Acyclic Nucleic Acid Analogues: Synthesis and Oligomerization of γ,4-Diamino-2-oxo-1(2*H*)-pyrimidinepentanoic Acid and δ,4-Diamino-2-oxo-1(2*H*)-pyrimidinehexanoic Acid

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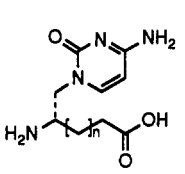
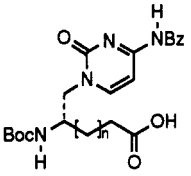
Alkylation of the tosylates of *N*-*t*-Boc-5-(hydroxymethyl)-2-pyrrolidinone and *N*-*t*-Boc-6-(hydroxymethyl)-2-piperidinone with the sodium salt of cytosine in dimethyl sulfoxide, followed by acylation of the base exocyclic amine and selective opening of the lactam ring by alkaline hydrolysis, gave the title compounds, respectively, in protected form. Oligomerization was achieved by activation of the carboxyl group as the *p*-nitrophenyl ester and coupling with the free amine of another subunit in dimethylformamide or dimethyl sulfoxide. A hexamer of the pentanoic acid system could be easily prepared by stepwise coupling of the monomeric units or by block synthesis via trimers. The hexanoic acid derived hexamer could only be prepared by stepwise elongation, mostly due to problems of solubility for this backbone.

We have undertaken a program for the preparation and study of oligomeric agents that are neutral, are either achiral or homochiral, and have the capability of binding in a sequence specific manner to DNA and RNA. We have recently completed modeling studies on a variety of non-sugar backbones of the amide type (polyamides, polycarbamates) for use as single-stranded nucleic acid binding agents.[1] One attractive structural type that emerged from this study was nylon, e.g., oligomers derived from the amino acids **1a** and **1b**. An interesting feature of the modeling is the predicted preference for binding of these species to DNA as opposed to RNA as well as the sensitivity of binding to the stereochemistry of the stereogenic atom in the backbone. In the present account we examine the feasibility of synthesis of the amino acids **1a,b** and the prospects for their oligomerization.



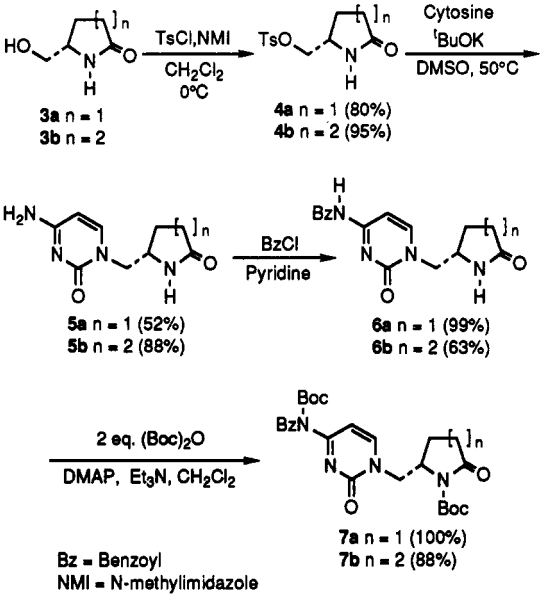
1a n = 1
1b n = 2



2a n = 1
2b n = 2

Oligomers derived from **1a** and **1b** are related to both peptides and oligonucleotides, and we borrowed upon protective group methodologies used for those systems. Our initial targets were the protected derivatives **2a,b**. The readily cleavable *tert*-butoxycarbonyl group should be suitable for both solution- or solid-phase oligomerization. While the *N*-benzoyl moiety on the base is not strictly required due to the low nucleophilicity of this amino group, the benzamide is expected to confer favorable solubility and chromatographic behavior upon oligomeric species. The key synthetic goal in the preparation of subunits **2a,b** appeared to be the mating of cytosine with a chiral backbone precursor. As chiral precursors we chose the widely used alcohol **3a** and the analogous, but previously unknown, **3b**. For our purposes, it is critical that the chiral precursors **3** be as pure as possible. Incorporation of optically impure subunits into an oligomer will lead to a complex mixture of diastereomeric products. We have discussed elsewhere the problems associated with conversion of glutamic and α-aminoadipic acids into the optically pure alcohols **3a,b**, respectively, and both are conveniently available.[2]

Scheme I



The initially employed strategy is outlined in Scheme I. Reaction of the alcohols with tosyl chloride and *N*-methylimidazole in methylene chloride gave the tosylates **4a,b**. Treatment of the tosylates with the potassium salt of cytosine in dimethyl sulfoxide provided the alkylated species **5a,b** in moderate to high yield. Introduction of the base protecting group proceeded smoothly upon treatment of **5** with benzoyl chloride in pyridine. At this stage, incorporation of a *tert*-butoxycarbonyl group on the lactam nitrogen would activate the ring toward hydroxide opening and conveniently provide the nascent amino group with the desired protection.[3] However, reactions of benzamides **6a,b** with excess di-*tert*-butyl dicarbonate in the presence of 4-(dimethylamino)pyridine produced the bis-acylation products **7a,b**. Selective reaction at the lactam nitrogen was not possible as the benzamide moiety proved more reactive than the lactam toward the acylation reagent. Attempted nucleophilic opening of the lactam in imides

(1) Weller, D. D.; Daly, D. T.; Olson, W. K.; Summerton, J. E. *J. Org. Chem.*, previous paper in this issue.

(2) Huang, S.-B.; Nelson, J. S.; Weller, D. D. *Synth. Comm.* **1989**, *19*, 3485.

(3) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424.

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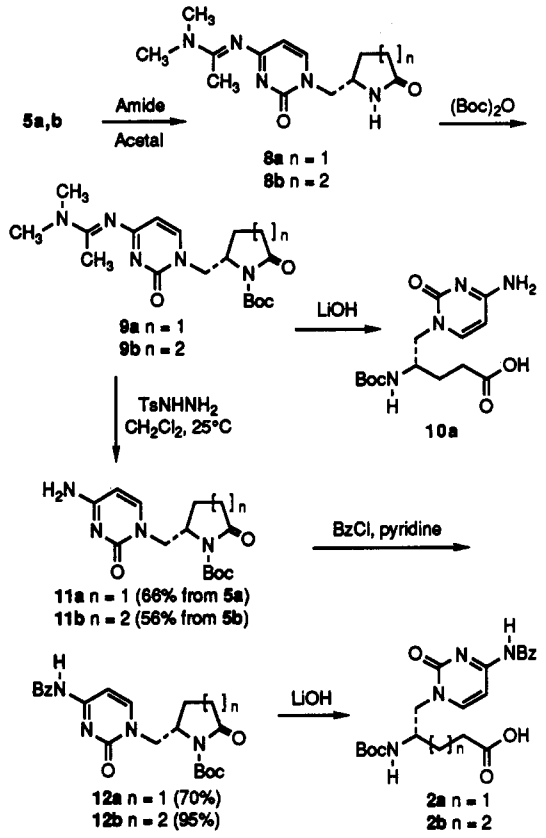
Scheme II



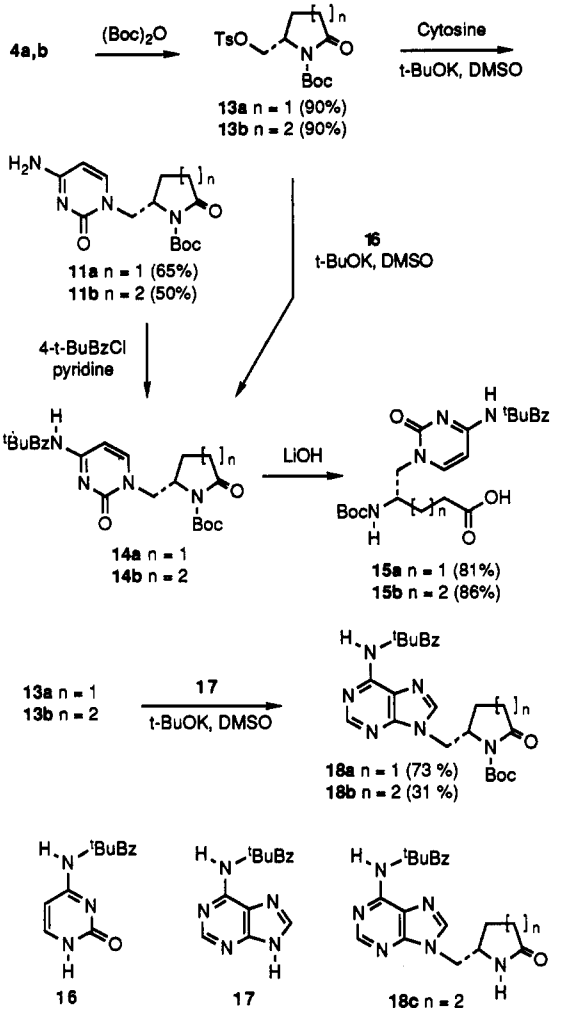
7b gave complex mixtures of products.

To avoid the competing reaction at cytosine during lactam activation, we turned to amidines for protection of the base amino group, a moiety suggested by Caruthers for use in oligonucleotide synthesis.[4] Reaction of amines **5a,b** with *N,N*-dimethylacetamide dimethyl acetal produced the amidines **8a,b** (Scheme II). Now, *tert*-butoxycarbonylation provided the imides **9a,b**, but all attempts to achieve selective lactam opening were thwarted by the facile cleavage of the amidine group by hydroxide. The product, free acid **10a**, proved to be unexpectedly labile and decomposed upon attempted benzoylation of the base amino group. More stable amidines derived from *N*-methylpyrrolidinone dimethyl acetal were also cleaved concurrently with ring opening. However, in analogy to the known sensitivity of acylated cytosines to hydrazine,[5] the amidine group was selectively cleaved by reaction with tosylhydrazine to give free amines **11a,b**. Following benzoylation, the lactam of **12a,b** underwent selective hydrolysis by lithium hydroxide to give the desired subunits **2a,b**.

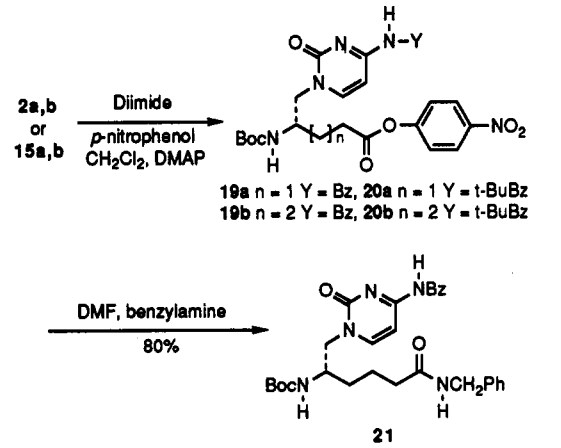
A significant improvement in the preparation of the subunits was achieved by early introduction of the *tert*-butoxycarbonyl group, thus avoiding the amidine protection/deprotection sequence. Acylation of the lactam tosylates **4a,b** provided **13a,b**, which underwent alkylation under rigorously anhydrous conditions to **11a,b** (Scheme III). Reaction with *tert*-butylbenzoyl chloride in pyridine produced **14a,b** and hydrolysis gave the superior subunits **15a,b**. The change to the more lipophilic *tert*-butylbenzoyl group was necessitated by the extreme polarity of these materials and their subsequent oligomerization products.

(4) McBride, C. J.; Kienzek, R.; Beaucage, S. C.; Caruthers, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 2040.
(5) Letsinger R. L.; Miller, P. S.; Grams, G. W. *Tetrahedron Lett.* **1968**, 2621.

Scheme III

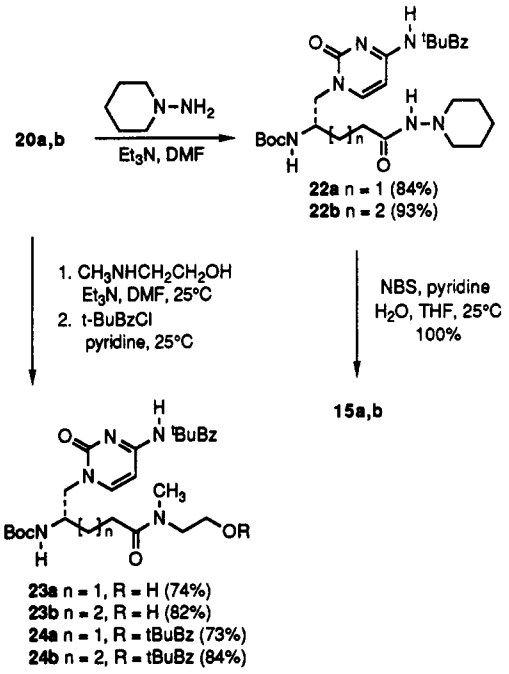


Scheme IV



In the case of **13a**, the alkylation could be successfully performed with the potassium salt of *N*-(*tert*-butylbenzoyl)cytosine (**16**) to provide **14a** directly in 71% yield. However, the lactam tosylate **13b** did not effectively alkylate the less reactive acylated cytosine derivative and **14b** was obtained in only 5% yield by this procedure. When the reaction was run at room temperature for 48 h, the yield was marginally improved (19%) and considerable amounts of the lactam tosylate **4b** (45% yield) could be isolated, suggesting that the *tert*-butoxycarbonyl group on this lactam is thermally labile. Alkylation of (*tert*-butylbenzoyl)adenine (**17**) by **13a** is also efficient, affording 73% of **18a** while **13b** yielded only 25% of **18c** at 75 °C

Scheme V



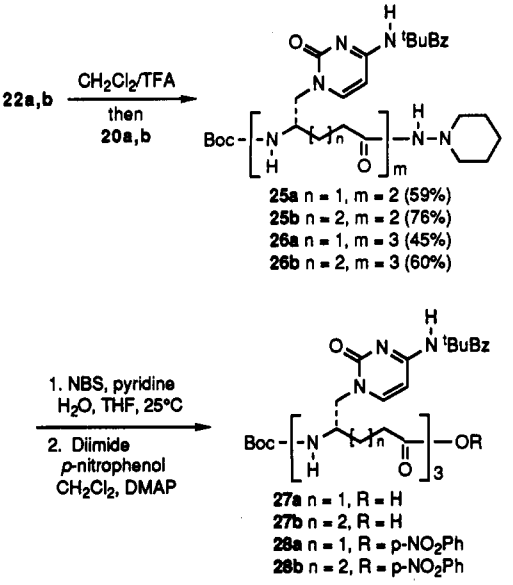
and 31% of **18b** at room temperature.

The activation of the carboxyl group of acids **2a,b** and **15a,b** and their conversion into amide derivatives was initially investigated by formation of the benzylamide **21** (Scheme IV). The *p*-nitrophenyl esters **19a,b** and **20a,b** were conveniently prepared by carbodiimide coupling. Ester **19b** reacted in reasonable yield (80%) with benzylamine to give **21**, and these active esters were chosen as the standard. Satisfactory coupling yields were also obtained by using active esters derived by reaction of **2b** with bis(succinimidyl) carbonate and bis(oxazolidinyl)-phosphoryl chloride in 78% and 67% yields, respectively. The use of succinimidyl esters for coupling was halted after isolation of *N*-(benzoyloxy)succinimide, suggestive that a serious side reaction, namely, cleavage of the base protecting groups by *N*-hydroxysuccinimide, was occurring.

