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Synthesis of Pyrrolidinone PNA: A Novel Conformationally Restricted PNA Analogue

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To preorganize PNA for duplex formation, a new cyclic pyrrolidinone PNA analogue has been designed. In this analogue the aminoethylglycine backbone and the methylenecarbonyl linker are connected, introducing two chiral centers compared to PNA. The four stereoisomers of the adenine analogue were synthesized, and the hybridization properties of PNA decamers containing one analogue were measured against complementary DNA, RNA, and PNA strands. The (3*S*,5*R*) isomer was shown to have the highest affinity toward RNA, and to recognize RNA and PNA better than DNA. The (3*S*,5*R*) isomer was used to prepare a fully modified decamer which bound to rU_{10} with only a small decrease in T_m (ΔT_m/mod = 1 °C) relative to aminoethylglycine PNA.

Introduction

Peptide nucleic acid (PNA) is an acyclic mimic of natural nucleic acids.[1] Only the nucleobases are retained, linked together by an achiral, uncharged pseudopeptide backbone. PNA is an excellent structural mimic of DNA and RNA; it binds strongly and with high specificity to complementary oligonucleotides. The properties of PNA and PNA analogues have recently been reviewed.[2a,b] PNA/DNA or PNA/RNA duplex formation is accompanied by a decrease in entropy. This entropy loss could be reduced by using a more rigid PNA analogue. This has been attempted by using conformationally constrained chiral backbones.[3a,b] We have now designed a new constrained structure, pyr-PNA, in which the aminoethylglycine backbone and the methylenecarbonyl linker are connected (Figure 1). NMR studies of single stranded PNA oligomers clearly show that a complex mixture (up to 2^n) of isomers are present.[4] Thus PNA hybridization may be disfavored by a slow rotamer equilibrium of the linker-backbone amide. The aim was to shift the equilibrium between single strands and duplexes toward duplex formation by preorganizing PNA in the duplex strand conformation and thereby reducing the entropy loss upon duplex formation. Examination of PNA/DNA, PNA/RNA, and PNA/PNA duplexes as well as PNA_2/DNA triplexes, reveals that the linker-carbonyl points toward the carboxyl end of PNA.[5a−d] Rotation around the methylene carbonyl linker in single stranded PNA can be prevented by connecting the linker to the backbone through a methylene bridge in a cyclic structure. A somewhat similar approach using olefinic PNA analogues has recently been published,[6a−c] where the central functionality was replaced by a configurationally stable carbon−carbon double bond to give *E*-OPA and *Z*-OPA (Figure 1). Incorporation of the OPA monomers (B = T) once in the middle of a PNA sequence showed that the *E* isomer, which has a configuration similar to the PNA rotamer preferred in duplexes, gave a higher affinity to antiparallel complementary DNA than the *Z* isomer. However, both OPA isomers resulted in a substantial decrease in affinity of the modified PNA toward DNA ($\Delta T_m = -6.5$ and -14.2 °C for a decamer PNA containing one central *E*-, respectively, *Z*-OPA unit). No data were given for the hybridization to RNA. Recently D'Costa et al. published the synthesis of "aminoethylprolyl PNAs", in which the glycyl component in the PNA backbone has been substituted by a prolyl unit, to which a thymine base is attached at position 4.[7] Most interestingly these chiral and cationic PNA analogues showed increased binding strength toward DNA, but further data is needed to fully evaluate the properties of these interesting analogues.

Here, we report the synthesis and hybridization properties toward DNA, RNA, and PNA of the first "pyrroli-

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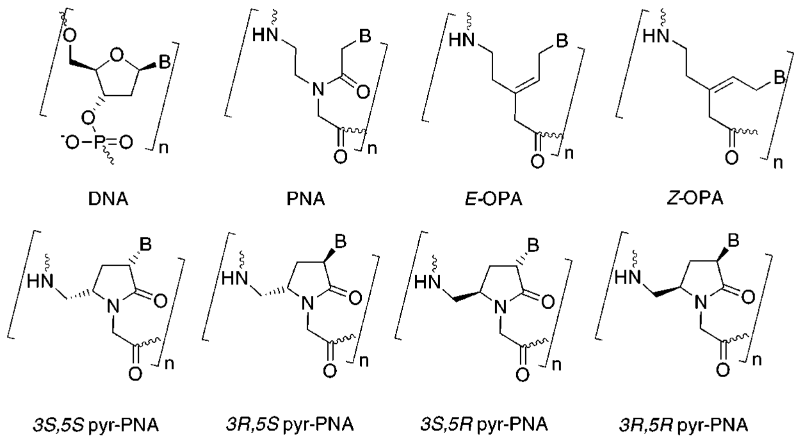

Figure 1. Structures of DNA, PNA, and PNA analogues.

