*C*H$_3$)$_3$], 29.3 [C(δ)], 37.2 [C(γ)], 38.4 [C(α)], 46.4 [C(β)], 66.4 (CH_2Ph), 79.8 [*C*(CH$_3$)$_3$], 128.1−128.4 (Ph), 135.8 (C_{ipso}, Ph), 155.7 ($NHCO_2$), 171.3 (*C*O$_2$Bzl) ppm. MS (ESI): *m*/*z* (%) = 408.4/410.1 (100/98) $[M + Na]^+$. $C_{17}H_{24}BrNO_4$·Na (408.1): calcd. 408.0786; found 408.0789 (HRMS).

Benzyl (*R*)-β-(*tert*-Butoxycarbonylamino)-δ-hydroxypentanoate (7): A 1 M solution of borane in THF (51.6 mL, 51.6 mmol) was added dropwise over 40 min to a solution of Boc-L-β-homoaspartic acid 5-benzyl ester (**6**) (2.90 g, 8.60 mmol) in dry THF (10 mL) at −5 °C under nitrogen and stirring continued at −5 °C for 5 h. Then, the reaction was quenched by slowly adding methanol/acetic acid (9:1, 20 mL). The solvents were removed under reduced pressure. The residue was dissolved in ethyl acetate (300 mL) and washed with 1 M aq. HCl (2 × 150 mL), sat. $NaHCO_3$ (2 × 150 mL), and brine (1 × 150 mL). The organic phase was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude compound was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate, 1:1) to afford **7** (2.03 g, 73%) as a colorless solid. R_f = 0.17 (*n*-hexane/ethyl acetate, 1:1). IR (solid): $\tilde{\nu}$ = 3390, 3335, 2986, 1728, 1668, 1517, 1449, 1274, 1245, 1219, 1161, 1123, 1027, 729 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.41 (s, 9 H, *t*Bu), 1.48−1.60 [m, 1 H, C(γ)-H], 1.72−1.81 [m, 1 H, C(γ)-H], 2.55 [dd, $^2J_{H,H}$ = 16, $^3J_{H,H}$ = 5 Hz, 1 H, C(α)-H], 2.67 [dd, $^2J_{H,H}$ = 16, $^3J_{H,H}$ = 5 Hz, 1 H, C(α)-H], 3.47 (s, br., 1 H, OH), 3.58−3.67 [m, 2 H, C(δ)-H], 4.02−4.04 [m, 1 H, C(β)-H], 5.15 (s, 2 H, CH_2Ph), 5.40 (s, br., 1 H, NH), 7.28−7.37 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 28.1 [C(*C*H$_3$)$_3$], 37.3 [C(γ)], 38.9 [C(α)], 43.9 [C(β)], 58.4 [C(δ)], 66.3 (CH_2Ph), 79.7 [*C*(CH$_3$)$_3$], 128.2−128.4 (Ph), 135.3 (C_{ipso}, Ph), 156.5 ($NHCO_2$), 171.4 (*C*O$_2$Bzl) ppm. MS (ESI): *m*/*z* (%) = 346.1 (20) $[M + Na]^+$, 669.2 (100) $[2 M + Na]^+$. $C_{17}H_{25}NO_5$·Na (346.2): calcd. 346.1630; found 346.1636 (HRMS).