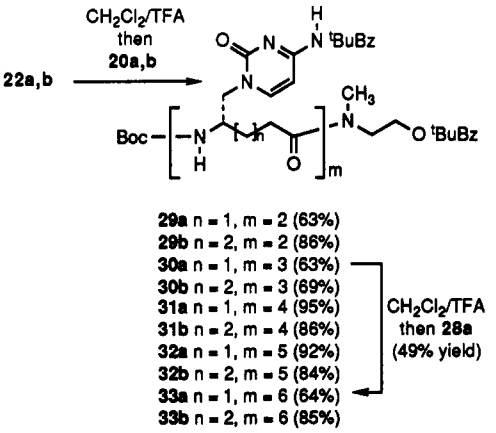
The extreme polarity of the model amide **21** prompted a shift to the *tert*-butylbenzoyl-protected subunit **15a,b**. Additionally, the prospect of working with oligomers containing a free carboxylic acid terminus was unattractive, and it appeared that a carboxyl masking group would be beneficial for the synthesis of oligomers by a block approach. Ideally, the acid protecting group would be relatively nonpolar, would be insensitive to trifluoroacetic acid cleavage of the *tert*-butoxycarbonyl group, and would not be prone to lactam formation with the free amino group. Protection of carboxylic acids as their hydrazides has been previously demonstrated, and such groups are cleaved by mild oxidative methods.[6] We chose 1-aminopiperidine in order to increase the nonpolar character of the hydrazide. It was necessary to purify the commercially available 1-aminopiperidine by recrystallization of the oxalate salt in order to remove contamination by piperidine. Because of the low nucleophilicity of 1,1-dialkylhydrazines, the secondary amine is a very effective competitor for activated acid derivatives. The hydrazides **22a,b** were formed in reasonable yields by reaction of **20a,b** with hydrazine in dimethylformamide (Scheme V). Although these hydrazides proved inert to lead tetraacetate and manganese dioxide, reaction with *N*-bromosuccinimide and pyridine

(6) Barton, D. H. R.; Girjavallabhan, M.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. I* **1972**, 929.

Scheme VI



Scheme VII



in aqueous tetrahydrofuran returned the free acids nearly quantitatively.

Prior to initiating chain extension we decided to adjust the functionality at the C-terminal subunit of the oligomers. During biophysical testing of the interaction of the nylon oligomers with nucleic acids, a charged carboxylate terminus is undesirable. Reaction of **20a,b** with 2-(methylamino)ethanol gave the alcohols **23a,b**, which were converted into the more lipophilic esters **24a,b** (Scheme V). This neutral cap on the C-terminus would be relatively nonpolar during oligomer synthesis, and, after ammonolysis to cleave the ester, should aid in solubilizing the oligomer in water during testing.

The targets chosen for the examination of the oligomerization process were hexamers **33a** and **33b**, and we employed a block synthesis strategy. To this end, hydrazides **22a,b** were treated with 25% trifluoroacetic acid in dichloromethane to effect removal of the *tert*-butoxycarbonyl group (Scheme VI). Reaction with active esters **20a,b** produced the dimers **25a,b** in 59% and 76% yields. Repetition of this procedure produced the hydrazine-capped trimer **26a,b** in 45% and 60% yields.

The corresponding end-capped species **24a,b** yielded the C-terminal dimers **29a,b** and the trimers **30a,b** in good yields by the same chain extension procedure as used for the hydrazides (Scheme VII). Oxidative cleavage of the trimer hydrazides **26a,b** afforded trimer acids **27a,b**. These were converted into the *p*-nitrophenyl esters **28a,b**. Activated ester **28a** was reacted with 1.2 equiv of the C-ter-

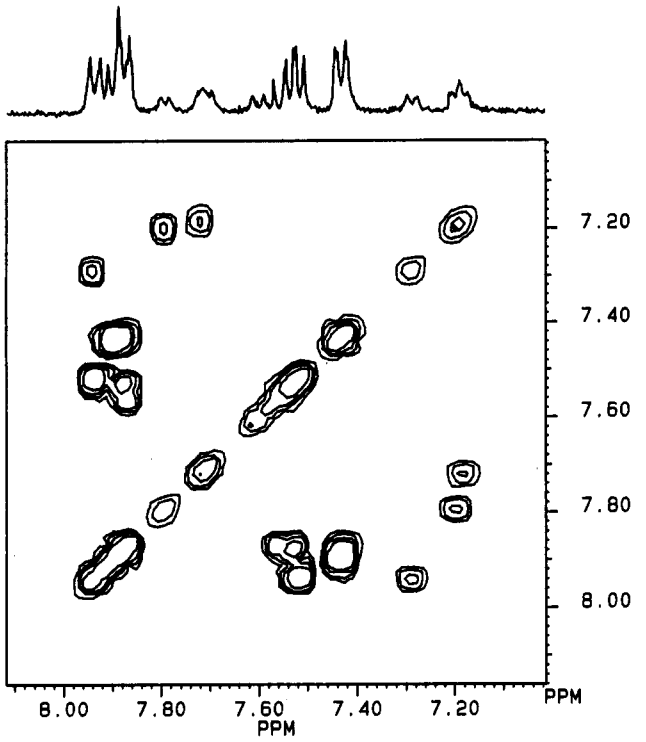
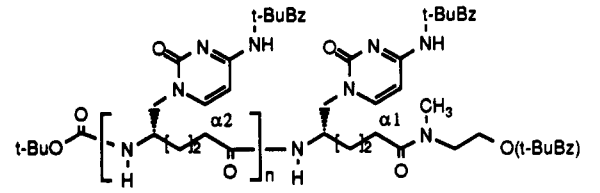


Figure 1. COSY expansion plot of trimer **30b**.

minal trimer amine derived from acid cleavage of **30a**. The hexamer **33a** was isolated in 49% yield from the trimer hydrazide. Unexpectedly, the six-atom backbone series was not efficiently prepared by the coupling of trimers. Deprotection of the hydrazide **26b** and activation of the acid to **27b** proceeded smoothly by TLC. However, no trace of hexamer **33b** could be obtained from the reaction of trimer active ester **28b** and the amine derived from C-terminal trimer **30b**. Isolated instead were acid **27b** along with the amine component. Alternatively, the stepwise addition of monomer units to **30b** was continued. The trimer **30b** was subjected to the deprotection/coupling scheme to produced the tetramer **31b** in 86% yield. Further reaction to pentamer **32b** and hexamer **33b** proved difficult in this series, primarily due to problems of solubility with their immediate precursors, the tetramer amine and pentamer amine, respectively. As a result, these coupling reactions were carried out in warm (60–65 °C) dimethyl sulfoxide. Samples of **32b** and **33b** were obtained in 84% and 85% crude yields, respectively. The corresponded tetramer **31a**, pentamer **32a**, and hexamer **33a** in the five-atom series were also efficiently prepared by this stepwise procedure without difficulty. In contrast to the five-atom long subunit series, the longer oligomers in the six-atom backbone series were not satisfactorily purified by column chromatography or preparative TLC on silica. Obtaining pure materials for characterization required further purification of these compounds on a silica gel HPLC column.

The fully protected oligomers **29–33** are very polar amorphous solids with adequate solubility in dimethylformamide, dimethyl sulfoxide, and methanol/chloroform mixtures. While characterization of synthetic intermediates through the monomer level was routine, upon chain elongation, the NMR spectra become extremely complex. The complexity is compounded by slow rotation about the tertiary amide at the C-terminus. The structures of the lower oligomers were successfully investigated by proton–proton 2D correlation spectroscopy (COSY). The signals for the 5-H and 6-H of the cytosine moieties of the oligomers are normally not resolvable in routine 1D proton NMR. The downfield protons (6-H) of the cytosine ring are close to, and hardly separate out from, the aromatic signals of the *tert*-butylbenzoyl groups. However, it proved possible to assign the coupled pairs of the 5-H and 6-H cytosine protons by the homonuclear COSY experiments. For instance, it is quite clear that three pairs of cytosine's 5-H and 6-H couplings can be identified in the COSY spectra of trimer **30b** (Figure 1). Unfortunately, this technique was unsuitable for the oligomers higher than trimer.

Table I. Relative Integration Values of the α-Methylene Groups for Six-Atom Backbone Oligomers



compd	chemical shifts at δ 2.29–2.46 (α1)	chemical shifts at δ 1.85–2.17 (α2) found	chemical shifts at δ 1.85–2.17 (α2) calcd
29b	2.00	2.00	2.0
30b	2.00	3.95	4.0
31b	2.00	5.48	6.0
32b	2.00	7.44	8.0
33b	2.00	9.34	10.0

Because of the hygroscopic nature of these nucleic acid analogues, accurate integration of the signals near the residual H_2O signal in the ^1H NMR spectra for oligomers higher than trimer could not be performed. Fortunately, upon a close inspection of the ^1H NMR spectra of the six-atom backbone oligomers, we found that the signals of the C-terminal end-capped α-methylene group (δ 2.29–2.46) of the amide linkages along the backbone were distinct from other α-methylene groups (δ 1.85–2.17). Identification of the chain length of the oligomers by relative integration of these two types of α-methylene groups is presented in Table I. For the oligomers of the five-atom backbone series, this method was valid through the trimer.

We relied more heavily on fast atom bombardment mass spectrometry (FABMS) for analysis of the oligomers. Although both positive and negative ion FABMS gave useful results for the five-atom backbone series, the negative ion technique appears to be superior for the six-atom backbone subunit. Unlike carbamate-linked oligonucleosides, in which sequence information could be obtained due to the occurrence of characteristic cleavage modes,[7] few peaks besides the parent clusters could be routinely identified for these nylon oligomers. One peak commonly seen was at 270 in the negative ion FABMS (272 in positive ion FAB) for (*tert*-butylbenzoyl)cytosine. Exact mass analysis of the parent ion $(M - H)^-$ or $(M + H)^+$ was obtained for all oligomers.

The major peak of the molecular cluster (M – H) in the negative FABMS analysis for the oligomers higher than trimer was routinely observed with one mass unit higher than the calculated mass. Analysis of the molecular clusters was performed with the software (DS90) provided

(7) (a) Griffin, D.; Laramee, J. A.; Deinzer, M. L.; Stirchak, E. P.; Weller, D. D. *Biomed. Environ. Mass Spectrom.* **1988**, *17*, 105. (b) Laramee, J. A.; Arbogast, B. C.; Deinzer, M. L.; Stirchak, E. P.; Weller, D. D. *Org. Mass Spectrom.* **1990**, *25*, 33. (c) Laramee, J. A.; Arbogast, B. C.; Stirchak, E. P.; Weller, D. D.; Deinzer, M. L. *Org. Mass Spectrom.* **1990**, *25*, 219.

with the mass spectrometer (KRATOS MS50RF). The peak pattern and the peak mass of the molecular clusters were closely matched with theoretical calculations.

In summary, block synthesis of oligomers containing subunits **1a** was readily achieved, which holds promise that these nylon polymers will be available by protected segment assembly of short oligomers on a solid phase.[8] For derivatives of **1b**, block assembly was not possible, and solubility of reaction intermediates was poor. For this series, efficient solid-phase assembly by monomer units will be essential. The difficulty we have experienced to date in characterizing the fully deprotected oligomers by mass spectrometry places a constraint on the application of solid-phase synthesis methodology. Most solid-phase synthetic methods for nucleic acids entail the ammonolytic liberation of the base-protected species from the resin. Since the base-deprotected oligomers are not readily analyzed by FABMS, degradative schemes or alternative methods of characterization would be required. We have addressed this problem by developing a cleavable anchor suitable for the removal of fully protected oligomers of nucleic acid analogues from solid supports. Work on the cleavable anchor and the results of biophysical testing of the nylon oligomers will be reported in due course.

Experimental Section

Methylene chloride (CH_2Cl_2), pyridine, dimethylformamide, and dimethyl sulfoxide were distilled from powdered calcium hydride (CaH_2) and stored over 3-Å/4-Å molecular sieves. Methanol (CH_3OH) and ethanol (EtOH) were distilled from the corresponding magnesium alkoxides and stored over 4-Å molecular sieves. Tetrahydrofuran and diethyl ether (Et_2O) were freshly distilled from sodium/benzophenone prior to use. All other reagents were purified by distillation or recrystallization prior to use whenever necessary. All moisture-sensitive reagents were transfered in a dry box or via a syringe under a positive pressure of nitrogen or argon atmosphere. All moisture-sensitive reactions were carried out under a positive pressure of inert gas. Column chromatography was performed by using silica gel 60 (Merck, 340–400-mesh ASTM) or basic alumina Brockman Activity I (Fisher Scientific, 80–200 mesh). Chromatography solvents were distilled before use. Analytical TLC was conducted on precoated Merck silica gel 60 F_{254}, J. T. Baker silica gel IB-F, or Merck aluminum oxide 60 F_{254} (neutral, type E) plates. Preparative TLC was performed on precoated Merck silica gel 60 F_{254} (1- or 2-mm thickness) plates. Melting points were determined on a capillary melting point apparatus and are not corrected.

(*S*)-(5-Oxo-2-pyrrolidinyl)methyl 4-Methylbenzenesulfonate (4a) and (*S*)-(6-Oxo-2-piperidinyl)methyl 4-Methylbenzenesulfonate (4b). The lactam alcohol **3b**[2] (1.15 g, 8.90 mmol) was dissolved in CH_2Cl_2 (50 mL) and cooled in an ice bath for 30 min, and *N*-methylimidazole (0.73 mL, 13.3 mmol) was added. To this cold reaction mixture was added dropwise a solution of tosyl chloride (1.87 g, 9.81 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at 0 °C for 24 h. The reaction was quenched by addition of H_2O (1.0 mL) with vigorous stirring, diluted with $CHCl_3$ (200 mL), quickly washed with saturated $NaHCO_3$ solution (1 × 50 mL), 1 M HCl (2 × 50 mL), and brine (1 × 50 mL), and then dried over anhydrous Na_2SO_4. Removal of solvent gave 2.35 g (93% yield) of crude product, which crystallized upon standing under high vacuum. This crude product was subjected to recrystallization from $CHCl_3$–hexanes to give 1.78 g (70.4%) of pure material as pale yellowish, needle-like crystals, mp 126 °C: $[\alpha]^{22}_D$ = +7.6 (*c* = 0.197, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (2 H, d, *J* = 8.3 Hz), 7.38 (2 H, d, *J* = 8.2 Hz), 5.85 (1 H, br, s), 4.08 (1 H, dd, *J* = 3.9, 9.7 Hz), 3.81 (1 H, m), 3.73 (1 H, m), 2.47 (3 H, s), 2.39 (1 H, m), 2.28 (1 H, m), 1.98 (2 H, m), 1.73 (1 H, m), 1.41 (1 H, m). IR ($CHCl_3$): 3195, 2956, 2913, 2841, 1675, 1363, 1189, 1171, 1097 cm^{-1}. EIMS, *m/z* (rel intensity): 285 (3.2), 284 (21.4), 283 (M^+, 2.5), 254 (5.3), 253 (40.9), 155 (13.2), 112 (6.8), 111 (43.1), 107 (4.5), 99 (36.3), 98 (100), 97 (5.9), 92 (16.0), 91 (89.0), 90 (6.7), 89 (10.6), 83 (9.1), 82 (9.4), 70 (16.0), 69 (9.1), 68 (5.7), 65 (40.5), 63 (8.4), 56 (10.6), 55 (100). Anal. Calcd for $C_{13}H_{17}NO_4S$: C, 55.12; H, 6.05; N, 4.95. Found: C, 54.89; H, 6.01; N, 4.78. HRMS (EI): calcd for $C_{13}H_{17}NO_4S$ (M^+) 283.0878, found 283.0878.

