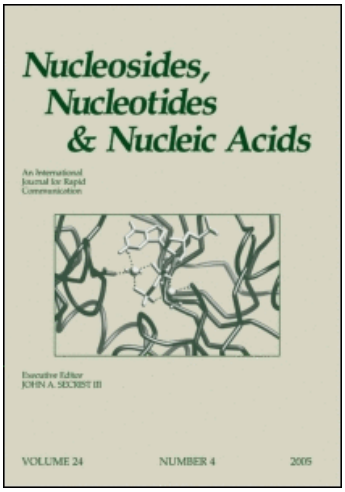

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An Improved Synthesis of 2'-Deoxy-9-deazaadenosine and an N-7 Blocked Derivative Useful for the Synthesis of Modified Oligonucleotides Containing 2'-Deoxy-9-deazaadenosine

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AN IMPROVED SYNTHESIS OF 2'-DEOXY-9-DEAZAADENOSINE AND AN N-7 BLOCKED DERIVATIVE USEFUL FOR THE SYNTHESIS OF MODIFIED OLIGONUCLEOTIDES CONTAINING 2'-DEOXY-9-DEAZAADENOSINE.[1]

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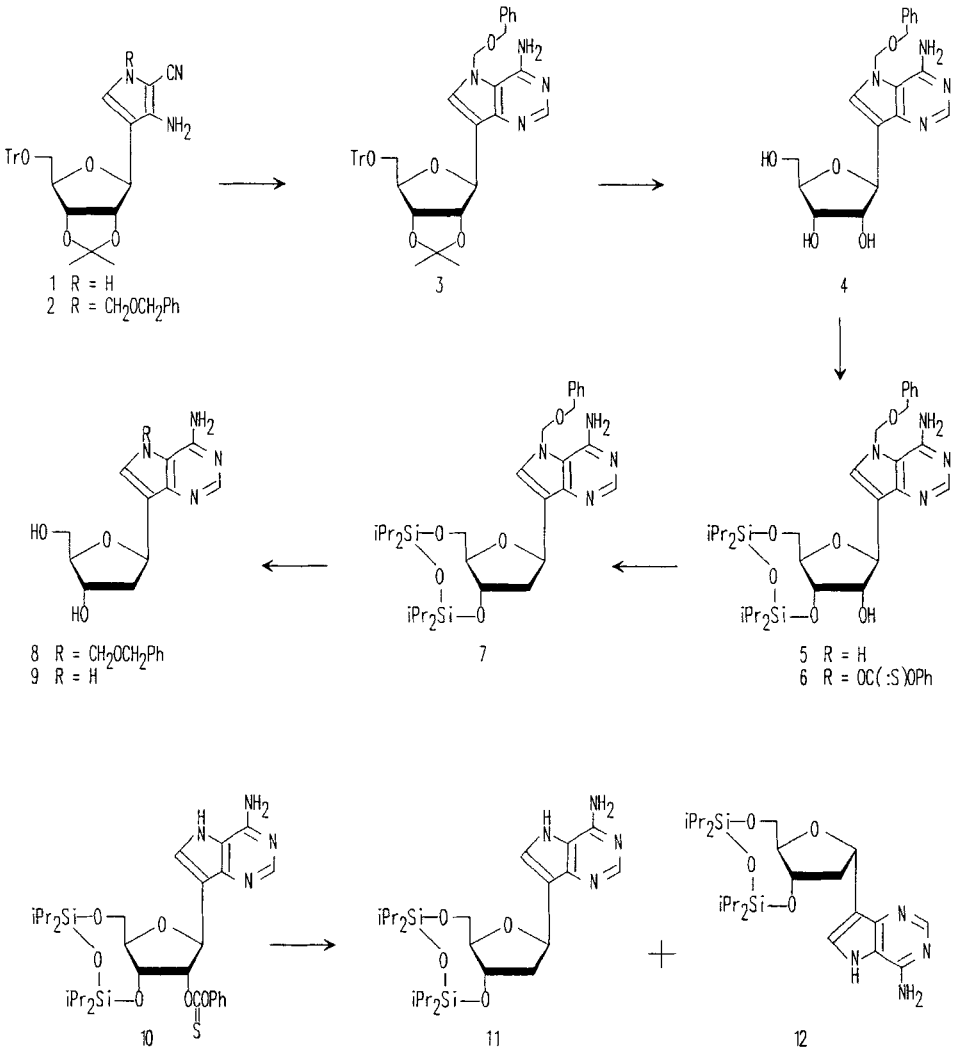
ABSTRACT: As an epimerization resistant synthon in the synthesis of oligonucleotides consisting of C-nucleoside analogues, hitherto unknown 5-benzyloxymethyl-3-(2-deoxy-β-D-erythro-pentofuranosyl)pyrrolo[3,2-d]pyrimidine (7-benzyloxymethyl-2'-deoxy-9-deazaadenosine) was prepared in seven steps from the known 3-amino-2-cyano-4-(2,3-O-isopropylidene-5-O-trityl-β-D-ribofuranosyl)-pyrrole (**1**). Treatment of **1** with benzyl chloromethyl ether in the presence of potassium *t*-butoxide and 18-crown-6 afforded the N-protected pyrrole **2**, which was converted into the 9-deazapurine derivative **3** in high yield by heating in EtOH. 7-Benzyloxymethyl-9-deazaadenosine **4** was obtained from **3** by acid hydrolysis in 2.5% methanolic hydrogen chloride. After protection of the hydroxyl groups of **4** with Markievicz's reagent, the product **5** was converted into the 2'-O-phenoxythiocarbonyl derivative **6**. Reduction of **6** with butyltin hydride in the presence of 2,2'-azobis(2-methylpropionitrile), followed by desilylation with triethylammonium fluoride, afforded the desired 7-benzyloxymethyl-2'-deoxy-9-deazaadenosine (**8**) in high overall yield. The benzyloxymethyl group of **8** was removed by hydrogenolysis over palladium hydroxide (Degussa type) to give 2'-deoxy-9-deazaadenosine (**9**) in quantitative yield. The structure of **9** is discussed.