Benzyl (*R*)-β-(*tert*-Butoxycarbonylamino)-δ-[*N*^{4}-(benzyloxycarbonyl)-cytosin-1-yl]pentanoate (8): A suspension of bromide **3** (1.16 g, 3.00 mmol), *N*^{4}-(benzyloxycarbonyl)cytosine (2.46 g, 10.0 mmol), K_2CO_3 (1.04 g, 7.53 mmol), and TBAI (111 mg, 301 μmol) in dry DMF (50 mL) was stirred at room temperature for 11 days under argon. Insoluble material was filtered off and washed with DMF and ethyl acetate. The filtrate and the washing solutions were pooled. After absorption on silica gel the crude product was purified by chromatography (silica gel, ethyl acetate/*n*-hexane, 3:1 to 5:1) to afford **8** (730 mg, 44%) as a colorless solid. M.p. 55 °C. R_f = 0.26 (ethyl acetate/*n*-hexane, 3:1). $[\alpha]_D^{20}$ = +21.9 (*c* = 0.24, MeOH). IR (KBr): $\tilde{\nu}$ = 3366, 2976, 1738, 1694, 1627, 1503, 1366, 1214, 1055, 788, 746, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.41 (s, 9 H, *t*Bu), 1.83−2.06 [m, 2 H, C(γ)-H], 2.57 [d, $^3J_{H,H}$ = 5 Hz, 2 H, C(α)-H], 3.58−3.76 [m, 1 H, C(δ)-H], 3.84−4.01 [m, 1 H, C(β)-H], 4.03−4.17 [m, 1 H, C(δ)-H], 5.08 (s, 2 H, CH_2Ph), 5.20 (s, 2 H, CH_2Ph), 5.27 (d, $^3J_{H,H}$ = 10 Hz, 1 H, NH), 7.12−7.22 [m, 1 H, C(5)-H], 7.26−7.31 (m, 10 H, 2 Ph), 7.83−7.85 [m, 1 H, C(6)-H] ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 28.3 [C(*C*H$_3$)$_3$], 33.2 [C(γ)], 39.4 [C(α)], 45.0 [C(β)], 48.5 [C(δ)], 66.5 (CH_2Ph), 67.8 (CH_2Ph), 79.7 [*C*(CH$_3$)$_3$], 94.7 [C(5)], 128.1−128.6 (Ph), 135.1 (C_{ipso}, Ph), 135.5 (C_{ipso}, Ph), 149.4 [C(6)], 152.4, 155.6, 162.4, 162.5, 171.2 (CH_2CO_2Bzl) ppm. MS (ESI): *m*/*z* (%) = 573.4 (82) $[M + Na]^+$, 1123.3 (100) $[2 M + Na]^+$, 1673.4 (13) $[3 M + Na]^+$. $C_{29}H_{34}N_4O_7$ (550.2): calcd. 550.2428; found 550.2427 (HRMS).

Benzyl (*R*)-β-(*tert*-Butoxycarbonylamino)-δ-[*N*^{6}-(benzyloxycarbonyl)-adenin-9-yl]pentanoate (9): A mixture of bromide **3** (2.56 g, 6.63 mmol), (*N*^{6}-benzyloxycarbonyl)adenine (5.00 g, 18.6 mmol), K_2CO_3 (2.57 g, 18.6 mmol), and TBAI (254 mg, 688 μmol) in dry DMF (82 mL) was stirred under nitrogen at room temperature for 46 h. Then, the solvent was removed under reduced pressure, water (200 mL) was added, and the crude compound was extracted with ethyl acetate (6 × 100 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Purification by column chromatography (silica gel, ethyl acetate) afforded **9** (2.13 g, 56%) as a colorless solid. M.p. 75−79 °C. R_f = 0.59 (ethyl acetate/methanol, 9:1). IR (solid): $\tilde{\nu}$ = 3340, 2979, 1740, 1698, 1616, 1581, 1455, 1243, 1155, 987, 734 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.44 (s, 9 H, *t*Bu), 2.03−2.12 [m, 2 H, C(γ)-H], 2.59 [m, 2 H, C(α)-H], 3.87−4.00 [m, 1 H, C(β)-H], 4.10−4.19 [m, 1 H, C(δ)-H], 4.24−4.33 [m, 1 H, C(δ)-H], 5.08 (s, 2 H, CH_2Ph), 5.28 (s, 2 H, CH_2Ph), 5.31 (s, br., 1 H, NHBoc), 7.26−7.40 (m, 10 H, 2 Ph), 8.03 [s, br., 1 H, C(2)-H, C(8)-H], 8.74 [s, 1 H, C(2)-H, C(8)-H], 9.30 (s, br., 1 H, $NHCO_2Bzl$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 28.1 [C(*C*H$_3$)$_3$], 34.3 [C(γ)], 38.9 [C(α)], 41.1 [C(δ)], 44.8 [C(β)], 66.4 (CH_2Ph), 67.4 (CH_2Ph), 79.7 [*C*(CH$_3$)$_3$], 121.8 [C(5)], 128.1−128.4 (Ph), 135.1 (C_{ipso}, Ph), 135.3 (C_{ipso}, Ph), 143.3 [C(8)], 149.3 [C(6)], 151.0, 151.2, 152.4 [C(2)], 155.3 [C(4)], 170.9 (CH_2CO_2Bzl) ppm. MS (ESI): *m*/*z* (%) = 597.3 (100) $[M + Na]^+$, 1171.6 (43) $[2 M + Na]^+$. $C_{30}H_{34}N_6O_6$ (575.3): calcd. 575.2618; found 575.2635 (HRMS).