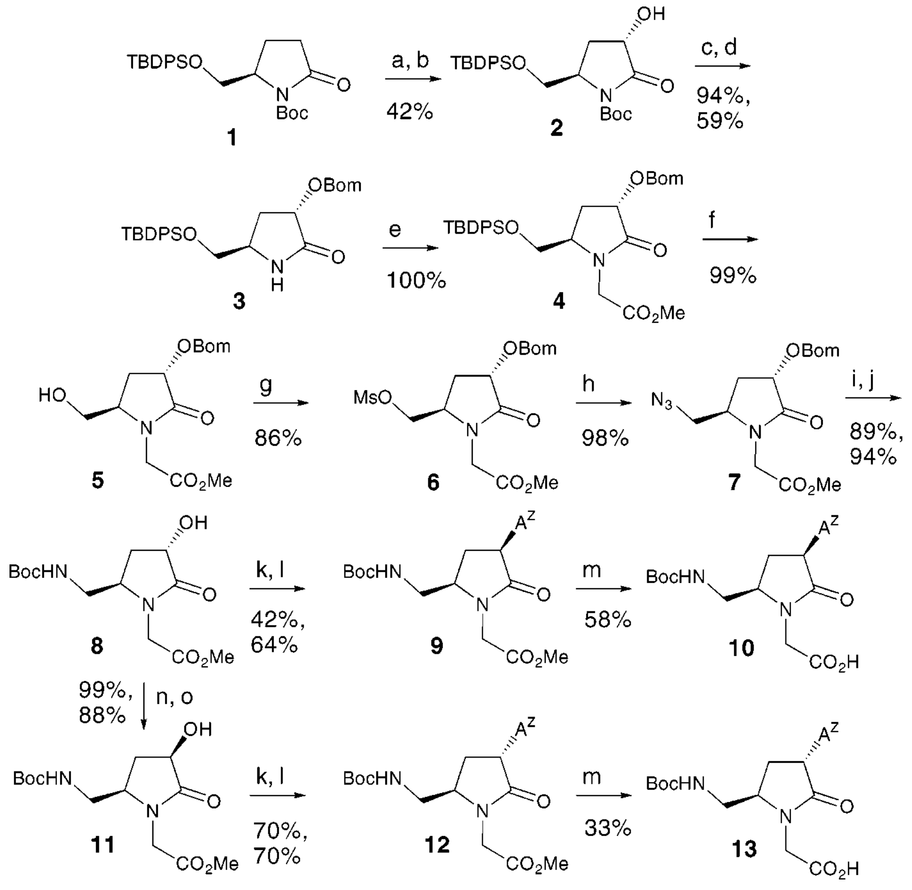

Figure 2. Synthesis of the (3*R*,5*R*) (**10**) and (3*S*,5*R*) (**13**) pyr-PNA A monomers. (a) HMDS, BuLi, THF; (b) MoOPH; (c) Bom-chloride, DIEA, CH_2Cl_2; (d) TFA: CH_2Cl_2 (1:1) 0 °C; (e) NaH, $BrCH_2CO_2CH_3$, THF; (f) $(C_2H_5)_3N{\cdot}3HF$, THF; (g) MsCl, pyridine; (h) NaN_3, DMF, 80 °C; (i) H_2, 10% Pd/C, Boc_2O, AcOEt; (j) H_2, 10% $Pd(OH)_2$/C, MeOH; (k) adenine, PPh_3, DEAD, dioxane; (l) *N*-benzyloxycarbonyl-*N*′-methylimidazolium triflate, CH_2Cl_2; (m) LiOH, THF, then HCl; (n) $PhCO_2H$, PPh_3, DEAD, dioxane; (o) NaOMe, MeOH.

dinone PNA" analogues, the adenine pyrrolidinone analogues; 3*S*,5*S* pyr-PNA, 3*R*,5*S* pyr-PNA, 3*R*,5*R* pyr-PNA, and 3*S*,5*R* pyr-PNA (Figure 1, B = adenin-9-yl).[8] Compared to PNA, two chiral centers are introduced making the syntheses of pyr-PNA more challenging since stereoselective synthesis is required.

Results and Discussion

Synthesis of the (3*R*,5*R*) and (3*S*,5*R*) Monomers. The adenine monomers were prepared as outlined in Figure 2. Compound **1** was synthesized from D-pyroglutamic acid in five steps and 49% yield.[9] The stereoselective hydroxylation of **1** has been reported in the literature.[10] The procedure uses oxodiperoxymolybdenum−pyridine−hexamethylphosphoric triamide (MoOPH)

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Table 1. Melting Temperatures (T_m Values)[a]

entry	sequence	alone	DNA complement	RNA complement	PNA complement
1	5′-d(AGT-GTA-CTA-C)	<20	37 (13%)	37.0 (11%)	49.5
2	H-AGT-GTA-CTA-C-Lys-NH$_2$	44	49.0	55.5	67.0
3	H-AGT-GTA$_{SS}$-CTA-C-Lys-NH$_2$	50 (8%)	ntd[c]	39.5 (11%)	58.0 (21%)
4	H-AGT-GTA$_{RS}$-CTA-C-Lys-NH$_2$	37 (10%)	39.0[b]	38.0 (9%)[b]	65.0 (20%)
5	H-AGT-GTA$_{RR}$-CTA-C-Lys-NH$_2$	46 (7%)	45 (9%)[b]	41.0 (13%)	60.0
6	H-AGT-GTA$_{SR}$-CTA-C-Lys-NH$_2$	40 (5%)	43.0 (9%)	52.0 (11%)	64.0 (23%)

[a] T_m = melting temperature (measured in medium salt buffer: 100 mM NaCl, 10 mM phosphate, 0.1 mM EDTA, pH = 7.0). Heating rate: 1 K/min. UV absorbance measured at 254 nm. Hyperchromicity in parentheses. [b] UV-titration (Job-plot) failed to detect any binding. ntd = no transition detected.

Table 2. Mismatch against RNA[a]

entry	sequence	RNA-complement	MM-A[b]	MM-C[b]	MM-G[b]
7	H-AGT-GTA-CTA-C-Lys-NH$_2$	55.5	42.0	42.5	42.0
8	H-AGT-GTA$_{SR}$-CTA-C-Lys-NH$_2$	52.0 (11%)	37.5 (9%)	39.5 (11%)	41.0 (11%)

[a] T_m = melting temperature (measured in medium salt buffer: 100 mM NaCl, 10 mM phosphate, 0.1 mM EDTA, pH = 7.0). Heating rate: 1 K/min. UV absorbance measured at 254 nm. Hyperchromicity in parentheses. [b] MM-X = The T in the complement is substituted with X.