The chemistry, biochemistry and biophysics of oligonucleotides containing the C-nucleoside analogues have intrigued us recently.[2,3] It was found that displacement of thymidine by 2'-deoxy-1-methyl-ψ-uridine (the C-nucleoside isostere of thymidine) gives an oligomer which greatly destabilizes the duplex with oligo(dA). For example, undecathymidylate $(dT)_{11}$ formed a duplex with undecamer of deoxyadenosine $(dA)_{11}$

in a buffer (10 mM TRIS HCl, pH 7.5, 10 mM NaCl) with or without magnesium ion with the melting temperature of 31 °C. Displacement of the 5 and 7 thymidine moiety by $(dT)_{11}$ with 2'-deoxy-1-methyl-ψ-uridine gave the analogue, namely, the oligomer, d(TTTTψTψTTTT), incapable of forming a duplex with $(dA)_{10}$ without magnesium ion. The melting temperature dropped to 21 °C.[3] In the synthesis of oligomers containing certain C-nucleosides, the possibility of epimerization at C-1 has to be taken into consideration. Any C-nucleoside bearing a dissociable proton at the β position from C1' or at δ in the vinylogue undergoes α,β-isomerization *via* the β- or δ-elimination mechanism. ψ-Uridine, pyrazofurin and ψ-isocytidine are known to isomerize to their corresponding α-C-nucleosides in acid and base.[4] The 2'-deoxy analogues of ψ-uridine and ψ-isocytidine epimerized much more readily than the parent ribo-C-nucleosides.[5,6] Thus, it was necessary to protect the N^1 position by trimethylsilyl group during the synthesis of 2'-deoxy-ψ-uridine and 2'-deoxy-ψ-isocytidine.[6] For oligomer synthesis, the protecting group on N^1 of 2'-deoxy-ψ-uridine and 2'-deoxy-ψ-isocytidine derivatives or on N^7 of 2'-deoxy-9-deazaadenosine should be stable during the coupling, deblocking and washing cycles, but should be removed readily under neutral conditions at the end of oligomer formation. We selected the benzyloxymethyl group for protection of the N^7 position of 9-deazaadenosine, since this group can be removed readily by mild reduction under neutral conditions.