Benzyl (*R*)-β-(*tert*-Butoxycarbonylamino)-δ-[*N*^{3}-(benzoyl)thymin-1-yl]pentanoate (10): A mixture of bromide **3** (2.10 g, 5.44 mmol), 3-benzoylthymine (2.77 g, 12.0 mmol), K_2CO_3 (1.66 g, 12.0 mmol), and TBAI (201 mg, 544 μmol) in dry DMF (66 mL) under nitrogen was stirred at room temperature for 70 h. The solvent was removed under reduced pressure, water (200 mL) was added, and the crude compound was extracted with ethyl acetate (6 × 100 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Compound **10** was obtained as a colorless solid (2.69 g, 92%) after column chromatography (silica gel, *n*-hexane/ethyl acetate, 2:1, to ethyl acetate, 100% gradient). M.p. 125−126 °C. R_f = 0.67 (ethyl acetate/methanol, 9:1). IR (solid): $\tilde{\nu}$ = 3337, 2980, 2931, 1733, 1697, 1673, 1640, 1520, 1437, 1341, 1247, 1203, 1148, 1055 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.42 (s, 9 H, *t*Bu), 1.91 [s, 3 H, C(5)-CH$_3$], 1.80−1.93 [m, 2 H, C(γ)-H], 2.55 [d, $^3J_{H,H}$ = 7 Hz, 2 H, C(α)-H], 3.52−3.67 [m, 1 H, C(δ)-H], 3.83−4.01 [m, 2 H, C(β)-H, C(δ)-H], 5.09 (m, 2 H, CH_2Ph), 5.18 (m, 1 H, NH), 7.20 [m, 1 H, C(6)-H], 7.28−7.37 (m, 5 H, Ph), 7.46 (m, 2 H, Ph$_m$), 7.61 (m, 1 H, Ph$_p$), 7.91 (m, 2 H, Ph$_o$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 12.3 [C(5)-*C*H$_3$], 28.3 [C(*C*H$_3$)$_3$], 33.5 [C(γ)], 39.4 [C(α)], 45.1 [C(β)], 46.4 [C(δ)], 66.6 (CH_2Ph), 79.8 [*C*(CH$_3$)$_3$], 110.5 [C(5)], 128.3−128.6 (Ph), 129.1 (2 C, CO*Ph*), 130.4 (2 C, CO*Ph*), 131.6 (CO*Ph*), 134.9 (CO*Ph*), 135.5 (C_{ipso}, CH_2*Ph*), 140.9 [C(6)], 149.8 ($NHCO_2$), 155.5 [C(4)], 163.2 [C(2)], 169.1 (NHCOPh), 171.0 (CO_2Bzl) ppm. MS (ESI): *m*/*z* (%) = 558.2 (40) $[M + Na]^+$, 1093.3 (100) $[2 M + Na]^+$. $C_{29}H_{33}N_3O_7$·Na (558.2): calcd. 558.2216; found 558.2210 (HRMS).

Benzyl (*R*)-β-(*tert*-Butoxycarbonylamino)-δ-(2-amino-6-chloropurin-9-yl)pentanoate (11): Bromide **3** (3.77 g, 9.76 mmol) was added to a suspension of 2-amino-6-chloropurine (2.48 g, 14.6 mmol), K_2CO_3 (2.02 g, 14.6 mmol), and TBAI (361 mg, 977 μmol) in dry DMF (100 mL). The mixture was stirred at room temperature for 6 days under argon. After removal of the solvent the residue was absorbed