Treatment of 3.20 g of alcohol **3a**[2,9] with tosyl chloride by the same procedure produced 5.86 g (80%) of **4a**. Physical properties and spectroscopic data of **4a** were identical with those reported by von Hardegger and Ott.[10]

(*S*)-4-Amino-1-[(6-oxo-2-piperidinyl)methyl]-2(1*H*)-pyrimidinone (5b). Cytosine (1.03 g, 9.28 mmol) was mixed with potassium *tert*-butoxide (1.04 g, 9.28 mmol) in DMSO (10 mL). The resulting mixture was swirled with occasional heating until a homogeneous solution formed. This freshly prepared cytosine anion containing solution was added to the tosylate **4b** (1.66 g, 5.86 mmol) solution in DMSO (15 mL) at room temperature. The reaction mixture was stirred at 50 °C for 8 h. The reaction was quenched with 20% $AcOH/CH_3OH$ (10 mL). After removal of solvents under high vacuum, 20% $CH_3OH/CHCl_3$ (150 mL) was added to the residual oil with vigorous stirring. The resulting mixture was allowed to sit at room temperature for 2–3 h. The precipitated tosylate salt and excess cytosine were filtered off and the filtrate was concentrated to dryness. This desalting process was repeated twice. Removal of solvents and column chromatography on basic alumina (5 to 15% $CH_3OH/CHCl_3$) gave 1.14 g (88% yield) of alkylated lactam **5b** as a white powder, mp 227 °C dec; $[\alpha]^{22}_D$ = +17.2 (*c* = 0.5, CH_3OH). ^1H NMR (300 MHz, DMSO-d_6): δ 7.51 (1 H, d, *J* = 7.3 Hz), 7.50 (1 H, br s, exchanged with D_2O), 7.07 and 6.98 (2 H, 2 br s, exchanged with D_2O), 5.63 (1 H, d, *J* = 7.3 Hz), 4.83 (1 H, dd, *J* = 12.2, 4.3 Hz), 3.52–3.63 (2 H, m), 2.09 (2 H, m), 1.76 (1 H, m), 1.67 (1 H, m), 1.54 (1 H, m), 1.33 (1 H, m). IR (KBr): 3251, 3055 (br), 2952, 2878, 1698, 1670, 1644, 1621, 1561, 1523, 1506, 1482, 1455, 1435, 1418, 1384, 1331, 1306, 1266, 1199, 1172, 1133 cm^{-1}. EIMS, *m/z* (rel intensity): 223 (1.2), 222 (M^+, 3.0), 221 (4.6), 206 (10.1), 205 (71.8), 125 (100), 112 (62.4), 110 (6.3), 109 (62.9), 98 (71.8), 96 (22.4), 83 (27.2), 81 (20.5), 70 (10.8), 69 (16.1), 56 (17.5), 55 (81.9), 53 (16.1). Negative ion FABMS, *m/z* (rel intensity): 257 (12.6), 222 (13.6), 221 (M − H, 100), 178 (7.8), 110 (5.7), 75 (12.4), 64 (6.6). HRMS (neg. FAB): calcd for $C_{10}H_1{}^3N_4O_2$ (M − H)$^-$ 221.1038, found 221.1043.

(*S*)-4-Amino-1-[(5-oxo-2-pyrrolidinyl)methyl]-2(1*H*)-pyrimidinone (5a). Cytosine (2.13 g, 19.2 mmol) and 3.44 g (12.8 mmol) of tosylate **4a** were dried separately by coevaporation with anhydrous DMF. Potassium *tert*-butoxide (2.0 g, 20.0 mL of 0.1 g/mL of *tert*-butoxide/DMSO solution) was added by cannulation to the round-bottom flask containing the predried cytosine, and the mixture swirled to promote solution. The reaction mixture was allowed to stir for 18 h at 25 °C. The homogeneous yellow solution was quenched by addition of 1 mL of acetic acid in 135 mL of 20% $MeOH/CHCl_3$ to give a milky white suspension. The suspension was filtered and the precipitate was found to contain predominantly unreacted cytosine and the potassium salt of *p*-toluenesulfonic acid, with only small amounts of product **4**. The filtrate was evaporated in vacuo and the residue dried on high vacuum. Pure samples of alkylation product were obtained on a small scale by neutral alumina chromatography (1:1–3:1 $MeOH/CHCl_3$) and recrystallization in MeOH containing a very small amount of water to provide a white, crystalline solid, mp 298 °C dec. Overall yield of purified **5a** was 1.38 g (52%) with an additional 5–10% generally being recoverable from the filtered solids; $[\alpha]^{22}_D$ = 113.3 (*c* = 0.15, H_2O). ^1H NMR (400 MHz, DMSO-d_6): δ 7.74 (1 H, s), 7.51 (1 H, d, *J* = 7.2 Hz), 7.14 (1 H, br s), 6.94 (1 H, br s), 5.62 (1 H, d, *J* = 7.1 Hz), 3.83 (1 H, m), 3.75 (1 H, dd, *J* = 13.0, 6.0 Hz), 3.55 (1 H, dd, *J* = 13.0, 5.6 Hz), 1.96–2.17 (3 H, m), 1.67–1.76 (1 H, m). UV (H_2O): λ_{max} = 274, ε = 20 400 at pH = 7.0. IR (KBr): 3376, 3101, 1702, 1677, 1635, 1622, 1520, 1500, 1277, 1262 cm^{-1}. HRMS (neg ion FAB): calcd for $C_9H_{11}N_4O_2$ (M − H)$^-$ 207.0882, found 207.0883.

(*S*)-*N*-[1,2-Dihydro-2-oxo-1-[(5-oxo-2-pyrrolidinyl)methyl]-4-pyrimidinyl]benzamide (6a) and (*S*)-*N*-[1,2-Dihydro-2-oxo-1-[(6-oxo-2-piperidinyl)methyl]-4-pyrimidinyl]benzamide (6b). To a suspension of cytosine lactam **5b** (165

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mg, 0.74 mmol) in dry pyridine (10 mL) was dropwise added distilled benzoyl chloride (86 μL, 0.74 mmol) at room temperature. The reaction mixture was stirred for 8 h and the reaction was quenched by addition of H_2O (0.5 mL). Solvents were evaporated off and the residual oil was redissolved in 10% 2-propanol/$CHCl_3$ (40 mL), washed with 1 M HCl (2 × 10 mL), saturated $NaHCO_3$ solution (1 × 10 mL), and brine (1 × 10 mL), and then dried over anhydrous Na_2SO_4. Removal of solvent gave 151 mg (63% yield) of crude product, which was further purified by column chromatography on silica (5% $CH_3OH/CHCl_3$) to give 120 mg of **6b** as a white solid (50% overall yield), mp 238 °C dec. ^1H NMR (400 MHz, DMSO-d_6): δ 11.20 (1 H, br s), 8.08 (1 H, d, J = 7.3 Hz), 8.01 (2 H, d, J = 7.6 Hz), 7.62 (2 H, m), 7.52 (2 H, t, J = 7.6 Hz), 7.31 (1 H, br s), 3.98 (1 H, dd, J = 12.9, 6.3 Hz), 3.81 (1 H, dd, J = 13.0, 6.0 Hz), 3.72 (1 H, m), 2.12 (2 H, t, J = 6.4 Hz), 1.76 (2 H, m), 1.60 (1 H, m), 1.43 (1 H, m). IR (KBr): 3180, 3128, 3092, 3072, 2955, 1697, 1669, 1563, 1485, 1446, 1444, 1425, 1376, 1358, 1343, 1329, 1304, 1248 cm^{-1}. EIMS, m/z (rel intensity): 326 (M^+, 8.3), 325 (5.9), 230 (7.7), 229 (48.1), 216 (18.3), 139 (6.1), 124 (9.2), 122 (4.0), 121 (5.1), 111 (4.2), 108 (6.0), 106 (8.2), 105 (100), 98 (21.9), 83 (6.3), 82 (4.6), 81 (4.5), 77 (49.0), 55 (25.0), 51 (9.5). Negative ion FABMS, m/z (rel intensity): 327 (6.6), 326 (27.0), 325 (M − H, 100), 282 (7.6), 214 (15.2), 145 (6.7), 139 (6.1), 107 (34.5), 105 (6.1). HRMS (neg ion FAB): calcd for $C_{17}H_{17}N_4O_3$ (M − H)⁻ 325.1301, found 325.1304.

By the same procedure, 76 mg (0.365 mmol) of **5a** provided 112 mg (99%) of **6a** after chromatography. The analytical sample was crystallized from $CHCl_3$/hexanes, mp 216 °C dec: $[\alpha]^{22}_D$ = +69.5 (c = 0.2, MeOH). ^1H NMR (400 MHz, $CDCl_3$): δ 9.29 (1 H, br s), 7.93 (2 H, d, J = 7.6 Hz), 7.68 (1 H, d, J = 7.2 Hz), 7.60 (1 H, t, J = 7.3 Hz), 7.49–7.53 (3 H, m), 6.88 (1 H, bs), 4.19 (1 H, m), 4.11 (1 H, dd, J = 13.2, 4.2 Hz), 3.84 (1 H, dd, J = 13.5, 7.4 Hz), 2.28–2.44 (3 H, m), 1.82–1.95 (1 H, m). UV (MeOH): λ_{max} = 306 and 260, ε = 5275 and 15,280 at pH = 7.0, λ_{max} = 318, ε = 16,560 at pH = 12.0. IR (KBr): 1697, 1693, 1687, 1655, 1646, 1639, 1625, 1568, 1559, 1552, 1485, 1357, 1304, 1279, 1262, 1246 cm^{-1}. HRMS (neg ion FAB): calcd for $C_{16}H_{15}N_4O_3$ (M − H)⁻ 311.1144, found 311.1138.

(*S*)-1,1-Dimethylethyl 2-[[4-[Benzoyl[(1,1-dimethylethoxy)carbonyl]amino]-1,2-dihydro-2-oxo-1-pyrimidinyl]methyl]-5-oxo-1-pyrrolidinecarboxylate (7a) and (*S*)-1,1-Dimethylethyl 2-[[4-[Benzoyl[(1,1-dimethylethoxy)carbonyl]amino]-1,2-dihydro-2-oxo-1-pyrimidinyl]methyl]-6-oxo-1-piperidinecarboxylate (7b). To a stirred solution of **6a** (55 mg, 0.173 mmol) in CH_2Cl_2 at 25 °C was added 24 μL (0.173 mmol) of Et_3N, 80 μL (0.345 mmol) of di-*tert*-butyl dicarbonate, and 19 mg (0.173 mmol) of 4-(dimethylamino)-pyridine. After 2 h at 25 °C, the volatiles were removed in vacuo, and the residue was purified by chromatography on silica (5% MeOH/$CHCl_3$). This resulted in a nearly quantitative yield of **7a**, identified on the basis of the following NMR spectrum. ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (2 H, dd, J = 9.1, 1.4 Hz), 7.59 (1 H, m), 7.56 (1 H, d, J = 7.3 Hz), 7.47 (2 H, t, J = 7.8 Hz), 7.14 (1 H, d, J = 7.3 Hz), 4.50 (1 H, m), 4.26 (1 H, dd, J = 13.3, 7.0 Hz), 3.92 (1 H, dd, J = 13.5, 4.9 Hz), 2.53–2.62 (1 H, m), 2.40–2.47 (1 H, m), 2.06–2.14 (2 H, m), 1.53 (9 H, s), 1.31 (9 H, s).

By the same procedure described, a sample of **6b** (18 mg, 55.2 μmol) was treated with 2 equivs of the reagent mixture to give 20 mg (69% yield) of **7b**. This compound tends to decompose upon routine storage at room temperature. ^1H NMR (400 MHz, DMSO-d_6): δ 8.05 (1 H, d, J = 7.2 Hz), 7.83 (2 H, d, J = 8.0 Hz), 7.75 (1 H, t, J = 8.0 Hz), 7.60 (2 H, t, J = 8.0 Hz), 6.95 (1 H, d, J = 7.2 Hz), 4.65 (1 H, m), 3.88–4.15 (2 H, m), 2.40–2.60 (2 H, m), 1.62–2.00 (4 H, m), 1.21–1.37 (18 H, m).

(*S*)-1,1-Dimethylethyl 2-[(4-Amino-1,2-dihydro-2-oxo-1-pyrimidinyl)methyl]-5-oxo-1-pyrrolidinecarboxylate (11a) and (*S*)-1,1-Dimethylethyl 2-[(4-Amino-1,2-dihydro-2-oxo-1-pyrimidinyl)methyl]-6-oxo-1-piperidinecarboxylate (11b). Method A. A sample of *N,N*-dimethylacetamide dimethyl acetal (0.52 mL, 3.56 mmol) was added to a suspension of cytosine lactam **5b** (530 mg, 2.39 mmol) in DMF (20 mL). This reaction mixture was allowed to stir at 40 °C for 8 h. Solvent and excess reagent were removed under reduced pressure and the residue amidine derivative further dried under high vacuum overnight. The crude amidine derivative was dissolved in CH_2Cl_2 (30 mL) and treated with 4-(dimethylamino)pyridine (320 mg, 2.62 mmol). To this solution was added dropwise di-*tert*-butyl dicarbonate (1.1 mL, 4.79 mmol) and Et_3N (0.35 mL, 2.51 mmol) at the same time. The reaction was followed by TLC every 30 min until complete disappearance of starting amidine was achieved. Removal of volatiles and flash column chromatography on silica gave **9b** as a dark brown oil, which was immediately redissolved in CH_2Cl_2 (40 mL) and treated with (*p*-toluenesulfonyl)hydrazine (1.77 g, 9.50 mmol) and *p*-toluenesulfonic acid monohydrate (227 mg, 1.19 mmol). The resulting mixture was allowed to stirred at room temperature for 24 h. Removal of solvent and column chromatography on silica (2–10% $CH_3OH/CHCl_3$) gave 432 mg (56% yield) of cytosine Boc lactam **11b** as a fine white powder, mp 190–191 °C. $[\alpha]^{22}_D$ = +129.2 (c = 0.54, CH_3OH). ^1H NMR (400 MHz, DMSO-d_6): δ 7.38 (1 H, d, J = 7.2 Hz), 7.04 and 6.94 (2 H, 2 br s, exchanged with D_2O), 5.62 (1 H, d, J = 7.2 Hz), 4.56 (1 H, br, m), 3.90 (1 H, dd, J = 13.3, 5.8 Hz), 3.68 (1 H, dd, J = 13.4, 8.3 Hz), 2.38–2.48 (2 H, m), 1.95 (1 H, m), 1.80 (1 H, m), 1.70 (2 H, m), 1.31 (9 H, s). IR (KBr): 3357, 3132, 2980, 1756, 1722, 1659, 1628, 1523, 1490, 1441, 1391, 1370, 1302, 1285, 1257, 1158, 1135, 1106, 1062 cm^{-1}. Negative ion FABMS, m/z (rel intensity): 359 (17.3), 358 (10.3), 357 (43.8), 322 (17.0), 321 (M − H, 100), 249 (15.2), 221 (13.2), 145 (7.3), 143 (20.3), 110 (15.1), 105 (7.1). HRMS (neg ion FAB): calcd for $C_{15}H_{21}N_4O_4$ (M − H)⁻ 321.1563, found 321.1560.

Compound **5a** (0.195 g) was subjected to the above procedure to provide 0.297 g of the amorphous amidine **9a**, in 84% overall yield. ^1H NMR (400 MHz, $CDCl_3$): δ 7.21 (1 H, d, J = 6.7 Hz), 5.90 (1 H, d, J = 7.0 Hz), 4.46–4.51 (1 H, m), 4.25 (1 H, dd, J = 13.7, 6.6 Hz), 3.92 (1 H, dd, J = 13.7, 4.8 Hz), 3.10 (6 H, s), 2.55–2.65 (1 H, m), 2.39–2.46 (1 H, m), 2.31 (3 H, s), 2.05–2.26 (2 H, m), 1.54 (9 H, s).