Rao *et al.*[7] synthesized 2'-deoxy-9-deazaadenosine (**9**, Scheme **1**) by reduction of 7-[3',5'-O-(1,1,3,3-tetraisopropyldisiloxan-1,3-yl)-2'-deoxy-2'-bromo-β-D-arabinofuranosyl]-N^6,N^6,N^7-tribenzoyl-9-deazaadenine, followed by deprotection with ammonia and fluoride treatments. They isolated the free nucleoside as the HCl salt. This methodology, however, was not suitable for our purposes, since the procedure to obtain **9** is too lengthy, and **9** has to be converted back into the N^7 protected C-nucleoside.

Our starting material was the known 4-(2',3'-O-isopropylidene-5'-O-trityl-β-D-ribofuranosyl)-3-amino-4-cyanopyrrole (**1**),[8] which was treated with benzyl chloromethyl ether in tetrahydrofuran (THF) in the presence of potassium *t*-butoxide and 18-crown-6 at room temperature to afford **2** (Scheme **1**). Compound **2** can be purified by column chromatography, but crude **2** is pure enough to be directly



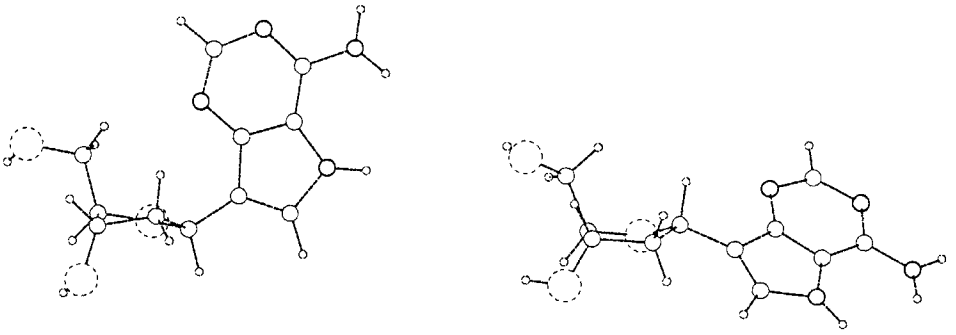
Scheme 1

converted into the pyrrolo[3,2-d]pyrimidine **3** in high yield by treatment with excess formamidine in boiling ethanol. Treatment of **3** with dilute HCl/MeOH (2.5%) afforded 7-benzyloxymethyl-9-deazaadenosine (**4**), which was converted into the 3',5'-di-O-protected intermediate **5** by treatment with the Markiewicz reagent in pyridine in the presence of 4-(N,N-dimethylamino)pyridine (DMAP). After phenoxythio-

carbonylation of **5** to **6**, followed by Barton reduction[9,10] with *t*-Bu_3SnH in the presence of 2,2'-azobis(2-methylpropionitrile) (AIBN), according to Robins *et al.*,[11] the protected 7-benzyloxymethyl-2'-deoxy-9-deazaadenosine **7** was obtained. De-O-silylation of **7** with Et_3NHF gave 7-benzyloxymethyl-2'-deoxy-9-deazaadenosine (**8**). Each step in this sequence went smoothly, and all the intermediate isolated directly from reaction mixtures were sufficiently pure. The overall yield of **8** from **1** was 36%. After hydrogenolysis of **8** over palladium hydroxide (Degussa type), 2'-deoxy-9-deazaadenosine (**9**) was obtained in almost quantitative yield.

The ^{1}H NMR spectrum of the sugar portion of **8** was very similar to that reported[12,13] for 2'-deoxyformycin B, but somewhat different to that reported by Rao *et al.*[7] The H-1' signal of **8** at δ 5.22 appeared as a double doublet as that reported for 2'-deoxyformycin B, but not an apparent triplet as reported for the HCl salt of **9**. Deprotection of **8** by hydrogenolysis over palladium hydroxide (Degussa type) afforded 2'-deoxy-9-deazaadenosine, which also showed a double doublet for H-1'. Since N^7 is protected by benzyloxymethyl group, there was little possibility for α,β-isomerization during the process for preparation of **9**, and reductive deprotection was carried out in neutral conditions. Barton reduction of the N^7 *unprotected* analogue **10** gave a mixture of two products **11** and **12**, in a 4:1 ratio, which, after deprotection, were separated by HPLC using 0.1M tetraethylammonium bicarbonate and 70% aqueous acetonitrile in linear gradient on a Dynamax-300A and isolated as **9** and **9-α** C18 column (retention time for **9** = 18.07, for the minor product = 18.89 min). The ^{1}H NMR spectrum of the latter showed the H1' signal as an apparent *triplet* as reported for β-9-deazaadenosine.[7]