on silica gel (MeOH). Compound **11** was isolated by chromatography (silica gel, ethyl acetate/*n*-hexane, 2:1, to ethyl acetate, 100% gradient) as a colorless solid (2.17 g, 47%). M.p. 51−55 °C. R_f = 0.46 (ethyl acetate/*n*-hexane, 3:1). $[\alpha]_D^{20}$ = +31.1 (*c* = 0.29, MeOH). IR (KBr): $\tilde{\nu}$ = 3332, 3212, 2976, 2362, 1705, 1615, 1561, 1520, 1459, 1410, 1367, 1285, 1248, 1163, 1054, 997, 912, 785, 748, 698, 642 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.42 (s, 9 H, *t*Bu), 2.03 [m, 2 H, C(γ)-H], 2.59 [m, 2 H, C(α)-H], 3.88−4.02 [m, 1 H, C(β)-H], 4.02−4.18 [m, 2 H, C(δ)-H], 5.07 (s, 2 H, CH_2Ph), 5.21 (s, 2 H, NH_2), 5.31 (m, 1 H, NH), 7.25−7.36 (m, 5 H, Ph), 7.81 [s, 1 H, C(8)-H] ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 28.3 [C(CH_3)$_3$], 34.3 [C(γ)], 39.1 [C(α)], 41.0 [C(δ)], 45.3 [C(β)], 66.6 (CH_2Ph), 79.9 [C(CH_3)$_3$], 125.3 [C(5)], 128.3−128.6 (Ph), 135.3 (C_{ipso}, Ph), 142.7 [C(8)], 151.2, 153.7, 155.4, 158.9, 171.1 (CH_2CO_2) ppm. MS (ESI): *m*/*z* (%) = 497.4/499.3 (100/32) [M + Na]$^+$. $C_{22}H_{27}ClN_6O_4$ (474.2): calcd. 474.1782; found 474.1788 (HRMS).

(*R*)-β-(*tert*-Butoxycarbonylamino)-δ-[N^4-(benzyloxycarbonyl)-cytosin-1-yl]pentanoic Acid (12): A mixture of benzyl ester **8** (551 mg, 1.00 mmol), 1 M aq. NaOH (1.80 mL), dioxane (5.00 mL), and water (3.00 mL) was stirred at room temperature for 1 day. After neutralization with 2 M aq. HCl and freeze drying, the residue was subjected to chromatography (RP-C18 silica gel, H_2O, 100%, to H_2O/MeOH, 1:4 gradient) to afford **12** (288 mg, 63%) as a colorless solid. M.p. 131−133 °C. R_f = 0.44 (ethyl acetate/MeOH/H_2O/acetic acid, 20:2:2:1, sat. with NaCl). $[\alpha]_D^{20}$ = −23.6 (*c* = 0.61, DMSO). IR (KBr): $\tilde{\nu}$ = 1749, 1695, 1630, 1563, 1507, 1370, 1218, 1057, 785, 747, 697 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO, 35 °C): δ = 1.36 (s, 9 H, *t*Bu), 1.64−1.87 [m, 2 H, C(γ)-H], 2.22 [m, 2 H, C(α)-H], 3.68 [m, 2 H, C(β)-H, C(δ)-H], 3.79 [m, 1 H, C(δ)-H], 5.17 (s, 2 H, CH_2Ph), 6.93 [d, $^3J_{H,H}$ = 7 Hz, 1 H, C(5)-H], 7.29−7.42 (m, 5 H, Ph), 8.02 [d, $^3J_{H,H}$ = 7 Hz, 1 H, C(6)-H] ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 35 °C): δ = 28.2 [C(CH_3)$_3$], 33.6 [C(γ)], 41.0 [C(α)], 45.6 [C(β)], 47.1 [C(δ)], 66.3 (CH_2Ph), 77.5 [C(CH_3)$_3$], 93.8 [C(5)], 127.8−128.4 (Ph), 135.9 (C_{ipso}, Ph), 149.7 [C(6)], 153.2, 154.7, 154.9, 162.5, 173.4 (CO_2H) ppm. MS (ESI): *m*/*z* (%) = 427.5 (16) [M − *t*Bu + H + Na]$^+$, 483.5 (100) [M + Na]$^+$, 505.6 (42) [M +2 Na − H]$^+$, 943.4 (33) [2 M + Na]$^+$, 965.4 (68) [2 M +2 Na − H]$^+$, 987.4 (94) [2 M +3 Na −2 H]$^+$. $C_{22}H_{28}N_4O_7 \cdot H_2O$ (478.5): calcd. C 55.22, H 6.32, N 11.71; found C 55.61, H 6.29, N 17.35.