The amidine **9a** (100 mg, 0.265 mmol) was dissolved in 2 mL of anhydrous CH_2Cl_2 and 197 mg (1.06 mmol) of (*p*-toluenesulfonyl)hydrazine was added in one portion. The reaction mixture was stirred at 25 °C for 24 h. The reaction mixture was evaporated to dryness and purified by chromatography on silica (0–20% MeOH/$CHCl_3$), providing 65 mg of **11a**, mp 117–179 °C, in 79% yield. $[\alpha]^{22}_D$ = +60.7 (c = 0.15, MeOH). ^1H NMR (400 MHz, DMSO-d_6): δ 7.44 (1 H, d, J = 7.3 Hz), 7.08 (1 H, br s), 6.98 (1 H, br s), 5.63 (1 H, d, J = 7.2 Hz), 4.47 (1 H, m), 3.90 (1 H, dd, J = 13.5, 5.6 Hz), 1.38 (9 H, s), 3.77 (1 H, dd, J = 13.6, 7.3 Hz), 2.23–2.33 (2 H, m), 2.02–2.10 (1 H, m), 1.72–1.77 (1 H, m). IR (KBr): 3428, 3354, 1778, 1725, 1709, 1654, 1523, 1494, 1390, 1372, 1313, 1257, 1154 cm^{-1}. HRMS (neg ion FAB): calcd for $C_{14}H_{19}N_4O_4$ (M − H)⁻ 307.1406, found 307.1407.

Method B. A sample of Boc lactam tosylate **13a** (1.22 g, 3.29 mmol) was alkylated with cytosine (548 mg, 4.93 mmol) by the procedure given for the preparation of cytosine lactam **5b** (except the reaction was run at room temperature for 24 h instead of 8 h at 50 °C) to provide 627 mg (62% yield) of alkylated Boc lactam **11a** after column chromatography on silica (5–10% $CH_3OH/CHCl_3$). Similarly, tosylate **13b** (225 mg, 0.59 mmol) was converted to 81 mg (43% yield) of **11b** after routine column chromatography.

(*S*)-1,1-Dimethylethyl 2-[[4-(Benzoylamino)-1,2-dihydro-2-oxo-1-pyrimidinyl]methyl]-5-oxo-1-pyrrolidinecarboxylate (12a) and (*S*)-1,1-Dimethylethyl 2-[[4-(Benzoylamino)-1,2-dihydro-2-oxo-1-pyrimidinyl]methyl]-6-oxo-1-piperidinecarboxylate (12b). To a suspension of cytosine Boc lactam **11b** (713 mg, 2.21 mmol) in pyridine (15 mL) was dropwise added distilled benzoyl chloride (0.28 mL, 2.41 mmol). The resulting mixture was stirred at room temperature for 8 h and the reaction was quenched by addition of H_2O and solvent was removed under reduced pressure. The residual oil was dissolved in $CHCl_3$ (150 mL), washed with saturated $NaHCO_3$ solution (1 × 50 mL), 0.5 M HCl (2 × 50 mL), and brine (1 × 50 mL), and then dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave 1.0 g of crude product, which was further purified by recrystallization from $CHCl_3$–hexanes to give 890 mg (85% yield) of pure **12b**, mp >260 °C. $[\alpha]^{22}_D$ = +114.8 (c = 0.5, $CHCl_3$). ^1H NMR (400 MHz, DMSO-d_6): δ 11.18 (1 H, s, exchanged with D_2O), 8.00 (2 H, d, J = 7.5 Hz), 7.98 (1 H, d, J = 7.2 Hz), 7.63 (1 H, t, J = 7.3 Hz), 7.51 (2 H, t, J = 7.7 Hz), 7.29 (1 H, d, J = 7.2 Hz), 4.70 (1 H, m), 4.10 (1 H, dd, J = 13.3, 4.9 Hz), 3.97 (1 H, dd, J = 13.3, 9.3 Hz), 2.48–2.60 (2 H, m), 1.70–2.04 (4 H, m), 1.31 (9 H, s). IR (KBr): 3270, 3251, 3239, 3148, 3064, 2979, 2935, 2905, 1764, 1728, 1699, 1659, 1624, 1561, 1488, 1454, 1426, 1393, 1371, 1327, 1305, 1275, 1249, 1189, 1149, 1112, 1068 cm^{-1}. EIMS,

m/z (rel intensity): 426 (M^+, 2.1), 327 (2.4), 326 (6.1), 325 (2.6), 231 (2.7), 230 (14.9), 229 (94.3), 217 (2.3), 216 (22.3), 200 (7.4), 155 (2.6), 130 (5.6), 125 (2.3), 124 (12.3), 122 (9.5), 111 (4.5), 106 (8.6), 105 (100), 98 (25.8), 85 (5.5), 84 (2.5), 83 (6.4), 82 (2.4), 81 (3.4), 78 (2.5), 77 (32.4), 70 (2.3), 69 (2.1), 66 (3.0), 58 (6.6), 57 (20.2), 56 (52.5), 55 (29.7), 54 (3.8), 53 (6.1), 51 (9.7), 50 (6.8). Negative ion FABMS, m/z (rel intensity): 427 (14.5), 426 (49.7), 425 (M - H, 100), 325 (10.9), 321 (5.4), 215 (11.2), 214 (34.0), 171 (11.1), 145 (8.8), 143 (8.1), 139 (6.3), 107 (81.2), 106 (7.6), 105 (7.4). HRMS (neg ion FAB): calcd for $C_{22}H_{25}N_2O_5$ $(M - H)^-$ 425.1825, found 425.1816.

Compound **11a** (0.31 g, 1.03 mmol) provided 0.297 g of product **12a** (70% yield), mp 190–191 °C. **12a**: $[\alpha]^{22}_D = +97.0$ ($c = 0.1$, MeOH). ^1H NMR (400 MHz, DMSO-d_6): δ 8.65 (1 H, s), 7.89 (2 H, d, $J = 7.3$ Hz), 7.75 (1 H, d, $J = 7.6$ Hz), 7.62 (1 H, t, $J = 7.3$ Hz), 7.52 (2 H, t, $J = 7.3$ Hz), 7.30 (1 H, m), 4.56 (2 H, m), 4.39 (1 H, dd, $J = 13.2$, 7.9 Hz), 3.90 (1 H, dd, $J = 13.2$, 4.7 Hz), 2.62–2.74 (1 H, m), 2.46–2.54 (1 H, m), 2.12–2.22 (2 H, m), 1.51 (9 H, s). IR (KBr): 3416, 1783, 1725, 1710, 1696, 1691, 1664, 1658, 1626, 1560, 1487, 1368, 1309, 1250, 1157 cm^{-1}. HRMS (neg ion FAB): calcd for $C_{21}H_{23}N_4O_5$ $(M - H)^-$ 411.1668, found 411.1667.

(*S*)-δ-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-(benzoylamino)-1,2-dihydro-2-oxo-1-pyrimidinehexanoic Acid (2b). To a solution of *N*-benzoyl-protected cytosine Boc lactam (420 mg, 0.99 mmol) in THF (20 mL) was dropwise added a 1 M LiOH solution (5 mL). The reaction mixture was allowed to stir at room temperature and monitored by TLC every 10 min to minimize hydrolysis of the benzamide. The reaction was normally done within 30–40 min. The reaction was quenched by addition of 10% AcOH/MeOH (5 mL) and solvents were evaporated off under reduced pressure. The residue was redissolved in 20% MeOH/$CHCl_3$ and the precipitated solid was filtered. Removal of solvent and column chromatography on silica (5–10% $CH_3OH/CHCl_3$) gave 281 mg (64% yield) of monomer acid **2b** as a white solid, mp 211–212 °C. $[\alpha]^{22}_D = +101.3$ ($c = 0.157$, CH_3OH). ^1H NMR (400 MHz, DMSO-d_6): δ 11.18 (1 H, br s, exchanged with D_2O), 7.99 (2 H, d, $J = 7.5$ Hz), 7.89 (1 H, d, $J = 7.3$ Hz), 7.62 (1 H, t, $J = 7.2$ Hz), 7.51 (2 H, t, $J = 7.7$ Hz), 7.26 (1 H, m; after D_2O exchange turn to br d, $J = 6.4$ Hz), 6.74 (1 H, d, $J = 9.3$ Hz, exchanged with D_2O), 4.05 (1 H, m), 3.77 (1 H, m), 2.20 (2 H, br, t, $J = 7.1$ Hz), 1.33–1.68 (4 H, m), 1.27 and 1.20 (9 H, 2 s). IR (KBr): 3360, 3318, 3309, 3289, 3249, 3185, 3066, 3007, 2978, 2936, 1713, 1701, 1674, 1626, 1572, 1561, 1531, 1492, 1448, 1422, 1374, 1348, 1301, 1278, 1246, 1204 cm^{-1}. Positive ion FABMS: 468 (10), 467 ($(M + Na)^+$, 24), 445 ($(M + H)^+$, 8), 389 (15), 367 (14), 345 (10), 327 (8), 263 (11), 261 (10), 254 (11), 251 (19), 185 (22), 115 (84), 113 (20), 105 (92), 93 (96), 91 (22), 77 (20), 75 (53), 61 (64), 57 (100). Negative ion FABMS, m/z (rel intensity): 445 (12), 444 (43), 443 ($(M - H)^-$, 100), 370 (12), 369 (35), 307 (17), 273 (9), 214 (51), 201 (12). HRMS (neg ion FAB): calcd for $C_{22}H_{27}N_4O_6$ $(M - H)^-$ 443.1930, found 443.1933.

(*S*)-γ-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-(benzoylamino)-1,2-dihydro-2-oxo-1-pyrimidinepentanoic Acid (2a). Compound **12a** (0.50 g, 1.21 mmol) was dissolved in 10 mL of THF, cooled to 0 °C, and treated with 3.64 mL (3.64 mmol) of 1 M LiOH. After being stirred at 0 °C for 15 min, the solution was gradually warmed to 25 °C over 30 min. A solution of 1 M HCl (3.64 mL) was added and the reaction mixture evaporated to dryness. The residue was purified by chromatography on silica (20:1 20% MeOH/$CHCl_3$). The combined fractions were diluted with an equal volume of $CHCl_3$ and filtered to remove precipitated silica. This solution was concentrated in vacuo to approximately 10 mL, and hexanes were added dropwise until the solution became cloudy. The flask was placed in a refrigerator and 48 h later filtered to provide 0.3632 g (0.845 mmol) of pure acid **2a** (70% yield), mp 235–236 °C. $[\alpha]^{22}_D = +118.0$ ($c = 0.1$, MeOH). ^1H NMR (400 MHz, DMSO-d_6): δ 12.15 (1 H, br s), 11.15 (1 H, br s), 7.99 (2 H, d, $J = 7.6$ Hz), 7.90 (1 H, d, $J = 7.2$ Hz), 7.62 (1 H, t, $J = 7.5$ Hz), 7.51 (2 H, t, $J = 7.8$ Hz), 7.25–7.28 (1 H, m), 6.80 (1 H, d, $J = 9.2$ Hz), 4.06–4.11 (1 H, m), 3.74–3.88 (1 H, m), 3.36–3.47 (1 H, m), 2.22–2.33 (2 H, m), 1.48–1.79 (2 H, m), 1.38 (9 H, s). UV (MeOH): λ_{max} = 303, 256, and 224, ϵ = 6900, 17 030, and 14 120 at pH = 7.0, λ_{max} = 316, ϵ – 12 500 at pH = 12.0. IR (KBr): 3408, 1709, 1700, 1686, 1682, 1675, 1667, 1652, 1644, 1641, 1638, 1627, 1623, 1578, 1574, 1572, 1560, 1522, 1503, 1491, 1372, 1253, 1150 cm^{-1}. HRMS (neg ion FAB): calcd for $C_{21}H_{25}N_4O_6$ $(M - H)^-$ 429.1774, found 429.1705.

(*S*)-1,1-Dimethylethyl 2-[(4-Methylbenzenesulfonyl)oxy]methyl]-5-oxo-1-pyrrolidinecarboxylate (13a) and (*S*)-1,1-Dimethylethyl 2-[(4-Methylbenzenesulfonyl)oxy]methyl]-6-oxo-1-piperidinecarboxylate (13b). To a mixture of lactam tosylate **4a** (1.50 g, 5.58 mmol) and DMAP (818 mg, 6.69 mmol) in CH_2Cl_2 (30 mL) were added di-*tert*-butyl dicarbonate (2.02 mL, 8.80 mmol) and Et_3N (2.15 mL, 15.4 mmol) simultaneously. After stirring for 8 h at room temperature, H_2O (1.0 mL) was added to this reaction mixture with vigorous stirring. The resulting mixture was diluted with $CHCl_3$ (150 mL), washed with 0.5 M HCl (3 × 40 mL), saturated $NaHCO_3$ solution (1 × 40 mL), and brine (1 × 40 mL), and then dried over anhydrous Na_2SO_4. Removal of solvent gave 1.97 g (96% yield) of crude product as a yellowish oil. This compound can be further purified by recrystallization from EtOAc–hexanes after column chromatography on silica (1% $CH_3OH/CHCl_3$) to provide 1.74 g of pure **13a** as white crystals (85% overall yield), mp 106–107 °C. $[\alpha]^{22}_D = -40.3$ ($c = 1.024$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.77 (2 H, d, $J = 8.3$ Hz), 7.36 (2 H, d, $J = 8.2$ Hz), 4.32 (1 H, m), 4.14–4.30 (2 H, m), 2.63 (1 H, m), 2.45 (3 H, s), 2.41 (1 H, m), 2.17 (1 H, m), 2.00 (1 H, m), 1.44 (9 H, s). IR (KBr): 3067, 2981, 2956, 2942, 1788, 1775, 1702, 1596, 1474, 1460, 1398, 1371, 1355, 1341, 1318, 1290, 1257, 1206, 1146, 1096, 1044, 1023 cm^{-1}. EIMS, m/z (rel intensity): 296 ($(M - 73)^+$, 2.1), 270 (8.0), 239 (2.7), 187 (4.7), 184 (7.3), 155 (15.4), 140 (2.3), 98 (8.9), 97 (10.1), 92 (3.1), 91 (18.2), 85 (4.9), 84 (100), 83 (3.1), 65 (5.2), 57 (39.2), 56 (8.7), 55 (5.9). Anal. Calcd for $C_{17}H_{23}NO_6S$: C, 55.27; H, 6.28; N, 3.79. Found: C, 55.54; H, 6.32; N, 3.66.

By the same procedure, lactam tosylate **4b** (759 mg, 2.68 mmol) was reacted with di-*tert*-butyl dicarbonate (1.23 mL, 5.36 mmol) to provide 911 mg (89% yield) of the corresponding Boc lactam tosylate **13b** as a pale yellowish oil upon column chromatography on silica (1% $CH_3OH/CHCl_3$). This compound can be further purified by recrystallization from EtOAc–hexane to provide 614 mg of pure material as white crystals (60% overall yield), mp 68–69 °C. $[\alpha]^{22}_D = -29.9$ ($c = 0.408$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.78 (2 H, d, $J = 8.3$ Hz), 7.36 (2 H, d, $J = 8.2$ Hz), 4.38 (1 H, m), 4.11 (1 H, dd, $J = 9.7$, 4.0 Hz), 4.02 (1 H, dd, $J = 9.7$, 7.9 Hz), 2.45 (5 H, s with m), 1.71–2.10 (4 H, m), 1.44 (9 H, s). IR (KBr): 3309, 2966, 2900, 1735, 1662, 1617, 1481, 1400, 1334, 1188, 1177, 1094 cm^{-1}.