We assigned, however, the β-C-nucleoside structure to **8** and **9**, and α (**α-9**) to the minor product based on the CD and ^{1}H NMR spectrometric as well as computer modeling studies. The CD spectra of **9**, **α-9**, adenosine and 2'-deoxyadenosine were measured in molar ellipticity at 190-350 nm range. Negative troughs are found at ~265 nm for **9** and ~280 for adenosine and deoxyadenosine. Positive peaks appear ~240 nm for **9** and ~220 for adenosine and deoxyadenosine. On the other hand, **α-9** showed an almost inverted spectrum compared to the others. These results strongly suggest that **9** has the configuration at C1' similar to that of adenosine and deoxyadenosine, *e.g.*, the β-configuration. The refined structures of



β-D-isomer (**9**) α-D-isomer (**α-9**)

Figure 1. Average solution structures of α and β-isomers of 2'-deoxy-9-deazaadenosine.

9 and **α-9** were obtained by constrain dynamic structure search. We selected the $J_{H3',H4'}$ value as reference to the constrained angle, since this appears to be the most unambiguous value reflected by the dihedral angle. The final room temperature average equilibration structures for **9** and **α-9** are shown in Figure 1. Compound **9** is the β-nucleoside with the C2'-*endo* for sugar and the anti conformation the glycosyl linkage, with the dihedral angles 32.67° for H1',H2'; 152.91° for H1',H2"; 89.59° for H2',H3'; 29.89° for H2",H3'; and 99.09° for H3',H4'. The respective, calculated coupling constants are shown in Table 1. These values are very similar to those observed for **9**. On the other hand, **α-9**, is an α-nucleoside with the C1'-*endo* and the anti conformation for the glycosylic linkage, with the dihedral angles of 26° for H1',H2'; 142° for H1',H2"; 10° for H2',H3'; 120° for H2",H3'; and 120° for H3',H4'. The calculated J values based on the dihedral angles between vicinal protons on the sugar ring are consistent with those observed for the reported values of "2'-deoxy-9-deaza-adenosine." The ^{1}H NMR data of **8**, **9**, and **9-α** were also interpreted in terms of a dynamic systems of conformers.[14] The observed vicinal proton spin-spin coupling constants were subjected to conformational analyses using the PSEUROT program.[15] For assignment of the anomeric configuration of 2'-deoxy-N-nucleosides, there is a widely accepted empirical rule that the H-1' signal for β-nucleosides appears as an apparent triplet whereas a distinct double doublet for α-nucleosides.[16,17] This empirical rule, however, is not applicable for C-nucleosides.[12,18]

Table 1. The observed and calculated ^{1}H NMR parameters of α- and β-isomers of 2'-deoxy-9-deazaadenosine.

Compound	Chemical Shifts	Coupling constants					
	H1' H2'β H2'α H3' H4'	$J_{1',2'}$	$J_{1',2''}$	$J_{2',2''}$	$J_{2',3'}$	$J_{2'',3'}$	$J_{3',4'}$
8 (found)	5.22 1.92 2.32 4.27 3.83	5.3	10.9	12.7	<.1	5.0	0.0
9 (found)	5.23 1.94 2.36 4.27 3.83	5.4	10.9	12.5	<.1	5.0	0.0
9 (calcd.)		5.44	10.62	----	1.41	5.15	0.96
α-**9** (found)	5.15 2.05 2.57 4.16 3.83	7.2	7.2	13.4	7.1	3.6	4.2
α-**9** (calcd.)		6.63	6.57	----	6.42	3.28	4.8
9 (reported)[7]	5.29 2.00-2.13 4.29 3.71-3.85						