(*R*)-β-(*tert*-Butoxycarbonylamino)-δ-[N^6-(benzyloxycarbonyl)adenin-9-yl]pentanoic Acid (13): A solution of **9** (1.06 g, 1.84 mmol) in dioxane (9 mL) and 1 M aq. NaOH (3.7 mL) was stirred at room temperature for 22 h. After evaporation to dryness, the residue was dissolved in water (100 mL) and washed with diethyl ether (2 × 250 mL). The aqueous layer was acidified with 1 M aq. HCl (pH, 2−3) and extracted with ethyl acetate (3 × 100 mL). The combined organic phases were washed with brine (100 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford **13** (819 mg, 92%) as a colorless solid. M.p. 164−165 °C. R_f = 0.39 (ethyl acetate/methanol, 9:1). IR (solid): $\tilde{\nu}$ = 3425, 3280, 2975, 1748, 1703, 1617, 1586, 1495, 1212, 1160, 1004, 740 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO, 25 °C): δ = 1.26 (s, 1 H, *t*Bu), 1.38 (s, 8 H, *t*Bu), 1.83−1.95 [m, 1 H, C(γ)-H], 2.03−2.12 [m, 1 H, C(γ)-H], 2.36−2.39 [m, 2 H, C(α)-H], 3.62−3.81 [m, 1 H, C(β)-H], 4.15−4.30 [m, 2 H, C(δ)-H], 5.20 (s, 2 H, CH_2Ph), 6.54 (d, $^3J_{H,H}$ = 9 Hz, 0.1 H, NHBoc), 6.92 (d, $^3J_{H,H}$ = 9 Hz, 0.9 H, NHBoc), 7.30−7.47 (m, 5 H, Ph), 8.42 [s, 1 H, C(8)], 8.60 [s, 1 H, C(2)], 10.66 (s, br., 1 H, $NHCO_2Bzl$), 12.18 (1 H, CO_2H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 25 °C): δ = 28.6 [C(CH_3)$_3$], 34.4 [C(γ)], 40.7 [C(α)], 40.9 [C(δ)], 45.4 [C(β)], 66.5 (CH_2Ph), 78.2 [C(CH_3)$_3$], 123.7 [C(5)], 128.2−128.7 (Ph), 136.7 (C_{ipso}, Ph), 144.6 [C(8)], 149.7 [C(4)], 151.7 [C(2)], 152.3, 152.5, 155.5 [C(6)], 172.6 (CO_2H) ppm. MS (ESI): *m*/*z* (%) = 507.2 (100) [M + Na]$^+$, 991.4 (35) [2 M + Na]$^+$. $C_{23}H_{28}N_6O_6$ (507.2): calcd. 507.1968; found 507.1956 (HRMS).

(*R*)-β-(*tert*-Butoxycarbonylamino)-δ-(thymin-1-yl)pentanoic Acid (14): Ammonium formate (1.26 g, 20.0 mmol) was added to a solution of benzyl ester **10** (2.68 g, 5.00 mmol) in MeOH (76 mL). Oxygen was removed (3 × vacuo−nitrogen−vacuo), and palladium (10 wt.%) on activated carbon (537 mg, 20 wt.%) was slowly added at room temperature. The mixture was refluxed for 6 h, cooled to room temperature and filtered through Celite. The catalyst was washed with MeOH. The filtrate was evaporated, and the residue was dissolved in EtOH (40 mL). A solution of hydrazine monohydrate (24.3 mL, 501 mmol) in EtOH (25 mL) was added dropwise and the mixture was heated at reflux for 40 h. After concentration of the mixture, the residue was dissolved in water (200 mL) and washed with diethyl ether (2 × 100 mL). The aqueous phase was acidified with 1 M aq. HCl (pH, 2−3) and extracted with ethyl acetate (4 × 150 mL). The organic phase was dried ($MgSO_4$), and the solvent was removed under reduced pressure to afford acid **14** (804 mg, 47%) as a colorless solid. M.p. 130−131 °C. R_f = 0.20 (*n*-hexane/ethyl acetate/acetic acid, 6:4:0.3). IR (solid): $\tilde{\nu}$ = 3411, 3330, 2976, 1689, 1583, 1355, 1243, 1157 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO, 25 °C): δ = 1.48 (s, 9 H, *t*Bu), 1.71 [s, 3 H, C(5)-CH_3], 1.57−1.80 [m, 2 H, C(γ)-H], 2.28−2.39 [m, 2 H, C(α)-H], 3.48−3.80 [m, 3 H, C(β)-H, C(δ)-H], 6.81 (m, 1 H, NHBoc), 7.44 [s, 1 H, C(6)-H], 11.19 [s, br., 1 H, NH] ppm. ^{13}C NMR (75 MHz, [D_6]DMSO, 25 °C): δ = 12.1 [C(5)-CH_3], 28.3 [C(CH_3)$_3$], 33.4 [C(γ)], 39.6 [C(α)], 44.9 [C(δ)], 45.3 [C(β)], 77.8 [C(CH_3)$_3$], 108.3 [C(5)], 141.6 [C(6)], 150.8 ($NHCO_2$), 155.1 [C(4)], 164.4 [C(2)], 172.4 (CO_2H) ppm. MS (ESI): *m*/*z* (%) = 340.2 (100) [M − H]$^-$, 681.4 (32) [2 M − H]$^-$. $C_{15}H_{23}N_3O_6$ (340.2): calcd. 340.1509; found 340.1508 (HRMS).