(*S*)-1,1-Dimethylethyl 2-[[4-[[4-(1,1-Dimethylethyl)benzoyl]amino]-1,2-dihydro-2-oxo-1-pyrimidinyl]methyl]-5-oxo-1-pyrrolidinecarboxylate (14a) and (*S*)-1,1-Dimethylethyl 2-[[4-[[4-(1,1-Dimethylethyl)benzoyl]amino]-1,2-dihydro-2-oxo-1-pyrimidinyl]methyl]-6-oxo-1-piperidinecarboxylate (14b). Method A. A sample of cytosine Boc lactam **11b** (246 mg, 0.76 mmol) was reacted with 4-*tert*-butylbenzoyl chloride (158 μL, 0.84 mmol) to provide 349 mg (95% yield) of product **14b** according to the procedures described for the preparation of compound **12b**. This fully protected cytosine lactam was further purified by recrystallization from $CHCl_3$–hexanes to provide **14b** as a hygroscopic, pale brownish color solid, mp >260 °C. $[\alpha]^{22}_D = +115.5$ ($c = 1.009$, $CHCl_3$). ^1H NMR (400 MHz, DMSO-d_6): δ 11.11 (1 H, s, exchanged with D_2O), 7.97 (1 H, d, $J = 7.0$ Hz), 7.91 (2 H, d, $J = 8.4$ Hz), 7.53 (2 H, d, $J = 8.5$ Hz), 7.30 (1 H, d, $J = 7.2$ Hz), 4.70 (1 H, br s), 4.10 (1 H, dd, $J = 13.3$, 4.8 Hz), 3.96 (1 H, dd, $J = 13.3$, 9.3 Hz), 2.42–2.62 (2 H, m), 1.69–2.03 (4 H, m), 1.308 and 1.304 (18 H, 2 s). IR (KBr): 3231, 2964, 1766, 1764, 1716, 1670, 1624, 1556, 1489, 1424, 1385, 1367, 1341, 1299, 1256, 1155, 1146, 1065 cm^{-1}. Positive ion FABMS, m/z (rel intensity): 484 (4.1), 483 ($(M + H)^+$, 15.0), 397 (6.0), 384 (7.3), 308 (56.0), 307 (96.8), 306 (24.9), 305 (25.5), 303 (11.0), 223 (7.8), 162 (15.7), 161 (100), 146 (8.3), 145 (7.4), 105 (20.0), 100 (22.5), 99 (34.7), 98 (24.7), 93 (11.1), 84 (24.6), 83 (9.9), 81 (7.2), 60 (10.3), 57 (23.6), 56 (8.8), 55 (19.6). Negative ion FABMS, m/z (rel intensity): 483 (16.2), 482 (53.9), 481 ($(M - H)^-$, 100), 381 (12.8), 271 (6.0), 201 (6.9), 107 (42.9). HRMS (neg ion FAB): calcd for $C_{26}H_{33}N_4O_5$ $(M - H)^-$ 481.2451, found 481.2448.

By the same procedure as for the preparation of **12a**, 1.030 g (3.34 mmol) of **11a** was converted into 1.140 g of the corresponding *tert*-butylbenzoyl derivative **14a** (83% yield), mp 159–161 °C, and 0.153 g of a di-*tert*-butylbenzoylated-cytosine adduct (7% yield).

14a: $[\alpha]^{22}_D$ = +88.2 (c = 0.1, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.78 (1 H, bs), 7.84 (2 H, d, J = 8.3 Hz), 7.64 (1 H, d, J = 7.2 Hz), 7.53 (3 H, d, J = 8.3 Hz), 4.56–4.60 (1 H, m), 4.40 (1 H, dd, J = 13.5, 6.9 Hz), 3.93 (1 H, dd, J = 13.5, 5.2 Hz), 2.62–2.69 (1 H, m), 2.45–2.52 (1 H, m), 2.13–2.19 (2 H, m), 1.53 (9 H, s), 1.36 (9 H, s). IR (KBr): 3406, 2968, 1782, 1716, 1710, 1698, 1690, 1687, 1666, 1657, 1654, 1645, 1627, 1559, 1550, 1489, 1370, 1309, 1255, 1155 cm^{-1}. HRMS (neg ion FAB): calcd for $C_{25}H_{31}N_4O_5$ (M − H)$^-$ 467.2294, found 467.2309.

Method B. To a solution of 4-*N*-(4-*tert*-butylbenzoyl)cytosine (**16**) (815 mg, 3.0 mmol) and potassium *tert*-butoxide (337 mg, 3.0 mmol) in DMSO (5 mL) was added dropwise a DMSO (5 mL) solution of tosylate **13a** (590 mg, 1.60 mmol). After 10 h at 65 °C, the reaction was quenched by addition of 10% AcOH/$CHCl_3$ (10 mL) and diluted with $CHCl_3$ (150 mL). The resulting mixture was washed with 50% saturated NaCl solution (3 × 50 mL), saturated $NaHCO_3$ solution (1 × 50 mL), and brine (1 × 50 mL) and then dried over anhydrous Na_2SO_4. Removal of solvent and column chromatography on silica (5–10% MeOH/$CHCl_3$) gave 532 mg (71% yield) of **14a**.

By the same procedure, **14b** can be obtained from **13b** (150 mg, 0.39 mmol) in relatively low yield (5%). However, when the reaction was carried out at room temperature for 48 h, the yield was marginally improved (19%) and considerable amounts of lactam tosylate **4b** (45%) could be isolated.

(*S*)-γ-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-[[4-(1,1-dimethylethyl)benzoyl]amino]-2-oxo-1(2*H*)-pyrimidinepentanoic Acid (15a). Lactam **14a** (2.0 g, 4.27 mmol) was dissolved in a mixture of THF (12.8 mL), *tert*-butyl alcohol (8.5 mL), ethanol (4.2 mL), and H_2O (4.2 mL) and stirred in a room temperature bath. To this was added an ice-cold solution of 1 M LiOH (29.9 mL) all at once. The pale yellow solution was stirred for 8 min and then diluted with H_2O (100 mL) and neutralized by the addition of 80% acetic acid (5 mL). The precipitate was filtered, washed with H_2O, and dried in vacuo over P_2O_5 to provide 1.52 g (73% yield) of the pure acid **15a**, mp 238–240 °C. $[\alpha]^{22}_D$ = +112.8 (c = 0.25, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.15 (1 H, br s), 11.15 (1 H, br s), 7.95 (2 H, m), 7.90 (1 H, d, J = 7.1 Hz), 7.52 (2 H, d, J = 8.6 Hz), 7.25 (1 H, br s), 6.83 (1 H, d, J = 9.1 Hz), 4.09 (1 H, dd, J = 13.2, 3.7 Hz), 3.72–3.83 (1 H, m), 3.44 (1 H, dd, J = 14.4, 7.6 Hz), 2.06–2.19 (2 H, m), 1.53–1.74 (2 H, m), 1.28 and 1.31 (18 H, 2 singlets, 2:1). IR (KBr): 3371, 2968, 1705, 1703, 1680, 1653, 1644, 1626, 1623, 1571, 1560, 1550, 1545, 1522, 1496, 1409, 1390, 1372, 1350, 1299, 1260, 1168, 1114 cm^{-1}. HRMS (neg ion FAB): calcd for $C_{25}H_{33}N_4O_6$ (M − H)$^-$ 485.2400, found 485.2425.

(*S*)-δ-[[(1,1-Dimethylethoxy)carbonyl]amino]-4-[[4-(1,1-dimethylethyl)benzoyl]amino]-2-oxo-1(2*H*)-pyrimidinehexanoic Acid (15b). A sample of 4-*N*-(4-*tert*-butylbenzoyl)-cytosine Boc lactam **14b** (96.2 mg, 199.6 μmol) was dissolved in a mixture of THF/*tert*-butyl alcohol/EtOH/H_2O (2.0 mL, 3:2:2:1) and stirred at room temperature. To this solution was added 1 M LiOH (2.0 mL) all at once. The pale yellow reaction mixture was stirred for 3–5 min and then quenched with excess AcOH (1.0 mL). The resulting mixture was concentrated to ~1/2 volume under reduced pressure and then H_2O (15 mL) was added. The white precipitate was filtered, washed with H_2O, and dried in vacuo over P_2O_5 to provide 88.1 mg (88% yield) of the acid **15b**. This carboxylic acid was used for the activation reaction without further purification; however, it was further purified by column chromatography on silica (5 to 15% $CH_3OH/CHCl_3$) to provide pure material for analysis as a white solid, mp 193 °C. $[\alpha]^{22}_D$ = +93.7 (c = 0.479, CH_3OH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.07 (1 H, s, exchanged with D_2O), 7.95 (2 H, d, J = 8.6 Hz), 7.88 (1 H, d, J = 7.2 Hz), 7.53 (2 H, d, J = 8.4 Hz), 7.27 (1 H, br s), 6.77 (1 H, d, J = 9.3 Hz), 4.10 (1 H, dd, J = 13.3, 4.8 Hz), 3.77 (1 H, m), 3.38 (1 H, m), 2.21 (2 H, br t, J = 7.0 Hz), 1.22–1.76 (4 H, m), 1.31 and 1.27 (18 H, 2 s). IR (KBr): 3357, 3228, 3149, 3071, 3014, 2967, 2869, 2619, 2566, 2513, 1708, 1699, 1675, 1660, 1644, 1627, 1561, 1527, 1502, 1461, 1425, 1376, 1323, 1299, 1287, 1250, 1200, 1165, 1115 cm^{-1}. Positive ion FABMS, m/z (rel intensity): 501 ((M + H)$^+$, 1.5), 4.59 (1.7), 421 (2.6), 415 (6.2), 401 (2.6), 307 (2.7), 278 (1.9), 272 (5.5), 162 (12.8), 161 (100), 160 (1.7), 159 (3.9), 147 (1.8), 146 (9.0), 145 (6.9), 130 (1.8), 118 (7.0), 115 (2.3), 112 (5.8), 105 (5.5), 91 (5.5), 77 (2.1), 73 (2.0), 61 (3.1) 57 (14.4), 55 (2.6). Negative ion FABMS, m/z (rel intensity): 501 (16.8), 500 (54.7), 499 ((M − H)$^-$, 100), 426 (8.1), 425 (30.1), 271 (8.2), 270 (41.8), 143 (8.8). HRMS (neg ion FAB): calcd for $C_{26}H_{35}N_4O_6$ (M − H)$^-$ 499.2556, found 499.2559.

4-(1,1-Dimethylethyl)-*N*-[1,2-dihydro-2-oxo-4-pyrimidinyl]benzamide (16). To a suspension of cytosine (5.0 g, 43 mmol) in pyridine–CH_2Cl_2 (1:4; 50 mL) was added dropwise *tert*-butylbenzoyl chloride (10.6 mL, 56.6 mmol). After 4 h at room temperature, H_2O (10 mL) and $CHCl_3$ (40 mL) were added to the reaction mixture with vigorous stirring. The precipitates were collected and washed with H_2O. The organic layer of the filtered solution was separated and washed with 1 M HCl (30 mL × 2) and brine (30 mL × 1), quickly dried over anhydrous Na_2SO_4, and evaporated to 1/3 volume (~20 mL). Hexanes (50 mL) were added and the combined precipitates were dried under high vacuum over P_2O_5 for 8 h to provide 11.2 g (92% yield) of desired product, mp >260 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.59 (1 H, br s, exchanged with D_2O), 11.03 (1 H, br s, exchanged with D_2O), 7.96 (2 H, d, J = 8.42 Hz), 7.87 (1 H, d, J = 7.08 Hz), 7.53 (2 H, d, J = 8.43 Hz), 7.22 (1 H, br s), 1.31 (9 H, s). IR (KBr): 3600–2100 (br), 1850, 1680, 1580, 1440, 1300, 1240, 1110 cm^{-1}. Negative ion FABMS, m/e (rel intensity): 271 (17.9), 270 ((M − H)$^-$, 100). HRMS (neg ion FAB): calcd for $C_{15}H_{16}N_3O_2$ (M − H)$^-$ 270.1242, found 270.1237.

4-(1,1-Dimethylethyl)-*N*-[1*H*-purin-6-yl]benzamide (17). Adenine (1.35 g, 10 mmol) was suspended in 15 mL of pyridine, 4-*tert*-butylbenzoyl chloride (5.91 g, 30 mmol) was added, and the mixture was heated at reflux for 2 h. The mixture was cooled to room temperature and treated with water (0.54 mL) and the solution again brought to reflux. After 1 h water (0.54 mL) was added and heating continued for 1 h more. To the cooled mixture were added 20% 2-propanol/$CHCl_3$ (100 mL) and water (50 mL). After vigorous mixing and separation of the layers, the water layer was washed with $CHCl_3$ (20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated. The residue was dissolved in dry pyridine (50 mL) and treated with hexane (200 mL). The product precipitates as a pure, off-white solid (1.75 g, 59%), mp 258 °C. An analytical sample was obtained by recrystallization from $CHCl_3$/hexanes. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.37 (1 H, s, exchanged with D_2O), 11.48 (1 H, s, exchanged with D_2O), 8.73 (1 H, s), 8.50 (1 H, d, J = 1.3 Hz; s after D_2O shake), 8.08 (2 H, d, J = 8.4 Hz), 7.60 (2 H, d, J = 8.4 Hz), 1.34 (9 H, s). IR (KBr): 3193, 3111, 2961, 1686, 1551, 1518, 1507, 1457, 1386, 1342, 1276, 1265, 1193, 1144, 1113, 1095 cm^{-1}. Negative ion FABMS, m/z (rel intensity): 295 (21.2), 294 ((M − H)$^-$, 100), 278 (8.3), 201 (12.8), 160 (11.0), 134 (10.4), 133 (6.6), 117 (11.3). HRMS (neg ion FAB): calcd for $C_{16}H_{16}N_5O$ (M − H)$^-$ 294.1355, found 294.1364. Anal. Calcd for $C_{16}H_{17}N_5O$: C, 65.07; H, 5.80; N, 23.71. Found: C, 64.84; H, 5.66; N, 23.70.

(*S*)-1,1-Dimethylethyl 2-[[6-[[(1,1-Dimethylethyl)-benzoyl]amino]-9*H*-purin-9-yl]methyl]-1-pyrrolidinecarboxylate (18a) and (*S*)-1,1-Dimethylethyl 2-[[6-[[(1,1-Dimethylethyl)benzoyl]amino]-9*H*-purin-9-yl]methyl]-1-piperidinecarboxylate (18b). According to the same procedure as for **14a**, tosylate **13a** (309 mg, 0.84 mmol) was converted to 302 mg (73% yield) of the corresponding 6-*N*-(*tert*-butylbenzoyl)-adenine derivative **18a**, as an amorphous solid after purification by column chromatography on silica (5% MeOH/$CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.09 (1 H, s, exchanged with D_2O), 8.70 (1 H, s), 8.46 (1 H, s), 7.99 (2 H, d, J = 8.4 Hz), 7.57 (2 H, d, j = 8.5 Hz), 4.46–4.68 (3 H, m), 2.20 (3 H, m), 1.89 (1 H, m), 1.30–1.50 (18 H, m with 2 s). IR (KBr): 3500, 3400, 3250, 3050, 2950, 1720, 1565, 1440 cm^{-1}. Negative ion FABMS, m/z (rel intensity): 493 (5.2), 492 (16.1), 491 ((M − H)$^-$, 42.0), 392 (7.0), 391 (25.2), 306 (6.6), 295 (21.4), 294 (100), 278 (10.8), 201 (22.1), 185 (6.1), 160 (15.0), 134 (15.3), 133 (8.6), 117 (13.0), 92 (6.2). HRMS (neg ion FAB): calcd for $C_{26}H_{31}N_6O_4$ (M − H)$^-$ 491.2407, found 491.2407.

Similarly, tosylate **13b** (99 mg, 0.26 mmol) yielded 41 mg (31% yield) of **18b** after column purification, except that the reaction was carried out at room temperature for 36 h. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.10 (1 H, s, exchanged with D_2O), 8.72 (1 H, s), 8.38 (1 H, s), 7.98 (2 H, d, J = 8.4 Hz), 7.57 (2 H, d, J = 8.4 Hz), 4.74 (1 H, m), 4.50 (2 H, m), 2.07 (1 H, br m), 1.89 (1 H, br m), 1.74 (2 H, br m), 1.30–1.47 (11 H, m with s), 1.22 (9 H, s). IR (KBr): 3440, 3350, 3100, 3050, 2950, 1760, 1690, 1605, 1585, 1460, 1415, 1350, 1320, 1275, 1155, 1135 cm^{-1}. Negative ion FABMS,

m/z (rel intensity): 507 (6.0), 506 (32.7), 505 ($(M - H)^-$, 100), 405 (19.5), 295 (10.9), 294 (55.0), 278 (6.0), 201 (8.2), 172 (6.5), 171 (54.3), 160 (6.0), 151 (9.0), 122 (8.8), 117 (5.9), 92 (5.0). HRMS (neg ion FAB): calcd for $C_{27}H_{33}N_6O_4$ $(M - H)^-$ 505.2562, found 505.2574.