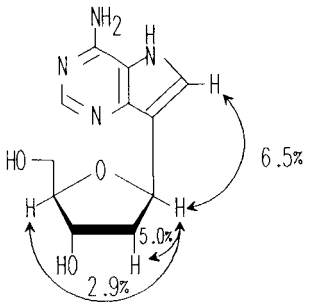


Figure 2. 2'-deoxy-9-deazaadenosine

The conclusive evidence for the structural assignments was obtained by measuring the nuclear Overhauser effect.[19] Upon irradiation of H-1' of **9** at δ 5.23, the signals for H2'(α) and H4' at δ 2.36 and 3.83 increased by 2.9% and 5.0%, respectively, establishing the all three protons (H1', H2'(α) and H4') to be on the

same side of the furanose ring. In addition, the H8 signal also increased by 6.5%, indicating that the nucleoside is in the *syn* conformation (Figure **2**).

These data, however, did not provide us with information about the structure of the C-nucleoside obtained by Rao *et al.*[7] We, therefore, repeated the reported procedure, and found that the reaction mixture (after deblocking) contained two products, one major and the minor compound **α-D-9**. The ^{1}H NMR spectrum of our HCl salt of the major product was identical to that of **9** taken in DCl. The signal for H1', however, appeared as a distinct double doublet, not as a triplet as originally reported. The chemical shifts for protons originally reported are very similar to those observed by Rao *et al.* for the HCl salt of **9**. We conclude that the procedure reported by Rao *et al.*[7] for the synthesis of 2'-deoxy-9-deazaadenosine (**9**) gives the correct C-nucleoside as the major product. For the synthesis of protected 2'-deoxy-9-deazaadenosine as an intermediate in preparation of modified oligonucleotides, the procedure we developed would be the method of choice as it gives only the desired β-C-nucleoside, fewer steps, and good overall yield.

EXPERIMENTAL SECTION

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Column chromatography was performed on silica gel G60 (70-230 mesh, ASTM, Merck). TLC was performed on aluminun sheets silica gel 60 F_{254} (Merck) with short-wavelength UV light for visualization. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. ^{1}H NMR spectra were recorded on a Bruker ACF-400 spectrometer with Me_4Si as the internal standard. Chemical shifts are reported in ppm (δ), and signals are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad singlet) and (dd) (double doublet). Values given for coupling constants are first order.

3-Amino-1-benzyloxymethyl-2-cyano-4-(2,3-O-isopropylidene-5-O-trityl-β-D-ribofuranosyl)pyrrole (2). To a solution of **1**[8] (10g, 20 mmol) in anhydrous THF (150 mL) were added 18-crown-6 (0.5 g, 0.2 mmol) and *t*BuOK (2.6 g, 23 mmol). The mixture was stirred for 15 min at room temperature. A solution of benzyl

chloromethyl ether (3.6 g, 23 mmol) in THF (20 mL) was added dropwise, and the mixture was stirred for 2 h. The solvent was removed in vacuo, and the residue was dissolved in Et_2O (500 mL), washed with brine, (2 x 150 mL), dried (Na_2SO_4), and then concentrated in vacuo to give crude **2**, which was used directly in the next step.

A small part of the crude product was purified on a silica gel column using CCl_4/AcOEt (93:7 v/v) to give pure **2** as a white foam. ^1H NMR (Me_2SO-d_6) δ 1.28 (3H, s, iPr), 1.49 (3H, s, iPr), 3.10 (2H, m, H5',5"), 4.05 (1H, ψq, H4', $J_{3',4'}$ = 4.1, $J_{4',5'} = J_{4',5"}$ = 5.7 Hz), 4.34 (2H, s, CH_2O), 4.62 (1H, dd, H3', $J_{2",3'}$ = 6.1. $J_{3',4'}$ = 4.1 Hz), 4.71-4.76 (2H, m, H1',2'), 5.06 (2H, s, NH_2, exchangeable), 5.20 (2H, s, CH_2O), 7.09 (1H, s, H5), 7.18-7.38 (20H, m, Tr and Ph). *Anal.* Calcd for $C_{40}H_{39}N_3O_5$: C, 74.86; H, 6.13; N, 6.55. Found: C, 74.90; H, 6.16; N, 6.36.