General Procedure for Solid-Phase β-Peptide Synthesis: Oligomers were prepared by manual solid-phase peptide synthesis in a small column using 4-methylbenzhydrylamine polystyrene (MBHA-PS) resin loaded with H-β-HGly-OH (20.0 mg, 12.4 μmol β-homoglycine amide). For the first step of the double coupling, an excess of 5 equiv. amino acid (62.0 μmol) was used and activated by 1-[bis(dimethylamino)methyliumyl]-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-3-oxide hexafluorophosphate (HATU, 21.2 mg, 55.8 μmol), 1-hydroxy-7-azabenzotriazole [HOAt, 124 μL (62.0 μmol) of a 0.5 M solution in DMF], and *N*-ethyldiisopropylamine (DIEA, 30.3 μL, 174 μmol) in DMF (500 μL). For the second step of the double coupling, an excess of 3 equiv. amino acid (37.2 μmol) was used and activated by HATU (12.7 mg, 33.5 μmol), HOAt/DMF (74.4 μL, 37.2 μmol), and DIEA (19.5 μL, 112 μmol) in DMF (500 μL). After swelling the loaded resin for 1 h in 2 mL of CH_2Cl_2, the following procedure was repeated for every amino acid unit: 1) deprotection twice, for 3 min with TFA/*m*-cresol (95:5, 2 mL); 2) washing first five times with CH_2Cl_2/DMF (1:1, 2 mL) and then five times with pyridine (2 mL); 3) double coupling steps, each 1 h gentle moving at 50 °C; 4) washing with CH_2Cl_2/DMF (1:1, 3 × 2 mL), DMF/piperidine (95:5, 3 × 2 mL), and CH_2Cl_2/DMF (1:1, 3 × 2 mL). The resin was washed with TFA (3 × 2 mL) and CH_2Cl_2 (5 × 2 mL), dried overnight in vacuo, and suspended in *m*-cresol (200 μL)/thioanisole (200 μL)/ethanedithiol (100 μL). After stirring for 30 min at room temperature, TFA (2 mL) was added, and the suspension was cooled to −15 °C. Trifluoromethanesulfonic acid (200 μL) was added, the mixture was allowed to warm to room temperature within 1.5 h, and stirring continued for 1.5 h. The filtrate was

concentrated by freeze drying, and the β-homoalanyl PNA was precipitated with Et_2O (30 mL at −15 °C) as a colorless solid and purified by HPLC. The yield of each coupling step was estimated from HPLC to be higher than 97%.

H-(β-HLys-ApaC-ACHC-β-HLys-ApaG-ACHC-β-HLys-ApaC-ACHC-β-HGly)-NH_2 (15): Analytical HPLC: 23.5 min, gradient: 15−30% B (B = MeCN/H_2O, 9:1 + 0.1% TFA) in 30 min. MS (ESI): *m*/*z* (%) = 519.7 (64) $[M+3H]^{3+}$, 778.6 (100) $[M+2H]^{2+}$, 1552.2 (5) $[M+H]^{+}$.

H-(β-HLys-ApaG-ACHC-β-HLys-ApaC-ACHC-β-HLys-ApaG-ACHC-β-HGly)-NH_2 (16): Analytical HPLC: 22.9 min, gradient: 15−30% B (B = MeCN/H_2O, 9:1 + 0.1% TFA) in 30 min. MS (ESI): *m*/*z* (%) = 798.7 (100) $[M+2H]^{2+}$, 809.7 (30) $[M+H+Na]^{2+}$, 1595.0 (7) $[M+H]^{+}$.

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