When the reaction of **13b** with 6-*N*-(*tert*-butylbenzoyl)adenine was carried out at 75 °C, compound **18c** was isolated in 25% yield. ^1H NMR (300 MHz, DMSO-d_6): δ 11.09 (1 H, s, exchanged with D_2O), 8.74 (1 H, s), 8.44 (1 H, s), 7.99 (2 H, d, J = 8.4 Hz), 7.75 (1 H, s, exchanged with D_2O), 7.57 (2 H, d, J = 8.4 Hz), 4.42 (1 H, dd, J = 14.1, 5.1 Hz), 4.26 (1 H, dd, J = 14.0, 6.2 Hz), 3.87 (1 H, m), 2.08 (2 H, m), 1.72 (2 H, m), 1.54 (1 H, m), 1.34 (9 H, s), 1.28 (1 H, m). IR (KBr): 3200, 3075, 2950, 2875, 1650, 1600, 1580, 1520, 1480, 1450, 1405, 1300, 1260, 1160, 1120 cm^{-1}. Negative ion FABMS, m/z (rel intensity): 406 (26.7), 405 ($(M - H)^-$, 100), 404 (5.2), 403 (5.9), 295 (6.1), 294 (30.2), 201 (5.8), 188 (5.8), 151 (6.0). HRMS (neg ion FAB): calcd for $C_{22}H_{25}N_6O_2$ $(M - H)^-$ 405.2039, found 405.2043.

Standard Procedure for Formation of *p*-Nitrophenyl Esters To Be Used in Coupling Reactions. To a mixture of carboxylic acid **15b** (65 mg, 130 μmol), 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide methiodide (58 mg, 195 μmol), *p*-nitrophenol (90 mg, 650 μmol), and 4-(dimethylamino)pyridine (8 mg, 65 μmol) was added CH_2Cl_2 (5 mL). After complete disappearance of the starting carboxylic acid was achieved, TLC showed formation of a less polar material, which turned yellow when exposed to ammonia fumes. The reaction mixture was diluted with 20% 2-propanol/$CHCl_3$ (40 mL), washed with 0.15 M NaOH (3 × 10 mL), 0.5 M HCl (2 × 10 mL), and brine (1 × 10 mL), and then dried over anhydrous Na_2SO_4. After removal of solvent, the residual solid was dried further under high vacuum for 8 h and redissolved in CH_2Cl_2 or DMF (5 mL) for use in coupling reactions. Small amounts of **20a,b** were purified by column chromatography (2% $CH_3OH/CHCl_3$) to provide samples for spectroscopic analysis.

20b: ^1H NMR (300 MHz, DMSO-d_6): δ 11.06 (1 H, s, exchanged with D_2O), 8.31 (2 H, d, J = 9.1 Hz), 7.95 (2 H, d, J = 8.5 Hz), 7.91 (1 H, d, J = 7.1 Hz), 7.52 (2 H, d, J = 8.6 Hz), 7.45 (2 H, d, J = 9.0 Hz), 7.29 (1 H, d, J = 7.1 Hz), 6.84 (1 H, d, J = 9.3 Hz, exchanged with D_2O), 4.10 (1 H, m), 3.83 (1 H, m), 3.43 (1 H, m), 2.68 (2 H, t, J = 7.1 Hz), 1.70 (2 H, m), 1.51 (2 H, m), 1.15–1.40 (18 H, m). Negative ion FABMS, m/z (rel intensity): 622 (9.8), 621 (35.2), 620 ($(M - H)^-$, 70.0), 270 (16.0), 139 (7.4), 138 (100), 122 (10.2), 42 (12.1). HMRS (neg ion FAB): calcd for $C_{32}H_{38}N_5O_8$ $(M - H)^-$ 620.2720, found 620.2727.

20a: ^1H NMR (300 MHz, DMSO-d_6): δ 11.08 (1 H, s, exchanged with D_2O), 8.32 (2 H, d, J = 9.0 Hz), 7.96 (2 H, d, J = 8.2 Hz), 7.93 (1 H, d, J = 5.8 Hz), 7.53 (2 H, d, J = 8.4 Hz), 7.46 (2 H, d, J = 9.0 Hz), 7.30 (1 H, d, J = 7.3 Hz), 6.90 (1 H, d, J = 9.4 Hz, exchanged with D_2O), 4.16 (1 H, m), 3.93 (1 H, m), 3.49 (1 H, m), 2.70 (2 H, t, J = 6.9 Hz), 1.64–1.98 (2 H, m), 1.13–1.42 (18 H, m). Negative ion FABMS, m/z (rel intensity): 607 (6.3), 606 ($(M - H)^-$, 14.4), 467 (5.2), 325 (7.8), 270 (21.9), 188 (11.0), 139 (7.2), 138 (100), 122 (7.6), 113 (8.3), 42 (12.1). HRMS (neg ion FAB): calcd for $C_{31}H_{36}N_5O_8$ $(M - H)^-$ 606.2564, found 606.2570.

(*S*)-1,1-Dimethylethyl [1-[[4-[[4-(1,1-Dimethylethyl)-benzoyl]amino]-1,2-dihydro-2-oxo-1-pyrimidinyl]methyl]-5-oxo-5-(benzylamino)pentyl]carbamate (21). Method A. To a mixture of carboxylic acid **2b** (21.6 mg, 0.049 mmol), 1,3-dicyclohexylcarbodiimide (13 mg, 0.063 mmol), *p*-nitrophenol (13 mg, 0.093 mmol), and 4-(dimethylamino)pyridine (3 mg, 0.025 mmol) was added CH_2Cl_2 (3 mL). After 12 h at room temperature, the resulting mixture was diluted with 10% 2-propanol/$CHCl_3$ (20 mL), washed with H_2O (2 × 5 mL), 5% aqueous HOAc (2 × 5 mL), and brine (2 × 5 mL), and then dried over Na_2SO_4. Following evaporation, the residue was redissolved in CH_2Cl_2 (3 mL) and a sample of distilled benzylamine (10 μL, 0.092 mmol) was added. After 8 h at room temperature, the resulting mixture was diluted with 10% 2-propanol/$CHCl_3$ (20 mL), washed with saturated $NaHCO_3$ solution (2 × 5 mL), 0.5 M HCl (2 × 5 mL), and brine (2 × 5 mL), and dried over anhydrous Na_2SO_4. Removal of solvent and column chromatography on silica (1–5% $CH_3OH/CHCl_3$) gave 21 mg (80% yield) of **21**. ^1H NMR (400 MHz, DMSO-d_6): δ 11.14 (1 H, s exchanged with D_2O), 8.33 (1 H, s, exchanged with D_2O), 8.00 (2 H, d, J = 7.5 Hz), 7.90 (1 H, d, J = 7.0 Hz), 7.62 (1 H, t, J = 7.7 Hz), 7.51 (2 H, t, J = 7.6 Hz), 7.18–7.38 (6 H, m), 6.77 (1 H, d, J = 9.4 Hz, exchanged with D_2O), 4.26 (2 H, d, J = 5.8 Hz), 4.08 (1 H, dd, J = 13.0, 2.6 Hz), 3.79 (1 H, m), 3.40 (1 H, m), 2.15 (2 H, br t, J = 7.5 Hz), 1.35–1.70 (4 H, m), 1.28 and 1.20 (9 H, 2 s). IR (KBr): 3320, 3060, 3020, 2925, 1665, 1640, 1620, 1480, 1370, 1300, 1240, 1165, 1115 cm^{-1}. Negative ion FABMS, m/z (rel intensity): 534 (16.8), 533 (57.1), 532 ($(M - H)^-$, 100), 458 (13.4), 354 (19.5), 313 (10.7), 273 (13.6), 253 (10.3), 251 (22.2), 249 (12.8), 237 (33.4), 214 (37.4), 197 (15.8), 167 (18.7), 165 (51.3), 163 (20.9), 145 (34.2), 143 (70.4), 139 (27.6). HMRS (neg ion FAB): calcd for $C_{29}H_{34}N_5O_5$ $(M - H)^-$ 532.2560; found 532.2574.

Method B. A mixture of carboxylic acid **2b** (34 mg, 76.6 μmol), *N,N'*-disuccinimidyl carbonate[11,12] (DSC, 40 mg, 156 μmol), and pyridine (12 μL, 150 μmol) in DMF (2 mL) was stirred at room temperature. Upon complete consumption of the acid, the reaction was quenched with H_2O (0.5 mL). The reaction mixture was evaporated to dryness and diluted with 10% 2-propanol/$CHCl_3$ (20 mL). This solution was washed with H_2O (2 × 5 mL) and brine (5 mL) and then dried over Na_2SO_4. Following evaporation, the residue was redissolved in CH_2Cl_2 (2 mL) and a sample of distilled benzylamine (20 μL, 0.18 mmol) was added. After 8 h at room temperature, the resulting mixture was evaporated to dryness and the residue chromatographed on silica (5% $CH_3OH/CHCl_3$) to give 32 mg (78% yield) of product **21**. This procedure was abandoned due to the isolation of *N*-hydroxysuccinimidyl benzoate in the subsequent dimerization attempt. Succinimidyl benzoate. ^1H NMR (400 MHz, $CDCl_3$): δ 8.16 (2 H, d, J = 7.6 Hz), 7.68 (1 H, t, J = 7.6 Hz), 7.54 (2 H, d, J = 7.6 Hz), 2.92 (4 H, s).

Method C. To a mixture of carboxylic acid **2b** (18 mg, 40.5 μmol) and *N,N'*-bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride[13] (12 mg, 47.1 μmol) were added CH_2Cl_2 (2 mL) and Et_3N (10 μL, 71.7 μmol). After 12 h at room temperature, a sample of distilled benzylamine (10 μL, 92 μmol) was added and allowed to stir for an additional 12 h. The resulting mixture was evaporated to dryness and the residue chromatographed on silica (5% $CH_3OH/CHCl_3$) to give 14.2 mg (67% yield) of product **21**.

(*S*)-1,1-Dimethylethyl [1-[[4-[[4-(1,1-Dimethylethyl)-benzoyl]amino]-1,2-dihydro-2-oxo-1-pyrimidinyl]methyl]-4-oxo-4-(1-piperidinylamino)butyl]carbamate (22a) and (*S*)-1,1-Dimethylethyl [1-[[4-[[4-(1,1-Dimethylethyl)-benzoyl]amino]-1,2-dihydro-2-oxo-1-pyrimidinyl]methyl]-5-oxo-5-(1-piperidinylamino)pentyl]carbamate (22b). The carboxylic acid **15b** (28.1 mg, 56 μmol) was converted to its corresponding *p*-nitrophenyl ester **20b** according to the standard procedure. In a separate flask, a suspension of 1-aminopiperidine oxalate[14] (22 mg, 156 μmol) in dry DMF (1 mL) was treated with dry Et_3N (150 μL, 1.08 mmol) and stirred at room temperature for 30 min. This hydrazine-containing solution was then injected into the freshly prepared activated ester solution. After 12 h at room temperature, the volatiles were evaporated off under reduced pressure. The residual oil was diluted with 20% 2-propanol/$CHCl_3$ (30 mL), washed with 0.15 M NaOH (3 × 10 mL), 0.1 M HCl (2 × 10 mL), and brine (1 × 10 mL), and then dried over anhydrous Mg_2SO_4. Removal of solvent under reduced pressure and drying under high vacuum for 8 h provided 30 mg (93% yield) of crude product. This crude hydrazide derivative was generally subjected to further reaction without purification; however, it could be purified by column chromatography on silica (5% $CH_3OH/CHCl_3$) to give pure material as a hygroscopic, yellowish amorphous solid. ^1H NMR (400 MHz, DMSO-d_6): δ 11.05 (1 H, s), 8.70 and 8.30 (1 H, 2 s), 7.95 (2 H, d, J = 8.3 Hz), 7.89 (1 H, br d, J = 7.2 Hz), 7.53 (2 H, d, J = 8.4 Hz), 7.28 (1 H, br d, J = 6.8 Hz), 6.75 (1 H, m), 4.06 (1 H, m), 3.77 (1 H, m), 3.42 (1 H, m), 2.64 (2 H, m), 2.33 (2 H, m), 1.96 (2 H, m), 1.11–1.67 (28 H, m with singlets). IR (KBr): 3375, 3220, 3125, 2960, 1755, 1675, 1620, 1590, 1555, 1480, 1370, 1350, 1295, 1260, 1205, 1160, 1115 cm^{-1}. Negative ion FABMS, m/z (rel intensity): 583 (20), 582 (66), 581 ($(M - H)^-$, 100), 567 (12), 566 (21), 526 (12), 507 (16), 381 (12), 271 (11), 270 (63), 201 (13), 153 (94), 87 (16), 75 (12).

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HRMS (neg ion FAB): calcd for $C_{31}H_{45}N_6O_5$ $(M - H)^-$ 581.3451, found 581.3489.

By this procedure, **20a** (93.6 mg, 0.154 mmol) provided 74 mg of crude hydrazide-protected monomer **22a** (84% yield). The crude material was generally taken on directly to the next reaction, but could also be purified on silica (1.25–10% MeOH/$CHCl_3$) to provide 57 mg of pure **22a** (65% yield). ^1H NMR (300 MHz, DMSO-d_6): δ 11.05 (1 H, s, exchanged with D_2O), 8.80 and 8.32 (1 H, 2 s), 7.95 (2 H, d, J = 8.3 Hz), 7.88 (1 H, t, J = 6.5 Hz), 7.53 (2 H, d, J = 8.4 Hz), 7.27 (1 H, d, J = 7.1 Hz), 6.73 (1 H, dd, J = 9.5, 4.9 Hz), 4.08 (1 H, m), 3.76 (1 H, m), 3.42 (1 H, m), 2.65 (2 H, m), 2.25–2.48 (2 H, m), 2.02 (2 H, m), 1.25–1.80 (26 H, m with singlets). IR (KBr): 3353, 3245, 2956, 2936, 1695, 1685, 1680, 1675, 1658, 1626, 1623, 1559, 1550, 1545, 1522, 1489, 1369, 1350, 1297, 1268, 1255 cm^{-1}. Positive FABMS, m/z (rel abundance): 570 (19.4), 569 ($(M + H)^+$, 70.9), 469 (17.2), 457 (23.1), 451 (35.8), 307 (47.0), 272 (38.1), 198 (15.7), 146 (47.8), 145 (29.1), 118 (29.1), 105 (15.7), 101 (22.4), 100 (23.9), 99 (35.8), 84 (66.4), 61 (24.6), 57 (100.0), 55 (28.4). HRMS (neg ion FAB): calcd for $C_{30}H_{43}N_6O_5$ $(M - H)^-$ 567.3295, found 567.3288.