as the oxidizing agent, and it is reported to proceed in 58% yield with total stereoselectivity. In our hands, using the same conditions, the hydroxylation gave, on a 21 mmol scale, a 95:5 mixture of 3*S*- and 3*R*-**2**. Protection of the hydroxy group as its benzyloxymethyl (Bom)[11] ether was followed by removal of the Boc group. The Bom protective group was not completely stable to neat TFA, so milder conditions for removal of Boc (TFA/CH$_2$Cl$_2$ (1:1), 0 °C, 8 min) were used. At this point the pure 3*S*-isomer (**3**) could be obtained by recrystallization from AcOEt/hexane. The lactam nitrogen was alkylated[12] and the silyl protecting group was removed with Et$_3$N·3HF in THF to produce **5** in nearly quantitative yield. This was converted to the azide **7** via mesylate **6**. Using the mesyl derivative was found to give higher yield than using the corresponding tosyl derivative (see Supporting Information). The azide was hydrogenated to the amine which was Boc protected in a one-pot procedure using 10% Pd/C as catalyst.[13] The Bom protecting group was almost completely resistant to hydrogenation under these conditions. It was, however, removed by hydrogenation using Pearlman's catalyst to give **8**. Under Mitsunobu conditions, the configuration in the 3-position was inverted to yield the diasteromer **11**. The hydroxy groups in **8** and **11** were substituted with adenine under Mitsunobu conditions. ^{13}C NMR of these intermediates proved that the correct N-9 isomers had formed. The exocyclic amine in the nucleobase was *Z*-protected using Rapoport's reagent.[14] Finally, the methyl esters **9** and **12** were hydrolyzed to yield the fully protected monomers **10** and **13**. After purification by chromatography (MeOH:HOAc:CH$_2$Cl$_2$ 10:5:85) the monomers were evaporated several times from toluene and dried under a high vacuum for one week to remove the HOAc completely before oligomerization.[15]

Synthesis of the (3*R*,5*S*) and (3*S*,5*S*) Monomers. The (3*R*,5*S*) and the (3*S*,5*S*) adenine monomers were synthesized from L-pyroglutamic acid in a similar way as the (3*R*,5*R*) and (3*S*,5*R*) monomers except that the tosyl analogue of **6** was used and TBAF was used instead of Et$_3$N·3HF to remove TBDPS. Full experimental conditions are given in the Supporting Information.

Table 3. Melting Temperatures (T_m Values)[a]

entry	sequence	alone	rU$_{10}$	*ent*-rU$_{10}$
9	H-eg1-(A)$_{10}$-Lys-NH$_2$	44	35	nd
10	H−(A$_{SR}$)$_{10}$-Lys-NH$_2$	44	26	nd
11	H−(A$_{RS}$)$_{10}$-Lys-NH$_2$	44	nd	24

[a] T_m = melting temperature (measured in medium salt buffer: 100 mM NaCl, 10 mM phosphate, 0.1 mM EDTA, pH = 7.0). Heating rate: 1 K/min. UV absorbance measured at 254 nm. nd = not determined.

Thermal Stability. Each of the four novel monomers was incorporated once in the middle of a decameric PNA (Table 1, entries 3−6) and the thermal stability of the complexes of the decamers with a complementary oligonucleotide was compared with those formed by an unmodified PNA oligomer (Table 1, entries 1−2). The decamer incorporating the (3*S*,5*R*) analogue (Table 1, entry 6) binds stronger to complementary RNA compared to the other three decamers. In fact it binds only slightly less efficiently than unmodified PNA (ΔT_m = 3.5 °C). Furthermore the (3*S*,5*R*) PNA appears to discriminate more between binding to RNA versus DNA (ΔT_m = 9 °C). The remaining three stereoisomers (Table 1, entries 3−5) hybridize with lower stability to complementary RNA, although binding to the more flexible PNA was less impaired. These results are in accordance with models which indicated that the (3*S*,5*R*) analogue best approximates the conformation of PNA in a PNA:RNA[5b] double helix.

The (3*S*,5*R*) analogue was also shown to bind with high sequence specificity to RNA (Table 2). To further evaluate the affinity of the (3*S*,5*R*) analogue toward RNA, a fully modified adenine decamer was synthesized and the binding affinity toward oligo U-RNA was evaluated (Table 3 entries 9−10). The affinity of this analogue toward RNA is only slightly decreased (ΔT_m /mod = 1 °C) compared to unmodified PNA. This was confirmed by synthesizing a fully modified decamer of the (3*R*,5*S*) analogue and measure the binding affinity (entry 11) toward *ent*-RNA (also known as mirror-image RNA).[16a,b] Virtually the same T_m was found in this case.

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Surprisingly, the binding stoichiometry was found by titration (Job-plot) to be 2:1 (entry 10 versus rU_{10}) indicating a PNA_2−RNA triplex structure. Most likely the two PNA strands bind to each other through reverse Hoogsteen hydrogen bonding. Titration of the binding of the unmodified PNA to complementary rU_{10} showed the expected 1:1 binding mode.

Conclusion

Four new conformationally restricted PNA adenine monomers have been synthesized. The restriction, a five-membered ring, forces the carbonyl group of the linker to point toward the COOH-terminus of the backbone, as is usually the case when aminoethylglycine PNA oligomers are bound to complementary DNA, RNA, or PNA.

The novel monomers were built into PNA oligomers once by standard PNA synthesis, and the melting temperatures of the modified oligomers toward complementary DNA, RNA, and PNA strands were measured. The (3*S*,5*R*) isomer was shown to have the highest affinity toward RNA and to recognize RNA (and PNA) better than DNA. The (3*S*,5*R*) isomer was used to prepare a fully modified decamer which bound to rU_{10} with only a small decrease in T_m (ΔT_m/mod = 1 °C). The slightly decreased T_m compared to unmodified PNA indicates that the five-membered ring may not be the optimal modification to restrict PNA, and work is in progress to examine other ring structures.

Experimental Section

General. Reagents, except benzyl chloromethyl ether,[11] MoOPH,[17] and *N*-benzyloxycarbonyl-*N*′-methylimidazolium triflate,[18] which were prepared according to literature procedures, were purchased from Sigma-Aldrich and used without purification. Solvents were HPLC-grade from LAB-SCAN. Acetonitrile, *N*,*N*′-dimethylformamide, benzene, toluene, dioxane, methylene chloride, and pyridine were dried over 4 Å molecular sieves. Tetrahydrofuran was dried by distillation from sodium/ benzophenone. TLC was run on Merck 5554 silica 60 aluminum sheets. Column chromatography was performed as flash chromatography on Merck 9385 silica gel 60 (0.040−0.063 mm). Reactions were carried out under nitrogen except in the case of hydrogenations. FAB-MS were recorded in the positive ion mode. Elemental analyses were performed at the Microanalytical Laboratory, Department of Chemistry, University of Copenhagen. NMR spectra were obtained on a 300 or 400 MHz spectrometer. δ-Values are in ppm relative to DMSO-d_6 (2.50 for proton and 39.5 for carbon) or $CDCl_3$ (7.29 for proton and 76.9 for carbon) or CD_3OD (3.35 for proton and 49.1 for carbon).