4-Amino-5-benzyloxymethyl-7-(2,3-O-isopropylidene-5-O-trityl-β-D-ribofuranosyl)pyrrolo[3,2-d]pyrimidine (3). The crude **2** (obtained above) was treated with formamidine acetate (6.24 g, 60 mmol) in boiling EtOH (900 mL) for 24 h. An additional charge of formamidine (6.24 g) was added, and the mixture was kept under reflux for 8 h. The solvent was removed in vacuo, and the residue was dissolved in $CHCl_3$ (800 mL), and washed with H_2O (4 x 200 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo to dryness to give crude **3**, which was used directly in the next step. An analytical sample was obtained by chromatography on a silica gel column using CH_2Cl_2/MeOH (98.5:1.5 v/v). ^1H NMR (Me_2SO-d_6) δ 1.28 (3H, s, iPr), 1.51 (3H, s, iPr), 3.11 (2H, m, H5',5"), 4.10 (1H, ψq, H4', $J_{3',4'}$ = 4.1, $J_{4',5'} = J_{4',5"}$ = 5.4 Hz), 4.42 (2H, s, CH_2O), 4.73 (1H, dd, H3', $J_{2',3'}$ = 6.5. $J_{3',4'}$ = 4.1 Hz), 5.08 (1H, d, H1', $J_{1',2'}$ = 3.9 Hz), 5.18 (1H, dd, H2', $J_{1',2'}$ = 3.9, $J_{2',3'}$ = 6.5 Hz), 5.66 (2H, ABq, CH_2O), 6.62 (2H, s, NH_2, exchangeable), 7.20-7.36 (20H, m, Tr and Ph), 7.65 (1H, s, H6), 8.11 (1H, s, H2). *Anal.* Calcd for $C_{41}H_{40}N_4O_5$: C, 73.63; H, 6.03; N, 8.38. Found: C, 73.49; H, 6.15; N, 8.18.

4-Amino-5-benzyloxymethyl-7-(β-D-ribofuranosyl)pyrrolo[3,2-d]pyrimidine HCl (4). To a solution of crude **3** (obtained above) in MeOH (140 mL) was added 5% HCl/MeOH (140 mL), and the mixture was kept at room temperature for 40 min, and then concentrated in vacuo to dryness. The residue was coevaporated several times with EtOH, and then triturated in Et_2O (200 mL) to give crude **4**, which was used directly in the next step.

5-Benzyloxymethyl-7-[3,5-O-(1,1,3,3-tetraisopropyldisiloxan-1,3-yl)-β-D-ribofuranosyl]-4-aminopyrrolo[3,2-d]-pyrimidine.HCl (5). A mixture of crude **4** (20 mmol, obtained above) and $TiPDSiCl_2$ (6.94 g, 22 mmol) in pyridine (90 mL) was stirred at room temperature for 1.5 h, and then concentrated in vacuo. The residue was coevaporated several times with MePh, dissolved in CH_2Cl_2 (400 mL), washed with saturated NaCl (100 mL), dried (Na_2SO_4), and concentrated to give crude **5** which was sufficiently pure to be used directly in the next step. ^1H NMR (Me_2SO-d_6) δ 0.89 - 1.06 (28H, m, *i*-Pr), 3.90-4.04 (3H, m, H4',5',5"), 4.19 (1H, dd, H2', $J_{1',2'}$ = 2.6, $J_{2',3'}$ = 5.2 Hz), 4.27 (1H, dd, H3', $J_{2',3'}$ = 5.2, $J_{3',4'}$ = 7.4 Hz), 4.46 (2H, s, CH_2O), 4.94 (1H, d, H1', $J_{1',2'}$ = 2.5 Hz), 5.2 (1H, bs, OH, exchangeable), 5.78 (2H, ABq, CH_2O), 7.19-7.30 (5H, m, Ph), 7.79 (1H, s, H6), 7.9 (3H, brs, NH_3^+, exchangeable), 8.36 (1H, s, H2).