(*S*)-2-[[5-[[(1,1-Dimethylethoxy)carbonyl]amino]-6-[4-[[4-(1,1-dimethylethyl)benzoyl]amino]-1,2-dihydro-2-oxo-1-pyrimidinyl]-1-oxohexyl]methylamino]ethyl 4-(1,2-Dimethylethyl)benzoate (24b). Carboxylic acid **15b** (65 mg, 130 μmol) was converted into the active ester **20b** by the standard procedure and redissolved in CH_2Cl_2 (5 mL). To this solution was added 2-(methylamino)ethanol (30 μL, 370 μmol), and the resulting mixture was stirred at room temperature for 8 h. Removal of the volatiles and column chromatography on silica (5 to 10% $CH_3OH/CHCl_3$) gave 59 mg (82% yield) of **23b** as an amorphous yellowish solid. ^1H NMR (300 MHz, DMSO-d_6): δ 11.05 (1 H, s, exchanged with D_2O), 7.95 (2 H, d, J = 8.4 Hz), 7.89 (1 H, d, J = 6.8 Hz), 7.53 (2 H, d, J = 8.4 Hz), 7.28 (1 H, d, J = 6.9 Hz), 6.77 (1 H, d, J = 9.0 Hz; exchanged with D_2O), 4.81 and 4.65 (2 H, 2 t, J = 5.4 Hz), 4.05 (1 H, m), 3.78 (1 H, m), 3.40–3.57 (2 H, m), 2.98 and 2.81 (3 H, 2 s), 2.22–2.42 (2 H, m), 1.17–1.65 (22 H, m with singlets). Negative ion FABMS, m/z (rel intensity): 558 (9.8), 557 (40.7), 556 $(M - H)^-$, 100), 483 (5.3), 482 (16.7), 439 (6.0), 271 (3.7), 270 (20.3), 201 (4.6), 151 (4.2), 42 (17.8). HRMS (neg ion FAB): calcd for $C_{29}H_{42}N_5O_6$ $(M - H)^-$ 556.3135, found 556.3151.

To a mixture of 2-(methylamino)ethanol-capped monomer **23b** (24.6 mg, 44 μmol) and 4-(dimethylamino)pyridine (11 mg, 90 μmol) in CH_2Cl_2 (2.5 mL) was added 4-*tert*-butylbenzoyl chloride (10 μL, 51.2 μmol) at room temperature with stirring. The reaction was monitored by TLC every 2 h. After the reaction went to completion, the reaction mixture was diluted with 20% 2-propanol/$CHCl_3$ (30 mL), washed with saturated $NaHCO_3$ solution (2 × 10 mL), 0.5 M HCl (1 × 10 mL), and brine (1 × 10 mL), and then dried over anhydrous Na_2SO_4. Removal of solvent and column chromatography on silica (5% $CH_3OH/CHCl_3$) gave 26.5 mg (84% yield) of **24b** as a pale yellowish amorphous solid. ^1H NMR (300 MHz, DMSO-d_6): δ 11.04 (1 H, s, exchanged with D_2O), 7.95 (2 H, d, J = 8.2 Hz), 7.88 (3 H, m), 7.48–7.58 (4 H, m), 7.27 (1 H, d, J = 7.1 Hz), 6.76 (1 H, d, J = 9.4 Hz, exchanged with D_2O), 4.32–4.47 (2 H, m), 4.05 (1 H, m), 3.45–3.88 (4 H, m), 3.05 and 2.86 (3 H, 2 s), 2.27–2.43 (2 H, m), 1.15–1.64 (31 H, m, with singlets). IR (KBr): 3275, 3050, 2960, 1650, 1550, 1480, 1370, 1300, 1270, 1190, 1170, 1115 cm^{-1}. Negative ion FABMS, m/z (rel intensity): 718 (22), 717 (64), 716 $((M - H)^-$, 100), 529 (15), 470 (12), 413 (19), 353 (27), 289 (17), 271 (19), 270 (45), 211 (17), 201 (16), 189 (18), 177 (78), 153 (52), 133 (16). HRMS (neg ion FAB): calcd for $C_{40}H_{54}N_5O_7$ $(M - H)^-$ 716.4023, found 716.4026.

(*S*)-2-[[4-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-[4-[[4-(1,1-dimethylethyl)benzoyl]amino]-1,2-dihydro-2-oxo-1-pyrimidinyl]-1-oxopentyl]methylamino]ethyl 4-(1,2-Dimethylethyl)benzoate (24a). 2-(Methylamino)ethanol (15 μL, 0.185 mmol) was added to active ester **20a** (0.154 mmol) in DMF followed by 22 μL (0.154 mmol) of Et_3N. The reaction mixture was allowed to stir at 25 °C for 2 h, evaporated to dryness, and dissolved in 30 mL of 20% 2-propanol/$CHCl_3$. The organic layer was extracted once with a 5-mL portion of H_2O, six times with 5-mL portions of 0.20 M NaOH, twice with 5-mL portions of 0.02 M HCl, and once with a 5-mL portion of saturated brine. The aqueous layers were each back-extracted once with 20% 2-propanol/$CHCl_3$. The combined organic layers were dried over Na_2SO_4 and evaporated to dryness, providing 62 mg (0.114 mmol) of the corresponding alcohol (74% crude yield). This alcohol (**23a**) was neither purified nor characterized at this stage, but rather protected directly, and characterized as the 4-*tert*-butylbenzoyl ester **24a**. The crude alcohol was dried by two coevaporations with 3-mL portions of dry pyridine. This residue was dissolved in 0.60 mL of dry pyridine and 25 μL (0.125 mmol) of 4-*tert*-butylbenzoyl chloride was added at 25 °C. After being stirred for 30 min, a small amount of water was added, and the reaction mixture was evaporated to dryness. The residue was then purified on silica (1.25–5% MeOH/$CHCl_3$ gradient), providing 59 mg (0.084 mmol) of **24a** (73%). ^1H NMR (300 MHz, DMSO-d_6): δ 11.05 (1 H, s, exchanged with D_2O), 7.95 (2 H, d, J = 8.4 Hz), 7.87 (3 H, m), 7.55 (4 H, m), 7.28 (1 H, br d, J = 4.6 Hz), 6.77 (1 H, dd, J = 9.1, 4.4 Hz, exchanged with D_2O), 4.32–4.42 (2 H, m), 4.05 (1 H, m), 3.60–3.85 (4 H, m), 3.04 and 2.86 (3 H, 2 s), 2.25–2.48 (2 H, m), 1.50–1.75 (2 H, m), 1.17–1.35 (27 H, m with singlets). IR (KBr): 2964, 2961, 2928, 1730, 1717, 1709, 1694, 1687, 1653, 1644, 1637, 1627, 1622, 1612, 1560, 1493, 1422, 1411, 1366, 1318, 1289, 1270, 1160 cm^{-1}. Negative ion FABMS, m/z (rel abundance): 703 (20.0), 702 $((M - H)^-$, 100.0), 602 (5.2), 542 (3.4), 450 (4.0), 270 (39.7), 201 (6.9), 177 (29.3). HRMS (pos ion FAB): calcd for $C_{39}H_{54}N_5O_7$ $(M + H)^+$ 704.4023, found 704.4009.

General Procedure for Oligomerization. To a suspension of a terminal-capped *t*-Boc-protected subunit (5 μmol) in CH_2Cl_2 (1 mL) was added trifluoroacetic acid (0.25 mL). The reaction mixture was allowed to stir at room temperature until complete disappearance of starting material was achieved. The volatiles were evaporated off under reduced pressure at room temperature. To this residual oil was added 1.2 equiv of *p*-toluenesulfonic acid. The residue was then coevaporated three times with $CHCl_3$ (1 mL) and twice with dry DMF (0.5 mL) and dried further under high vacuum for 8 h. Prior to the coupling reaction, this *p*-toluenesulfonic acid salt of the subunit was dissolved in dry DMF (0.5 mL) and excess dry Et_3N (20 equiv). To this free amine containing solution was then added a CH_2Cl_2 solution of *p*-nitrophenyl ester of the acid (2.0 equiv), which was prepared separately by the standard procedure. The coupling reaction was followed by TLC until complete disappearance of the amine component was achieved. The reaction was normally done within 8 h. The resulting mixture was evaporated to dryness, and the residual oil was diluted with 20% 2-propanol/$CHCl_3$ (20 mL), washed with 0.15 M NaOH (3 × 5 mL), 0.5 M HCl (1 × 5 mL), and brine (1 × 5 mL), and then dried over anhydrous Mg_2SO_4. Removal of solvent under reduced pressure and purification either by column chromatography (2–10% $CH_3OH/CHCl_3$) or preparative TLC (1 × 2% $CH_3OH/CHCl_3$, 1 × 5% $CH_3OH/CHCl_3$, 1 × 10% $CH_3OH/CHCl_3$) provided the material for spectral analysis and for further coupling reactions. The purity of the oligomers was confirmed by analytical HPLC (30–40% CH_3OH/CH_2Cl_2 on Beckman Ultrasphere-Si column) as a evidenced by symmetrical peak. Collection of peaks from the HPLC allowed further characterization by negative ion FABMS, high field ^1H NMR, and COSY experiments.

Dimer Hydrazides 25a,b. According to the procedure for oligomerization, the hydrazide monomer **22b** (14.5 mg, 24.9 μmol) was coupled with the *p*-nitrophenyl ester **20b** to provide 18.2 mg (76% yield) of hydrazide dimer **25b** after purification. ^1H NMR (400 MHz, DMSO-d_6): δ 11.07 (1 H, s), 11.01 (1 H, s), 8.72 and 8.30 (1 H, 2 s), 7.85–8.02 (5 H, m), 7.73 (2 H, m), 7.52 (2 H, d, J = 8.4 Hz), 7.44 (2 H, d, J = 7.7 Hz), 7.29 (1 H, br d, J = 7.2 Hz), 7.20 (1 H, br s), 6.66 (1 H, m), 3.90–4.20 (3 H, m), 3.69 (1 H, m), 3.42–3.59 (2 H, m), 2.64 (2 H, m), 2.33 (2 H, m), 1.89–2.16 (4 H, m), 1.11–1.67 (41 H, m with singlets). Cytosine 5-H and 6-H coupled pairs by COSY: (δ 7.93 and 7.27), (δ 7.72 and 7.18). Negative ion FABMS, m/z (rel intensity): 965 (23), 964 (63), 963 $((M - H)^-$, 100), 908 (15), 306 (40), 305 (39), 270 (28), 199 (26), 169 (24), 154 (15), 153 (75), 152 (50), 151 (38), 122 (14). HRMS (neg ion FAB): calcd for $C_{52}H_{71}N_{10}O_8$ $(M - H)^-$ 963.5456, found 963.5425.

25a (59% yield from **20a** and **22a**). ^1H NMR (300 MHz, DMSO-d_6): δ 11.07 (1 H, s), 11.02 (1 H, s), 8.65 and 8.32 (1 H, 2 s), 7.95 (4 H, m), 7.87 (1 H, d, J = 6.7 Hz), 7.75 (1 H, br d, J = 9.9 Hz), 7.52 (4 H, m), 7.27 (1 H, d, J = 7.1 Hz), 6.79 (2 H, m), 3.95–4.15 (4 H, m), 3.73 (1 H, m), 3.40–3.65 (1 H, m), 2.63 (2 H, m), 2.33 (2 H, m), 1.90–2.15 (4 H, m), 1.10–1.80 (37 H, m with

singlets). Positive ion FAB, m/z (rel intensity): 939 (5.9), 938 ($(M + H)^+$, 9.7), 838 (3.6), 595 (5.9), 495 (3.5), 369 (2.7), 308 (21.2), 307 (100.0), 272 (15.2), 146 (15.2), 145 (12.1). HRMS (neg ion FAB): calcd for $C_{50}H_{67}N_{10}O_8$ $(M - H)^-$, 935.5143, found 935.5179.

Trimer Hydrazides 26a,b. According to the procedure for oligomerization, the hydrazide dimer **25b** (21 mg, 21.8 μmol) was coupled with the *p*-nitrophenyl ester **20b** to provide 17.6 mg (60% yield) of hydrazide trimer **26b** after purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.01 (3 H, br s), 8.72 and 8.30 (1 H, 2 s), 7.83–8.10 (8 H, m), 7.73 (2 H, m), 7.65 (1 H, br d, J = 9.6 Hz), 7.52 (2 H, d, J = 8.3 Hz), 7.44 (4 H, m), 7.29 (1 H, br s), 7.19 (2 H, m), 6.66 (1 H, d, J = 9.1 Hz), 3.87–4.22 (6 H, m), 3.48–3.74 (3 H, m), 2.64 (2 H, m), 2.32 (2 H, m), 1.89–2.18 (6 H, m), 1.02–1.70 (54 H, m with singlets). Negative ion FABMS, m/z (rel intensity): 1347 (40), 1346 (85), 1345.6 ($(M - H)^-$, 100), 1291 (24), 1290.5 (32), 963 (23), 909 (10), 908 (14), 306 (37), 305 (36), 270 (50), 199 (19), 169 (17), 153 (86), 152 (47), 151 (32), 122 (15). HRMS (neg ion FAB): calcd for $C_{73}H_{98}N_{14}O_{11}$ $(M - H)^-$ 1345.7461, found 1345.7298.

26a (45% yield from **20a** and **25a**). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.05 (1 H, s), 10.94 (1 H, s), 8.69 and 8.32 (1 H, 2 s), 7.70–8.00 (10 H, m), 7.40–7.55 (7 H, m), 7.20–7.34 (3 H, br s), 6.75–6.90 (1 H, m), 3.95–4.20 (5 H, m), 3.40–3.90 (3 H, m), 3.00–3.15 (1 H, m), 2.63 (2 H, m), 2.32 (2 H, m), 1.90–2.20 (6 H, m), 1.10–1.80 (48 H, m with singlets). Negative ion FABMS, m/z (rel intensity): 1304.6 (45.2), 1303.6 ($(M - H)^-$, 50.0), 1220.5 (4.0), 1143.6 (6.7), 991.5 (2.7), 906.5 (3.0), 367.2 (4.8), 307.1 (6.5), 270.1 (100.0), 227.1 (6.5), 201.1 (29.0). HRMS (pos ion FAB): calcd for $C_{70}H_{93}N_{14}O_{11}$ $(M + H)^+$ 1305.7148, found 1305.7005.

End-Capped Dimers 29a,b. According to the procedure for oligomerization, the capped monomer **24b** (78.5 mg, 109 μmol) was coupled with the *p*-nitrophenyl ester **20b** to provide 103.4 mg (86% yield) of capped dimer **29b** after purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.06 (1 H, s, exchanged with D_2O), 11.00 (1 H, s, exchanged with D_2O), 7.86–8.00 (7 H, m), 7.75 (1 H, d, J = 8.0 Hz), 7.66 (1 H, d, J = 8.5 Hz, exchanged with D_2O), 7.40–7.59 (6 H, m), 7.28 (1 H, br s), 7.19 (1 H, br s), 6.63 (1 H, d, J = 9.8 Hz, exchanged with D_2O), 4.32–4.46 (2 H, m), 4.16 (1 H, m), 3.92–4.08 (2 H, m), 3.63–3.75 (3 H, m), 3.43–3.52 (2 H, m), 3.06 and 2.87 (3 H, 2 s), 2.25–2.43 (2 H, m), 1.93–2.12 (2 H, m), 1.10–1.62 (44 H, m with singlets). Cytosine 5-H and 6-H coupled pairs by COSY: (δ 7.93 and 7.27), (δ 7.73 and 7.18). Negative ion FABMS, m/z (rel intensity): 1100 (30), 1099 (73), 1098.3 ($(M - H)^-$, 100), 716 (11), 306 (19), 305 (21), 270 (47), 199 (18), 168 (23), 154 (14), 153 (67), 151 (39), 122 (16). HRMS (neg ion FAB): calcd for $C_{61}H_{80}N_9O_{10}$ $(M - H)^-$ 1098.6028, found 1098.5870.

26a (63% yield from **20a** and **24a**). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.05 (2 H, m), 7.82–8.02 (8 H, m), 7.74 (1 H, d, J = 8.8 Hz), 7.46–7.61 (6 H, m), 7.28 (2 H, m), 6.76 (1 H, d, J = 9.8 Hz), 4.27–4.53 (2 H, m), 3.94–4.22 (3 H, m), 3.46–3.83 (5 H, m), 3.04 and 2.86 (3 H, 2 s), 2.25–2.48 (2 H, m), 2.08 (2 H, br t, J = 6.8 Hz), 1.42–1.79 (4 H, m), 1.07–1.42 (36 H, m). Negative ion FABMS, m/z (rel intensity): 1072 (7.8), 1071 ($(M - H)^-$, 20.9), 996 (2.0), 929 (1.6), 270 (100.0), 227 (7.8), 201 (19.4), 177 (17.1). HRMS (pos ion FAB): calcd for $C_{59}H_{78}N_9O_{10}$ $(M + H)^+$ 1072.5871, found 1072.5780.