(3*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-5-[(*tert*-butyldiphenylsilyloxy)methyl]-3-hydroxy-2-pyrrolidinone (2). BuLi (42.1 mL, 63.2 mmol, 1.5 M in hexane) was added dropwise to a solution of hexamethyldisilazane (13.3 mL, 63.2 mmol) in THF (50 mL) at −78 °C. The solution was stirred at −78 °C for 30 min. A solution of **1** (9.55 g, 21.05 mmol) in THF (50 mL) was added over a period of 5 min. Stirring was continued for another 30 min at −78 °C, and then the reaction mixture was heated to −40 °C during the next 20 min, before MoOPH (18.3 g, 42.1 mmol) was added in two portions. The green solution was stirred between −40 °C and −30 °C for 45 min, and the reaction was then quenched by the addition of half saturated aqueous NH_4Cl (150 mL). The THF was evaporated off, and the aqueous phase was extracted with AcOEt (3 ×). The organic phases were combined, washed with brine, dried (Na_2SO_4), and evaporated in vacuo to give 13.43 g of a crude product which was purified by chromatography (a stepwise gradient of AcOEt in hexane from 2:3 to 2:1). Yield: 4.12 g of **2** as a white solid (42%). The product was contaminated with 5% of the 3*R*,5*R*-isomer as judged by ^1H NMR. mp 145−147 °C. R_f = 0.15 (AcOEt/heptane 2:3). ^1H NMR (400 MHz, DMSO-d_6): (chemical shifts for the minor isomer are given in parentheses) δ 7.61−7.37 (m, 10 H), 5.80 (d, *J* = 7.5, 1H), 4.52 (m, 1H), 4.12 (m, 1H), 3.84 (dd, *J* = 10.5, 3.6, 1H), 3.64 (dd, *J* = 10.5, 2.0, 1H), 2.39 (m, 1H), 1.96 (m, 1H), 1.35 (1.32) (s, 9H), 0.95 (0.98) (s, 9H). Anal. Calcd for $C_{26}H_{35}NO_5Si$: C, 66.49; H, 7.51; N, 2.98. Found: C, 66.27; H, 7.61; N, 2.97.

(3*S*,5*R*)-3-Benzyloxymethoxy-5-[(*tert*-butyldiphenylsilyloxy)methyl]-2-pyrrolidinone (3). **2** (12.59 g, 26.8 mmol) was dried by coevaporation from CH_3CN/CH_2Cl_2 (1:1) and then redissolved in CH_2Cl_2 (60 mL). Bom-chloride (11.2 mL, 80.4 mmol) and then DIEA (14.0 mL, 80.4 mmol) were added at 0 °C. The solution was stirred at room temperature overnight. More CH_2Cl_2 was added, and the solution was extracted with half saturated aqueous NH_4Cl (2 ×). The organic phase was washed with brine, dried (Na_2SO_4), and evaporated in vacuo. Purification by chromatography (a stepwise gradient of AcOEt in heptane from 1:4 to 2:1) afforded the BOM-protected intermediate as a clear oil. Yield: 14.9 g (94%). R_f: 0.55 (AcOEt/hexane 2:3). ^1H NMR (300 MHz, DMSO-d_6): δ 7.59−7.28 (m, 15 H), 4.96 (d, *J* = 6.5, 1H), 4.86−4.79 (m, 2H), 4.60 (s, 2H) 4.21−4.18 (m, 1H), 3.85 (d, *J* = 7.6, 1H), 3.66 (d, *J* = 10.6, 1H), 2.45−2.38 (m, 1H), 2.18−2.07 (m, 1H), 1.36 (s, 9H), 0.92 (s, 9H). This purified intermediate (14.9 g, 25.2 mmol) was dissolved in CH_2Cl_2 (25 mL). TFA (25 mL) was added dropwise at 0 °C during 1 min, and the solution was stirred for 8 min. The solution was transferred to a 1 L Erlenmeyer flask and quenched by addition of saturated aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 and AcOEt (2 ×). The combined organic phases were dried (Na_2SO_4) and evaporated in vacuo. Purification by chromatography (AcOEt/heptane 2:1) afforded 9.27 g of a white solid. Recrystallization from a mixture of AcOEt (35 mL) and hexane (80 mL) afforded **3** as white needles. Yield: 7.31 g (59%). mp 108−109 °C. ^1H NMR (400 MHz, DMSO-d_6): δ 8.02 (s, 1H), 7.62−7.59 (m, 4H), 7.49−7.39 (m, 6H), 7.35−7.27 (m, 5H), 4.98 (d, *J* = 6.8, 1H), 4.79 (d, *J* = 6.6, 1H), 4.59 (s, 2H), 4.45 (t, *J* = 8.2, 1H), 3.66−3.63 (m, 1H), 3.55 (s, 2H), 2.30−2.24 (m, 1H), 2.07−2.01 (m, 1H), 0.97 (s, 9H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 174.6, 138.1, 135.2, 135.1, 132.8, 132.5, 130.0, 129.9, 128.2, 128.0, 127.9, 127.7, 127.4, 93.6, 72.3, 68.9, 66.4, 51.6, 31.6, 26.6, 18.8. Anal. Calcd for $C_{29}H_{35}NO_4Si$: C, 71.13; H, 7.20; N, 2.86. Found: C, 71.20; H, 7.17; N, 2.93. $[\alpha]^{22}_D$ −57.8 (*c* 1.45, MeOH).