5-Benzyloxymethyl-7-[2-O-phenoxythiocarbonyl-3,5-O-(1,1,3,3-tetraisopropyldisiloxan-1,3-yl)-β-D-ribofuranosyl]-4-aminopyrrolo[3,2-d]-pyrimidine (6). A mixture of crude **5** (20 mmol, obtained above) and DMAP (4.88 g, 40 mmol) and phenyl chlorothiocarbonate (3.79 g, 22 mmol) in dry MeCN (380 mL) was stirred at room temperature for 20 h. A second charge of phenyl chlorothiocarbonate (3.79 g) was added, and the stirring was continued for 10 additional h. The mixture was concentrated in vacuo, the residue was dissolved in CH_2Cl_2 (600 mL), washed (5% aq. AcOH 200 mL and then H_2O 2 x 200 mL), dried (Na_2SO_4), and concentrated in vacuo to give crude **6**, which was sufficiently pure to be used directly in the next step. A portion of the crude product was purified by chromatography on a silica gel column (CH_2Cl_2/MeOH 98.5:1.5 v/v) for elemental analyses. ^1H NMR (Me_2SO-d_6) δ 0.96 - 1.01 (28H, m, *i*-Pr), 3.82-4.02 (3H, m, H4',5',5"), 4.49 (2H, s, CH_2O), 5.23 (1H, s, H1'), 5.35 (1H, dd, H3', $J_{2',3'}$ = 5.2, $J_{3',4'}$ = 8.6 Hz), 5.72 (2H, s, CH_2O), 6.29 (1H, d, H2', $J_{2',3'}$ = 5.0 Hz), 6.68 (2H, s, NH_2, exchangeable), 7.43-7.50 (10H, m, 2 x Ph), 7.71 (1H, s, H6), 8.07 (1H, s, H2). *Anal.* Calcd for $C_{38}H_{52}N_4O_7Si_2$: C, 59.66; H, 6.85; N, 7.32. Found: C, 59.43; H, 7.01; N, 7.12.

5-Benzyloxymethyl-7-[2-deoxy-3,5-O-(1,1,3,3-tetraisopropyldisiloxan-1,3-yl)-β-D-*erythro*-pentofuranosyl]-4-aminopyrrolo[3,2-d]-pyrimidine (7). To a boiling solution of crude **6** (20 mmol, obtained above) in MePh (300 mL) was added dropwise a mixture of *n*-Bu_3SnH (26.3 g, 90.3 mmol) and 2,2'-azobis(2-methylpropionitrile)

(AIBN, 2.7 g, 16.4 mmol) in MePh (150 mL) over a duration of 1 h. The mixture was concentrated in vacuo, the residue was dissolved in CH_2Cl_2 (100 mL), and passed through a short silica gel column, which was then washed with CH_2Cl_2 (500 mL) and then CH_2Cl_2/MeOH (1:1 v/v, 1 L). The last eluent was concentrated in vacuo to give crude **7**, which was sufficiently pure to be used directly in the next step. An analytical sample was prepared from a small portion of crude **7** by chromatography on a silica gel column using CH_2Cl_2/MeOH (98.5:1.5 and 95:5 v/v). ^{1}H NMR (Me_2SO-d_6) δ 0.98 - 1.13 (28H, m, *i*-Pr), 2.24-2.48 (2H, m, H2',2"), 3.77-3.97 (3H, m, H4',5',5"), 4.47 (2H, s, CH_2O), 4.71 (1H, ψq, H3'), 5.22 (1H, t, H1', $J_{1',2"} = J_{1',2'} =$ 7.1 Hz), 5.69 (2H, s, CH_2O), 6.59 (2H, s, NH_2, exchangeable), 7.24-7.33 (5H, m, Ph), 7.58 (1H, s, H6), 8.10 (1H, s, H2). *Anal.* Calcd for $C_{31}H_{48}N_4O_5Si_2$: C, 60.75; H, 7.89; N, 9.14. Found: C, 60.75; H, 7.60; N, 8.99.