End-Capped Trimers 30a,b. According to the procedure for oligomerization, the capped dimer **29b** (8.9 mg, 8.1 μmol) was coupled with the *p*-nitrophenyl ester **20b** to provide 8.3 mg (69% yield) of capped trimer **30b** after purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.06 (1 H, br s, exchanged with D_2O), 11.02 (1 H, br s, exchanged with D_2O), 11.00 (1 H, br s, exchanged with D_2O), 7.84–7.99 (9 H, m), 7.79 (1 H, br d, J = 6.0 Hz), 7.72 (2 H, m), 7.60 (1 H, d, J = 9.3 Hz, exchanged with D_2O), 7.53 (4 H, m), 7.43 (4 H, m), 7.29 (1 H, br d, J = 7.2 Hz), 7.19 (2 H, br t, J = 7.5 Hz), 6.65 (1 H, d, J = 9.9 Hz, exchanged with D_2O), 4.30–4.45 (2 H, m), 4.16 (1 H, m), 3.87–4.20 (5 H, m), 3.60–3.75 (4 H, m), 3.40–3.53 (2 H, m), 3.05 and 2.86 (3 H, 2 s), 2.30–2.45 (2 H, m), 1.88–2.16 (4 H, m), 1.08–1.65 (57 H, m with singlets). Cytosine 5-H and 6-H coupled pairs by COSY: (δ 7.94 and 7.29), (δ 7.79 and 7.19), (δ 7.71 and 7.19). Negative ion FABMS, m/z (rel intensity): 1484 (18), 1483 (49), 1482 (96), 1481 ($(M - H)^-$, 100), 1480 (12), 270 (25), 153 (23), 152 (10). HRMS (neg ion FAB): calcd for $C_{82}H_{106}N_{13}O_{13}$ $(M - H)^-$ 1480.8033, found 1480.8091.

30a (63% yield from **20a** and **29a**). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.04 (2 H, s), 10.91 (1 H, s), 7.69–8.08 (12 H, m), 7.38–7.63 (9 H, m), 7.27 (3 H, br s), 6.84 (1 H, d, J = 8.6 Hz), 4.26–4.58 (2 H, m), 3.96–4.26 (6 H, m), 3.58–4.26 (5 H, m), 3.07 and 2.86 (3 H, 2 × s), 1.98–2.49 (6 H, m), 1.59–1.82 (6 H, m), 1.12–1.56 (45 H, m). Cytosine 5-H and 6-H coupled pairs by COSY: (δ 7.93 and 7.27), (δ 7.88 and 7.25), (δ 7.84 and 7.27). Negative ion FABMS, m/z (rel intensity): 1441 (9.9), 1440 ($(M - H)^-$, 40.4), 1279 (4.7), 1071 (4.2), 367 (3.8), 271 (18.3), 270 (100.0), 201 (35.2), 177 (11.3). HRMS (pos ion FAB): calcd for $C_{79}H_{102}N_{13}O_{13}$ $(M + H)^+$ 1440.7719, found 1440.7720.

End-Capped Tetramers 31a,b. According to the procedure for oligomerization, the capped trimer **30b** (30 mg, 20.2 μmol) was coupled with the *p*-nitrophenyl ester of the acid **20b** to provide 32.5 mg (86% yield) of capped tetramer after purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.68–8.02 (m) and 7.09–7.65 (m) with relative integration ratio (1.00/1.11 (i.e., 15 H/16 H), 6.65 (d, J = 9.8 Hz), 4.30–4.50 (m), 3.82–4.20 (m), 3.60–3.78 (m), 3.05 and 2.88 (2 s, 1.75:1.00), 2.29–2.46 (m) and 1.85–2.17 (m) with relative integration ratio 1.00/2.74 (i.e. ~2 H/6 H), 1.00–1.65 (m). Negative ion FABMS, m/z (rel intensity): 1867 (12), 1866 (31), 1865 (68), 1864 ($(M - H)^-$, 100), 1863 (91), 1862 (18), 1861 (10), 1100 (21), 1099 (46), 1098.7 (63), 937 (10), 936.6 (15), 853.5 (10), 526 (11), 306 (35), 270 (34), 199 (29), 168 (29), 154 (19), 153 (100), 152 (69), 151 (54). HRMS (neg ion FAB): calcd for $C_{103}H_{132}N_{17}O_{16}$ $(M - H)^-$ 1863.0036, found 1862.9994.

By the same procedure, the capped trimer **30a** (80.5 mg, 55.9 μmol) was coupled with the *p*-nitrophenyl ester of the acid **20a** to provide 95 mg (95% yield) of capped tetramer after purification. **31a**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.65–8.12 (m) and 7.20–7.65 (m) with relative integration ratio 1.13/1.00 (e.e. ~16 H/15 H), 3.85–4.45 (m), 3.65–3.80 (m), 3.09 and 2.86 (2 s, 15:1.0), 1.95–2.48 (m) and 1.42–1.79 (m) with relative integration ratio 1.17/1.00 (i.e ~8 H/7 H), 1.03–1.60 (m). HRMS (pos ion FAB): calcd for $C_{99}H_{126}N_{17}O_{16}$ $(M + H)^+$ 1808.9568, found 1808.9510.

End-Capped Pentamers 32a,b. The capped tetramer **31b** (31.8 mg, 17.06 μmol) was converted to the corresponding tosyl salt of tetramer amine as described previously. To this tosyl salt were added DMSO (1.0 mL), Et_3N (50 μL), and 4-(dimethylamino)pyridine (4 mg, 32.8 μmol), and the solution was then heated to 60–65 °C in an oil bath. To this warmed tetramer amine containing DMSO solution was injected a solution of *p*-nitrophenyl ester **20b** in CH_2Cl_2 (0.5 mL, ~0.101 M), and the solution was then stirred at 60–65 °C for 2 h. The reaction mixture was cooled to room temperature and evaporated to nearly dryness under high vacuum. The residue was redissolved in a minimum amount of CH_3OH and then diluted with Et_2O (40 mL). Upon centrifugation, the precipitate was separated and the precipitation process repeated twice. The final precipitate was redissolved in 20% 2-propanol/$CHCl_3$ (50 mL), washed with 0.15 M NaOH (2 × 15 mL), 0.5 M HCl (1 × 15 mL), and brine (1 × 15 mL), and then dried over anhydrous Mg_2SO_4. Removal of solvent under reduced pressure and drying under high vacuum over P_2O_5 gave 32.1 mg (84% yield) of capped pentamer as a yellowish amorphous solid. For a sample suitable for extensive spectral characterization to be obtained, further purification on HPLC (30–40% CH_3OH/CH_2Cl_2 on Beckman Ultrasphere-Si column) was normally necessary. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.72–8.05 (m) and 7.10–7.65 (m) with relative integration ratio 1.00/1.12 (i.e, 18 H/20 H), 4.30–4.48 (m), 3.83–4.22 (m), 3.62–3.77 (m), 3.05 and 2.88 (2 s, 1.65:1.00), 2.29–2.46 (m) and 1.85–2.17 (m) with relative integration ratio 1.00/3.72 (i.e. ~2 H/8 H), 1.06–1.70 (m). Negative ion FABMS, m/z (rel intensity): 2249 (14), 2248 (30), 2247 (61), 2246 ($(M - H)^-$, 100), 2245 (42), 2244 (16), 1766 (16), 1765 (19), 1764 (19), 1703 (14), 1702 (20), 1701 (19), 1469 (28), 1468 (46), 1467 (51), 1466 (12), 1454 (21), 1453 (30), 1319 (16), 1293 (47), 1292 (54), 1291 (63), 909 (14), 908 (23), 498 (16), 306 (26), 305 (28), 270 (37), 199 (25), 168 (30), 154 (19), 153 (100), 152 (82), 151 (54). HRMS (neg ion FAB): calcd for $C_{124}H_{158}N_{21}O_{19}$ $(M - H)^-$ 2245.2042, found 2245.2024.

By the standard oligomerization procedure, the capped tetramer **31a** (71 mg, 39.3 μmol) was coupled with the *p*-nitrophenyl ester of the acid **20a** to provide 78 mg (92% yield) of capped pentamer after purification. **32a**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.68–8.12 (m) and 7.14–7.68 (m) with relative integration ratio 1.00/1.01 (i.e. ~19 H/19 H), 3.85–4.55 (m), 3.50–3.80 (m), 3.08 and 2.87 (2 s, 1.5:1.0), 1.95–2.48 (m) and 1.42–1.79 (m) with relative integration ratio 1.74/1.00 (i.e. ~10 H/6 H), 1.00–1.35 (m).

HRMS (neg ion FAB): calcd for $C_{119}H_{148}H_{21}O_{19}$ $(M - H)^-$ 2175.1255, found 2175.1370.

End-Capped Hexamers 33a,b. Hydrazide-protected trimer **26a** (14 mg, 0.011 mmol) was dissolved in 0.20 mL of 75% aqueous THF. To this stirring solution was added 1.4 mL (0.017 mmol) of pyridine, followed by 2.3 mg (0.013 mmol) of *N*-bromosuccinimide. This reaction mixture was allowed to stir 15 min (longer for larger scale reactions). Upon completion of reaction, 0.315 mL of 0.1 M HCl was added and the reaction mixture was evaporated to dryness. The residue was dissolved in 10 mL of 20% 2-propanol/$CHCl_3$ and extracted twice with 3-mL portions of 0.02 M HCl. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The product was thoroughly dried on high vacuum with external heating (50 °C) before taking on to the activation reaction. Yield of the crude trimer free acid **27a** was quantitative (12.8 mg) and was taken on directly to the activation stage without purification.

The standard procedure was followed for coupling trimer portions. This involved Boc deprotection of cap-protected trimer **30a** (20 mg) to provide the trimer amine salt and activation of trimer free acid **27a** by the standard procedure to give **28a**. The same relative amounts of reagents were used to couple the trimer portions, but the standard aqueous workup was avoided. For purification, the DMF reaction mixture was evaporated to dryness and purified directly on 1.2 g of silica (2–30% MeOH/$CHCl_3$) and the crude product immediately rechromatographed on 1.0 g of silica (1.25–20% MeOH/$CHCl_3$) to provide 10.0 mg of fully protected hexamer **33a** (49% yield). ^1H NMR (300 MHz, DMSO-d_6): δ 7.67–8.18 (m) and 7.15–7.67 (m) with relative integration ratio 1.00/1.00 (i.e. ~23 H/23 H), 3.85–4.58 (m), 3.54–3.80 (m), 3.08 and 2.87 (2 s, 1.1:1.0), 1.95–2.48 (m) and 1.42–1.79 (m) with relative integration ratio 2.00/1.00 (i.e. ~12 H/6 H), 1.00–.135 (m). Negative ion FABMS, m/z (rel intensity): 2544 ($(M - H)^-$, 24.5), 2423 (5.9), 2174 (7.0), 271 (27.9), 270 (100.0), 201 (61.2), 177 (28.9). HRMS (neg ion FAB): calcd for $C_{139}H_{172}N_{25}O_{22}$ $(M - H)^-$ 2543.3108, found 2543.3240. Hexamer **33a** also can be prepared in high yield (62 mg, 87% yield) by a stepwise coupling procedure from pentamer **32a** (61 mg, 24.4 μmol). This hexamer **33a** has identical spectral properties with the species derived from the trimer–trimer coupling procedure.

When the trimer–trimer coupling procedure was applied to the six-atom backbone series, no hexamer was isolated. However, the corresponding trimer amine and trimer acid were recovered from crude reaction mixture by standard preparative TLC purification and were identified by FABMS. Negative ion FABMS for trimer amine, m/z (rel intensity): 1383 (25), 1382 (50), 1381 ($(M - H)^-$, 59), 270 (25), 153 (100). Negative ion FABMS for trimer acid, m/z (rel intensity): 1264 ($(M - H)^-$, 90), 365 (39), 307 (49), 270 (100). Instead, hexamer **33b** was prepared by the stepwise oligomerization procedure from pentamer **32b**. The capped pentamer **32b** (32 mg, 14.25 μmol) was coupled with the *p*-nitrophenyl ester **20b** by the procedure described for pentamer **32b** to provide 32.4 mg (85% yield) of capped hexamer **33b** after primary purification by precipitation and aqueous washes procedures. Further purification of this hexamer by HPLC (30–40% CH_3OH/CH_2Cl_2 on Beckman Ultrasphere-Si column) was generally required in order to provide a clean sample for extensive spectral characterization. ^1H NMR (400 MHz, DMSO-d_6): δ 8.06–8.28 (m), 7.68–8.05 (m) and 7.08–7.65 (m) with relative integration ratio 0.25/1.00/1.00 (i.e 5H/20 H/20 H), 4.25–4.50 (m), 3.80–4.20 (m), 3.58–3.80 (m), 3.05 and 2.88 (2 × s, 1.73:1.00), 2.29–2.46 (m) and 1.85–2.17 (m) with relative integration ratio 1.00/4.67 (i.e. ~2 H/10 H), 1.00–1.72 (m). Negative ion FABMS, m/z (rel intensity): 2628 ($(M - H)^-$, 30), 1468 (14), 1467 (18), 1310 (39), 1292 (40), 1291 (65), 1082 (26), 1045 (54), 909 (21), 908 (97), 306 (12), 305 (17), 270 (100). HRMS (neg ion FAB): calcd for $C_{145}H_{185}N_{25}O_{22}$ $(M - H)^-$ 2627.4049, found 2627.3954.

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Registry No. **2a**, 135697-20-0; **2b**, 135697-19-7; **3a**, 17342-08-4; **3b**, 128726-47-6; **4a**, 51693-17-5; **4b**, 135697-06-2; **5a**, 109205-50-7; **5b**, 135697-07-3; **6a**, 135697-09-5; **6b**, 135697-08-4; **7a**, 135697-10-8; **7b**, 135697-11-9; **8b**, 135697-12-0; **9a**, 135697-15-3; **9b**, 135697-13-1; **11a**, 135697-16-4; **11b**, 135697-14-2; **12a**, 135697-18-6; **12b**, 135697-17-5; **13a**, 135697-21-1; **13b**, 135697-22-2; **14a**, 135697-24-4; **14b**, 135697-23-3; **15a**, 135697-26-6; **15b**, 135697-27-7; **16**, 135697-25-5; **17**, 135697-28-8; **18a**, 135697-29-9; **18b**, 135697-30-2; **18c**, 135697-31-3; **20a**, 135697-33-5; **20b**, 135697-32-4; **21**, 135697-34-6; **22a**, 135697-36-8; **22b**, 135697-35-7; **23a**, 135697-39-1; **23b**, 135697-37-9; **24a**, 135697-40-4; **24b**, 135697-38-0; **25a**, 135697-42-6; **25b**, 135697-41-5; **26a**, 135697-44-8; **26b**, 135697-43-7; **27a**, 135697-51-7; **29a**, 135697-46-0; **29b**, 135697-45-9; **30a**, 135697-47-1; **30b**, 135720-70-6; **31a**, 135697-49-3; **31b**, 135697-48-2; **32a**, 135697-50-6; **32b**, 135720-71-7; **33a**, 135697-52-8; **33b**, 135697-53-9; *t*-BuBzCl, 1710-98-1; cytosine, 71-30-7; adenine, 73-24-5; 1-aminopiperidine oxalate, 118950-80-4.

Supplementary Material Available: Proton NMR spectra of **2a,b**, **4–7a,b**, **11–15a,b**, **16**, **17**, **18a–c**, **20a,b**, **21**, **22–26a,b**, and **29–33a,b** (53 pages). Ordering information is given on any current masthead page.