(3*S*,5*R*)-3-Benzyloxymethoxy-5-[(*tert*-butyldiphenylsilyloxy)methyl]-*N*-[methoxycarbonylmethyl]-2-pyrrolidinone (4). **3** (4.06 g, 8.29 mmol) was dissolved in THF (40 mL). NaH (60% suspension in mineral oil, 0.663 g, 16.6 mmol) and then methyl bromoacetate (1.57 mL, 16.6 mmol) were added at 0 °C, and the reaction mixture was warmed to room temperature and stirred overnight. More NaH (60% suspension in mineral oil, 0.663 g, 16.6 mmol) and methyl bromoacetate (1.57 mL, 16.6 mmol) were added, and the reaction mixture stirred for 2 h at room temperature. The reaction was quenched by the slow addition of half saturated aqueous NH_4Cl (125 mL), and the solution was extracted with AcOEt (2 ×). The combined organic phases were washed with brine, dried (Na_2SO_4), and evaporated in vacuo to give the crude product as an oil (6.2 g) which was purified by chromatography (AcOEt/heptane 2:3). Yield: 4.65 g (100%) of **4** as a clear oil. R_f: 0.52 (AcOEt/heptane 2:1). ^1H NMR (300 MHz, DMSO-d_6): δ 7.60−7.29 (m, 15 H), 4.98 (d, *J* = 7.0, 1H), 4.80 (d, *J* = 6.5, 1H), 4.60 (s, 2H), 4.17 (d, *J* = 17.6, 2H), 4.04−3.63 (m, 3H), 3.62 (s, 3H), 2.28 (m, 1H), 1.99 (m, 1H), 0.95 (s, 9H). Anal. Calcd for $C_{32}H_{39}NO_6Si$: C, 68.42; H, 7.00; N, 2.49. Found: C, 67.85; H, 7.24; N, 2.50.

(3*S*,5*R*)-3-Benzyloxymethoxy-5-hydroxymethyl-*N*-methoxycarbonylmethyl-2-pyrrolidinone (5). **4** (6.57 g, 11.7 mmol) was dried by coevaporation from CH_3CN/CH_2Cl_2 (1:1)

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and then redissolved in THF (60 mL). $Et_3N{\cdot}3HF$ (3.7 mL, 23 mmol)) was slowly added, and the reaction was stirred at 50 °C for 2 h after which another portion of $Et_3N{\cdot}3HF$ (3.7 mL, 23 mmol) was added. The reaction was stirred at 50 °C for an additional 8 h. The solvent was evaporated off and the crude product purified by chromatography (12% MeOH in CH_2Cl_2). Yield: 3.73 g (99%) of **5** as a clear oil. ^1H NMR (300 MHz, DMSO-d_6): δ 7.36−7.29 (m, 5H), 4.96 (d, J = 6.5, 1H), 4.85 (t, J = 4.8, 1H), 4.79 (d, J = 6.5, 1H), 4.60 (s, 2H), 4.44 (t, J = 8.1, 1H), 4.19 (d, J = 17.3, 1H), 3.93 (d, J = 17.3, 1H), 3.65 (s, 3H), 3.55 (m, 1H), 3.37 (m, 1H), 2.24 (m, 1H), 2.00 (m, 1H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 172.7, 169.3, 138.0, 128.3, 127.8, 127.5, 93.7, 72.5, 69.0, 61.4, 56.8, 52.0, 42.3, 30.4. Anal. Calcd for $C_{16}H_{21}NO_6{\cdot}{}^1/_4H_2O$: C, 58.63; H, 6.63; N, 4.28. Found: C, 58.44; H, 6.39; N, 4.20.

(3*S*,5*R*)-3-Benzyloxymethoxy-*N*-methoxycarbonylmethyl-5-[methylsulfonyloxymethyl]-2-pyrrolidinone (6). **5** (376 mg, 1.16 mmol) was dried by evaporation from CH_3CN/CH_2Cl_2 (3:5) and then redissolved in CH_2Cl_2 (6 mL). Et_3N (242 μL, 1.74 mmol) and methanesulfonyl chloride (99 μL, 1.28 mmol) were added at 0 °C. The reaction was stirred at 0 °C for 45 min after which more methanesulfonyl chloride (99 μL, 1.28 mmol) was added, and the reaction was stirred at 0 °C for 90 min, when TLC (MeOH:CH_2Cl_2 4:96) showed the reaction to be complete. The reaction mixture was quenched by addition of half saturated aqueous $NaHCO_3$ (25 mL) and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (2 ×). The combined organic phases were dried over $MgSO_4$ and evaporated in vacuo to give 520 mg of crude product which was purified by chromatography (a stepwise gradient of 2−4% MeOH in CH_2Cl_2). Yield: 346 mg (86%) of **6** as a clear oil. R_f: 0.46 (MeOH:CH_2Cl_2 4:96). ^1H NMR (300 MHz, $CDCl_3$): δ 7.38−7.28 (m, 5 H), 5.10 (d, J = 7.2, 1H), 4.89 (d, J = 6.9, 1H), 4.69 (s, 2H), 4.52 (t, J = 7.8, 1H), 4.35−4.00 (m, 5H), 3.76 (s, 3H), 3.03 (s, 3H), 2.29 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 173.1, 168.7, 137.4, 128.3, 127.8, 127.6, 94.2, 71.6, 69.9, 68.8, 55.9, 52.3, 43.1, 37.5, 30.1. FABMS *m*/*z* 402.1 (M + H). Anal. Calcd for $C_{17}H_{23}NO_8S$: C, 50.87; H, 5.77; N, 3.49. Found: C, 50.43; H, 5.94; N, 3.44.