5-Benzyloxymethyl-7-(2-deoxy-β-D-*erythro*-pentofuranosyl]-4-aminopyrrolo[3,2-d]-pyrimidine (8). To a solution of crude **7** (20 mmol, obtained above) in THF (230 mL) was added dropwise 1M solution of Et_3NHF in THF (60 mL), and the progress of the reaction was monitored by TLC. After the reaction was completed (24 h), the mixture was concentrated to dryness, and the residue was twice chromatographed on a silica gel column (CH_2Cl_2/MeOH 99:1 and CCl_4/MeOH 97.5:2.5 v/v) to give 2.7 g of **8** as a foam. ^{1}H NMR (Me_2SO-d_6) δ 1.97 (1H, dd, H2', $J_{2',2"} = 12.7$, $J_{1',2'} = 5.3$, $J_{2',3'} = 0$ Hz), 2.32 (1H, ddd, H2", $J_{2',2"} = 12.7$, $J_{1',2"} = 10.9$, $J_{2",3'} = 5.0$ Hz), 3.50 (2H, m, H5',5"), 3.83 (1H, s, H4'), 4.27 (1H, d, H3', $J_{2",3'} = 5.0$. $J_{3',4'} - 0$ Hz), 4.48 (2H, s, NCH_2O), 4.98 (1H, d, 3'-OH, exchangeable), 5.22 (1H, dd, H1', $J_{1',2"} = 10.9$, $J_{1',2'} =$ 5.3 Hz), 5.66 (2H, ABq, CH_2Ph), 5.92 (1H, t, 5'-OH, exchangeable), 6.69 (2H, s, NH_2, exchangeable), 7.24-7.33 (5H, m, Ph), 7.62 (1H, s, H6), 8.07 (1H, s, H2). *Anal.* Calcd for $C_{19}H_{22}N_4O_4$: C, 61.61; H, 5.99; N, 15.13. Found: C, 61.86; H, 6.06; N, 14.96.

7-(2-Deoxy-β-D-*erythro*-pentofuranosyl]-4-aminopyrrolo[3,2-d]-pyrimidine (9, 2'-Deoxy-9-deazaadenosine). To a solution of **8** (0.1 g, 2.7 mmol) in MeOH (10 mL) was added palladium hydroxide on carbon (20 mg, Degussa type), and the mixture was hydrogenated (H_2, 1 atm) for 1.5 h. The catalyst was removed by filtration, and the filtrate was removed in vacuo to give **9** in quantitative yield as colorless foam. ^{1}H NMR (Me_2SO-d_6) δ 1.94 (1H, dd, H2', $J_{2',2"} = 12.5$, $J_{1',2'} = 5.5$, $J_{2',3'} = 0$ Hz), 2.36

(1H, ddd, H2", $J_{2',2''}$ = 12.5, $J_{1',2''}$ = 10.9, $J_{2'',3'}$ = 5.4 Hz), 3.51 (2H, m, H5',5"), 3.83 (1H, s, H4'), 4.27 (1H, d, H3', $J_{2'',3'}$ = 5.0. $J_{3',4'}$ - 0 Hz), 4.94 (1H, dd, 3-OH, exchangeable), 5.23 (1H, dd, H1', $J_{1',2''}$ = 10.9, $J_{1',2'}$ = 5.5 Hz), 6.19 (2H, brs, 5'-OH, exchangeable), 6.83 (2H, s, NH_2, exchangeable), 7.49 (1H, s after exchange, H6), 8.02 (1H, s, H2), 11.9 (1H, s, NH exchangeable). *Anal.* Calcd for $C_{11}H_{14}N_4O_2$: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.61; H, 5.96; N, 22.12.

Molecular Modeling. Structures of **9** and its α-isomer (α-**9**) were generated on a Silicon Graphics Iris Personal Workstation using the QUANTA software, and the CHARMm program was used for energy calculation. The starting models were energy-minimized by Steepest descents and Adopted-basis Newton Raphson algorithm. The dynamics data set was generated in 300 steps from 0 °K to 300 °K, followed by equilibration and simulation (300 iterations each). The time step for this process was 0.001 pico second each. The structures for **9** and **α-9** were average structures obtained by equilibrating data sets, which represent more likely structures in solution.

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