(3*S*,5*R*)-5-Azidomethyl-3-benzyloxymethoxy-*N*-methoxycarbonylmethyl-2-pyrrolidinone (7). **6** (3.80 g, 9.47 mmol) was dissolved in DMF (50 mL), and NaN_3 was (3.08 g, 47.4 mmol) added. The solution was stirred at 80 °C overnight. The solvent was evaporated off and the resulting oil partitioned between half saturated aqueous $NaHCO_3$ and AcOEt. The aqueous phase was extracted with AcOEt (2 ×) and CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. The crude product was purified by chromatography (4% MeOH in CH_2Cl_2). Yield: 3.14 g (98%) of **7** as an oil. ^1H NMR (300 MHz, DMSO-d_6): δ 7.36−7.28 (m, 5H), 4.97 (d, J = 6.6, 1H), 4.81 (d, J = 6.7, 1H), 4.61 (s, 2H), 4.50 (t, J = 8.5, 1H), 4.17 (d, J = 17.6, 1H), 4.03 (d, J = 17.6, 1H), 3.80 (m, 1H), 3.73−3.68 (m, 1H), 3.67 (s, 3H), 3.53−3.49 (m, 1H), 2.27−2.21 (m, 1H), 2.10−2.02 (m, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 172.6, 169.0, 137.9, 128.3, 127.8, 127.5, 93.8, 71.9, 69.0, 54.5, 52.2, 52.0, 42.3, 30.9. Anal. Calcd for $C_{16}H_{20}N_4O_5{\cdot}{}^1/_4H_2O$: C, 54.47; H, 5.87; N, 15.88. Found: C, 54.65; H, 5.84; N, 16.00.

(3*S*,5*R*)-5-*tert*-Butoxycarbonylaminomethyl-3-hydroxy-*N*-methoxycarbonylmethyl-2-pyrrolidinone (8). 10% Pd/C (0.61 g) was added to a stirred solution of **7** (3.10 g, 8.90 mmol) and Boc_2O (3.90 g, 17.8 mmol) in AcOEt (90 mL) at 0 °C. The mixture was hydrogenated at 1 atm for 90 min at room temperature and then passed through Celite. The solvent was evaporated off, and the crude product (5.9 g) was purified by chromatography (AcOEt). Yield: 3.37 g (89%) of the BOM-protected intermediate. ^1H NMR (300 MHz, DMSO-d_6):δ 7.35−7.28 (m, 5H), 6.95 (t, J = 5.7, 1H), 4.97 (d, J = 6.9, 1H), 4.78 (d, J = 6.6, 1H), 4.59 (m, 2H), 4.39 (t, J = 8.4, 1H), 4.20 (d, J = 18.0, 1H), 4.02 (m, 2H), 3.88 (d, J = 18.0, 1H), 3.71 (m, 1H), 3.77 (s, 3H), 2.38−2.31 (m, 1H), 2.03−1.95 (m, 1H), 1.34 (s, 9H). ^{13}C NMR (75.5 MHz, DMSO-d_6):δ 172.4, 169.3, 156.0, 137.9, 128.2, 127.7, 127.5, 93.5, 78.1, 71.9, 69.0, 55.5, 52.0, 42.1, 40.9, 30.6, 28.1. This purified intermediate (3.32 g, 7.84 mmol) was dissolved in MeOH (112 mL), 10% $Pd(OH)_2/C$ (0.66 g) was added, and the mixture was hydrogenated overnight at 1 atm and room temperature and then passed through Celite. The solution was evaporated, and the crude product (2.75 g) was purified by chromatography (CH_2Cl_2/MeOH 9:1). Yield: 2.23 g of **8** as a white solid (94%), R_f: 0.16 (AcOEt). ^1H NMR (300 MHz, DMSO-d_6): δ 6.91 (t, J = 6.0, 1H), 5.58 (d, J = 5.1, 1H), 4.19 (m, 1H), 4.13 (d, J = 18.0, 1H) 3.87 (d, J = 17.9, 1H), 3.65 (s, 3H), 3.62 (m, 1H), 3.11 (m, 2H), 2.22 (m, 1H), 1.83 (m, 1H), 1.36 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 174.6, 169.5, 155.9, 78.0, 67.2, 55.1, 51.9, 42.2, 41.0, 32.3, 28.2. Anal. Calcd for $C_{13}H_{22}N_2O_6{\cdot}0.25\ H_2O$: C, 50.89; H, 7.39; N, 9.13. Found: C, 50.63; H, 7.37; N, 9.00.

(3*R*,5*R*)-3-[N^6-(Benzyloxycarbonyl)adenin-9-yl]-5-*tert*-butoxycarbonylaminomethyl-*N*-methoxycarbonylmethyl-2-pyrrolidinone (9). **8** (302 mg, 1.00 mmol) was dried by coevaporation from dry CH_3CN (5 mL) and then redissolved in dry dioxane (20 mL). PPh_3 (0.565 g, 2.50 mmol) was added followed by adenine (675 mg, 5.00 mmol). To this suspension was slowly (during 30 min) added DEAD (0.32 mL, 2.0 mmol) at room temperature and the suspension stirred at room temperature overnight. The solvent was evaporated off, and the residue was purified twice by chromatography (first column: AcOEt then 10% MeOH/CH_2Cl_2. Second column: 15% MeOH/ CH_2Cl_2). Yield: 175 mg white solid (42%). ^1H NMR (300 MHz, CD_3OD): δ 8.23 (s, 1H), 8.11 (s, 1H), 5.46 (t, J = 9.9, 1H), 4.45 (d, J = 18.0, 1H), 4.09 (d, J = 18.0, 1H), 4.08 (m, 1H), 3.76 (s, 3H), 3.53 (d, J = 15, 1H), 3.35 (d, J = 15, 1H), 2.86 (m, 1H), 2.38 (m, 1H), 1.42 (s, 9H, Boc). ^{13}C NMR (75.5 MHz, CD_3OD): δ 172.9, 170.5, 158.6, 157.4, 153.9, 150.5, 142.3, 120.3, 80.7, 56.4, 56.3, 53.1, 43.7, 42.2, 29.6, 28.8. This intermediate (155 mg, 0.37 mmol) was dissolved in dry CH_2Cl_2 (2.5 mL), and *N*-benzyloxycarbonyl-*N′*-methylimidazolium triflate (542 mg, 1.48 mmol) was added. The reaction was stirred overnight, after which more *N*-benzyloxycarbonyl-*N′*-methylimidazolium triflate (125 mg, 0.23 mmol) was added, and the reaction was stirred 3 h. Half-saturated aqueous $NaHCO_3$ (25 mL) and CH_2Cl_2 were added, and the aqueous phase was extracted with CH_2Cl_2 and AcOEt. The combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. The crude product was purified by chromatography (AcOEt then 15% MeOH/AcOEt). Yield: 132 mg (64%) of **9** as a white solid. Total yield 24%. ^1H NMR (300 MHz, $CDCl_3$): δ 8.66 (s, 1H), 7.96 (s, 1H), 7.33−7.22 (m, 5H), 6.56 (br s, 1H), 5.19 (s, 2H), 5.08 (m, 1H), 4.44 (d, J = 17.9, 1H), 4.07 (m, 1H), 3.82 (d, J = 17.9, 1H), 3.66 (s, 3H), 3.60 (d, J = 14.7, 1H), 3.24 (d, J = 13.5, 1H), 2.70 (m, 1H), 2.44 (m, 1H), 1.35 (s, 9H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.4, 168.4, 156.1, 152.2, 151.0, 150.2, 149.6, 143.2, 135.2, 128.3, 128.1, 122.2, 79.5, 67.4, 55.0, 53.4, 52.2, 42.0, 40.7, 28.1, 27.2. FABHRMS *m*/*z* 554.2364 (M + H, $C_{26}H_{32}N_7O_7$ requires 554.2363).

(3*R*,5*R*)-3-[N^6-(Benzyloxycarbonyl)adenin-9-yl]-5-*tert*-butoxycarbonylaminomethyl-*N*-carboxymethyl-2-pyrrolidinone (10). **9** (120 mg, 0.217 mmol) was dissolved in THF (2.2 mL), and 1 M aqueous LiOH (0.54 mL, 0.54 mmol) was added at 0 °C. After 20 min, H_2O (4 mL) was added and the THF was evaporated off. **10** was precipitated by addition of 4 M HCl (0.25 mL) at 0 °C. The crude product was purified by chromatography (CH_2Cl_2:MeOH:HOAc 80:15:5). Fractions containing **10** were pooled, and the solvent was removed in vacuo. HOAc was completely removed by coevaporation from MeOH/toluene (three times) and MeOH/CH_3CN. The resulting white solid was dried under a high vacuum for one week. Yield: 68 mg (58%) of **10** as a white solid, R_f: 0.24 ($CHCl_3$/EtOH/AcOH 80:15:5). ^1H NMR (400 MHz, DMSO-d_6): δ 10.65 (s, 1H), 8.59 (s, 1H), 8.42 (s, 1H) 7.47−7.32 (m, 5H), 7.12 (m, 1H), 5.49 (t, J = 9.9, 1H), 5.22 (s, 2H), 4.24 (d, J = 17.8, 1H), 3.96 (m, 1H), 3.95 (d, J = 17.6, 1H), 3.30 (s, 2H), 2.72 (m, 1H), 2.34 (m, 1H), 1.37 (s, 9H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 172.0, 170.3, 169.8, 156.0, 152.1, 151.6, 151.4, 149.7, 143.8, 136.4, 128.4, 128.0, 127.9, 123.6, 78.1, 66.3, 54.7, 54.4, 42.7, 41.1, 28.2, 21.1. FABHRMS *m*/*z* 540.2227 (M + H, $C_{25}H_{30}N_7O_7$ requires 540.2207). $[\alpha]^{22}{}_D$ +29.4 (c 0.333, MeOH).

(3*R*,5*R*)-5-*tert*-Butoxycarbonylaminomethyl-3-hydroxy-*N*-methoxycarbonylmethyl-2-pyrrolidinone (11). **8** (2.19 g, 7.24 mmol) was dried by evaporation from CH_3CN (15 mL) and then redissolved in THF (25 mL). A solution of PPh_3 (5.72 g, 21.72 mmol) in THF (25 mL) and a solution of benzoic acid (4.44 g, 36.2 mmol) in toluene (70 mL) was successively added at 0 °C, and the mixture stirred for 2 min, before DEAD (5.71 mL, 36.2 mmol) was added dropwise. The clear yellow solution was allowed to warm to room temperature and stirred overnight. AcOEt was added, and the mixture was extracted with 0.5 M aq citric acid, brine, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$) and evaporated. The crude product was purified by chromatography (AcOEt/hexane 4:1, then pure AcOEt). Yield: 2.92 g (99%) of the intermediate as a white foam. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.00−7.52 (m, 5H), 6.97 (br s, 1H), 5.51 (t, J = 7.8, 1H), 4.31 (d, J = 17.7, 1H), 4.05 (d, J = 18.3, 1H), 3.78 (br s, 1H), 3.68 (s, 3H), 3.23 (m, 2H), 2.66 (m, 1H), 1.88 (m, 1H), 1.34 (s, 9H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 170.4, 169.0, 164.9, 156.0, 133.7, 129.3, 129.1, 128.8, 78.0, 70.5, 54.7, 52.1, 42.3, 40.8, 28.6, 28.1. This intermediate (2.88 g, 7.09 mmol) was dissolved in MeOH (50 mL) and cooled to 0 °C. NaOMe in methanol (1.05 M, 13.5 mL, 14.18 mmol) was added dropwise, and the solution was stirred at 0 °C for 30 min. The reaction was quenched by addition of half-saturated aqueous NH_4Cl (100 mL). The aqueous phase was extracted with AcOEt (4 ×) and CH_2Cl_2. The organic phases were combined, dried over Na_2SO_4 and evaporated in vacuo. Chromatography (AcOEt, then CH_2Cl_2/MeOH 9:1) afforded **11** as a white foam. Yield: 1.88 g (88%). Total yield: 87%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.90 (t, J = 5.7, 1H), 5.66 (d, J = 5.1, 1H), 4.19 (d, J = 17.7, 1H), 4.11 (m, 1H), 3.94 (d, J = 18.0, 1H), 3.64 (s, 3H), 3.55 (m, 1H), 3.17 (m, 2H), 2.31 (m, 1H), 1.51 (m, 1H), 1.38 (s, 9H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 175.4, 169.3, 155.9, 78.0, 68.1, 53.5, 51.9, 41.9, 41.3, 31.8, 28.2. Anal. Calcd for $C_{13}H_{22}N_2O_6 \cdot 0.25 H_2O$: C, 50.88; H, 7.41; N, 9.13. Found: C, 50.87; H, 7.46; N, 8.93.

(3*S*,5*R*)-3-[*N*^{6}-(Benzyloxycarbonyl)adenin-9-yl]-5-*tert*-butoxycarbonylaminomethyl-*N*-methoxycarbonylmethyl-2-pyrrolidinone (12). **11** (604 mg, 2.0 mmol) was dried by coevaporation from dry CH_3CN and then redissolved in dry dioxane (40 mL). PPh_3 (1.13 g, 5.0 mmol) was added followed by adenine (1.35 g, 10.0 mmol). To this suspension was slowly (during 30 min) added DEAD (0.63 mL, 4.0 mmol) at room temperature, and the suspension stirred at room temperature overnight. The solvent was evaporated off and the residue purified by chromatography (AcOEt then 10% MeOH/CH_2Cl_2). Yield: 587 mg (70%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.13 (s, 1H), 8.04 (s, 1H), 7.27 (s, 2H), 7.07 (t, J = 5.7, 1H), 5.43 (t, J = 5.43, 1H), 4.23 (d, J = 17.8, 1H), 4.11 (d, J = 17.8, 1H), 3.94 (m, 1H), 3.70 (s, 3H), 3.26 (m, 2H), 2.66 (m, 1H), 2.56 (m, 1H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 170.2, 169.1, 156.1, 152.5, 149.6, 139.6, 118.6, 78.3, 56.0, 53.1, 52.2, 43.2, 41.3, 29.6, 28.2. The intermediate (547 mg, 1.31 mmol) was dissolved in dry CH_2Cl_2 (9 mL) and *N*-benzyloxycarbonyl-*N′*-methylimidazolium triflate (1.92 g, 5.24 mmol) was added. The reaction was stirred at room temperature overnight. Half-saturated aqueous $NaHCO_3$ (40 mL) and CH_2Cl_2 were added, and the aqueous phase was extracted with CH_2Cl_2 and AcOEt. The combined organic phases were dried ($MgSO_4$) and evaporated in vacuo. The crude product was purified by chromatography (AcOEt then 10% MeOH/AcOEt). Yield: 507 mg (70%) of **12** as a white solid. Total yield 49%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.68 (s, 1H), 8.60 (s, 1H), 8.38 (s, 1H), 7.45−7.36 (m, 5H), 7.05 (br s, 1 H), 5.53 (t, 1H), 5.19 (s, 2H), 4.23 (d, J = 17.8, 1H), 4.10 (d, J = 17.8, 1H), 3.98 (m, 1H), 3.68 (s, 3H), 3.24 (m, 2H), 2.75 (m, 1H), 2.58 (m, 1H), 1.40 (s, 9H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 169.8, 169.1, 156.1, 152.1, 152.0, 151.6, 149.7, 143.2, 136.4, 128.4, 128.0, 127.9, 123.4, 78.3, 66.3, 56.1, 53.6, 52.2, 43.2, 41.3, 29.2, 28.2. FABMS m/z 554.2 (M + H). Anal. Calcd for $C_{26}H_{31}N_7O_7 \cdot 1.5 H_2O$: C, 53.81; H, 5.92; N, 16.90. Found: C, 54.01; H, 5.52; N, 16.43.

(3*S*,5*R*)-3-[*N*^{6}-(Benzyloxycarbonyl)adenin-9-yl]-5-*tert*-butoxycarbonylaminomethyl-*N*-carboxymethyl-2-pyrrolidinone (13). LiOH (1M, 2.1 mL, 2.1 mmol) was slowly added to a stirred solution of **12** (467 mg, 0.84 mmol) in THF (9 mL) at 0 °C, and the reaction was stirred at 0 °C for 20 min. H_2O (20 mL) was added, and the THF was evaporated off. The product was precipitated by the slow addition of 4 M HCl (0.6 mL) at 0 °C. The crude product was purified by chromatography (CH_2Cl_2:MeOH:HOAc 85:10:5). Fractions containing **13** were pooled, and the solvent was removed in vacuo. HOAc was completely removed by coevaporation from MeOH/toluene (three times) and MeOH/CH_3CN. The resulting white solid was dried in high vacuum for one week. Yield: 152 mg (33%). R_f: 0.55 ($CHCl_3$/EtOH/AcOH 80:15:5). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.68 (s, 1H), 8.59 (s, 1H), 8.42 (s, 1H), 7.44−7.29 (m, 5H), 7.11 (m, 1H), 5.49 (t, J = 9.0, 1H), 5.20 (s, 2H), 3.97 (m, 2H), 3.28−3.22 (m, 2H), 2.76−2.60 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 170.5, 169.6, 156.1, 152.2, 152.0, 151.6, 149.7, 143.2, 136.4, 128.4, 128.0, 127.9, 123.3, 78.3, 66.3, 56.5, 53.7, 44.3, 41.2, 29.5, 28.3. FABHRMS m/z 540.2212 (M + H, $C_{25}H_{30}N_7O_7$ requires 540.2207). Anal. Calcd for $C_{25}H_{29}N_7O_7 \cdot 2H_2O$: C, 52.17; H, 5.78; N, 17.03. Found: C, 52.60; H, 5.33; N, 16.71. $[\alpha]^{22}_D$ −11.7 (c 0.3, MeOH).

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Supporting Information Available: Experimental procedures for the synthesis of the (3*R*,5*S*) and (3*S*,5*S*) monomers. Copies of ^{1}H and ^{13}C NMR spectra of compound **10**. UV-melting curves and UV-titration curves. This material is available free of charge via the Internet at http://pubs.acs.org.

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