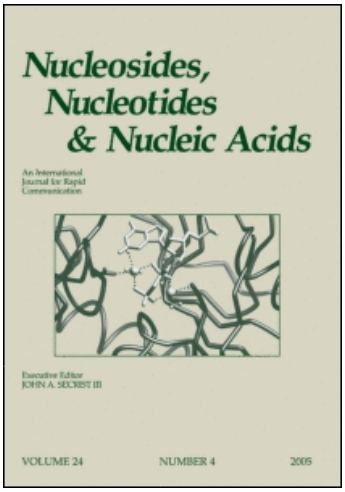

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Nucleic Acid Related Compounds. LXXXI. Efficient General Synthesis of Purine (Amino, Azido, and Triflate)-Sugar Nucleosides

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NUCLEIC ACID RELATED COMPOUNDS. 71. EFFICIENT GENERAL SYNTHESIS OF PURINE (AMINO, AZIDO, AND TRIFLATE)-SUGAR NUCLEOSIDES[1]

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Abstract: Treatment of 3',5'-*O*-(tetraisopropyldisiloxanyl)adenosine and its arabino epimer with trifluoromethanesulfonyl chloride/DMAP gave the 2'-triflates in high yields. Displacements (LiN_3/DMF) and deprotection gave 2'-azido-2'-deoxyadenosine and its arabino epimer which were reduced with Bu_3SnH/AIBN/DMAC/benzene (or Staudinger reduction) to give 2'-amino-2'-deoxyadenosine and its epimer. Oxidation of 2',5'-bis-*O*-(*tert*-butyldimethylsilyl)adenosine, stereoselective reduction, triflation, azide displacement, deprotection, and reduction gave 3'-amino-3'-deoxyadenosine.

Various nucleoside antibiotics have aminosugar moieties and several 2'(and 3')-amino-2'(and 3')-deoxynucleosides have antibacterial, anticancer, and biosynthetic inhibitory activity.[2] Puromycin, the well-known inhibitor of protein biosynthesis, is a derivative of 3'-amino-3'-deoxyadenosine (**9**), and the 5'-triphosphate of **9** inhibits RNA synthesis.[2] Both 2'-amino-2'-deoxyadenosine (**5b**) and 2'-amino-2'-deoxyguanosine have been isolated from microbial cultures and found to have biological activity.

Aminosugar nucleosides have been prepared by: (1) coupling of aminosugar derivatives with heterocyclic bases;[3] (2) elaboration of base rings on functionalized carbohydrate derivatives;[4] and (3) various types of

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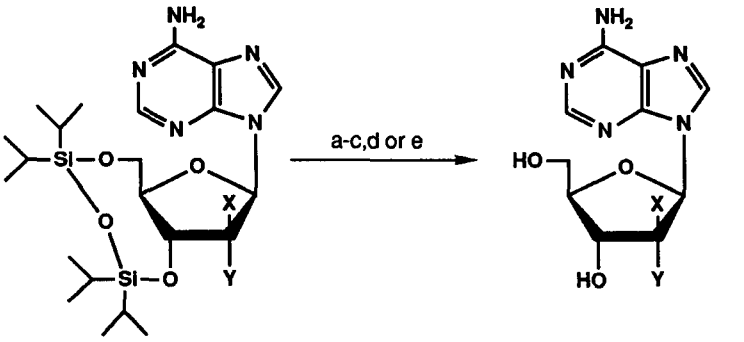
This paper is dedicated to the late Professor Tohru Ueda.

transformations with intact nucleosides.[2c,5-9] Recently we described the synthesis of 2',3'-diamino-2',3'-dideoxyadenosine,[10,11] the first vicinal diamino analogue of ribonucleosides,[2c] from adenosine. We now report efficient conversions of adenosine to 2'-amino-2'-deoxyadenosine (**5b**), its arabino epimer (**5a**), and 3'-amino-3'-deoxyadenosine (**9**).

We had observed that a number of procedures which efficiently effected trifluoromethanesulfonylation of alcohols, including sugar derivatives, gave poor yields of nucleoside triflates. However, treatment of selectively protected nucleosides with trifluoromethanesulfonyl chloride (TfCl) and 4-(dimethylamino)pyridine (DMAP) (3 equiv) in methylene chloride at 0 °C gave smooth and rapid conversions to triflate esters,[12] and this method has proven to be generally applicable.[13] Triflation of 9-[3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanyl)-β-D-arabinofuranosyl]adenine[14] (**1b**) by this procedure followed by chromatographic purification gave the 2'-*O*-triflyl ester **2b** (87%) as an analytically pure powder. Analogous conversions of the 3',5'-*O*-TPDS-adenosine (**1a**) and guanosine (**1c**) derivatives[14] gave **2a** (74%) and **2c** (68%). This triflation is sensitive to solvent, and no reaction was observed when tetrahydrofuran (THF) was substituted for methylene chloride. Preliminary experiments gave substantially lower isolated yields of triflates when triflic anhydride was used. Conditions reported for 2'-*O*-triflation of neplanocin A[15] (1 equiv of DMAP in pyridine) gave incomplete reaction, even with excess triflyl chloride. Addition of >1 equiv of DMAP resulted in complete conversion of **1a** and **1b** to the triflates **2a** and **2b**.

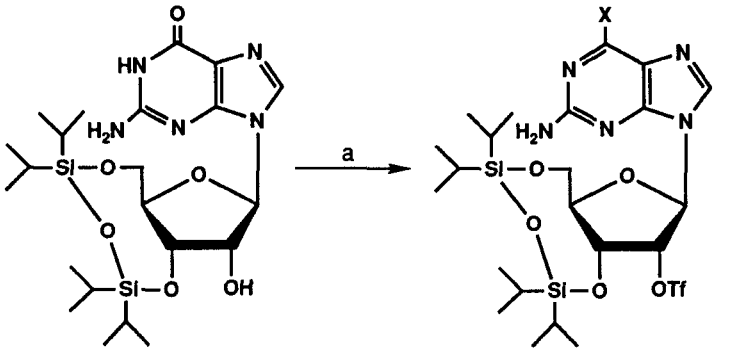
Analogous treatment of **1c** resulted in formation of a relatively nonpolar byproduct in addition to **2c**. UV and ^{1}H NMR spectral data were compatible with formation of 2',6-bis-*O*-(trifluoromethanesulfonyl)-3',5'-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanyl)guanosine (**2d**). Herdewijn and van Aerschot have obtained 6-*O*-triflyl derivatives of protected guanosines with triflic anhydride in pyridine/CH_2Cl_2.[16]

Displacements of triflate from **2a** and **2b** with lithium azide in dimethylformamide (DMF) proceeded smoothly at ambient temperature over



	X	Y
1a	H	OH
1b	OH	H
2a	H	OTf
2b	OTf	H
3a	N_3	H
3b	H	N_3

	X	Y
4a	N_3	H
4b	H	N_3
5a	NH_2	H
5b	H	NH_2



1c

Tf = SO_2CF_3

2c X = OH

2d X = OTf

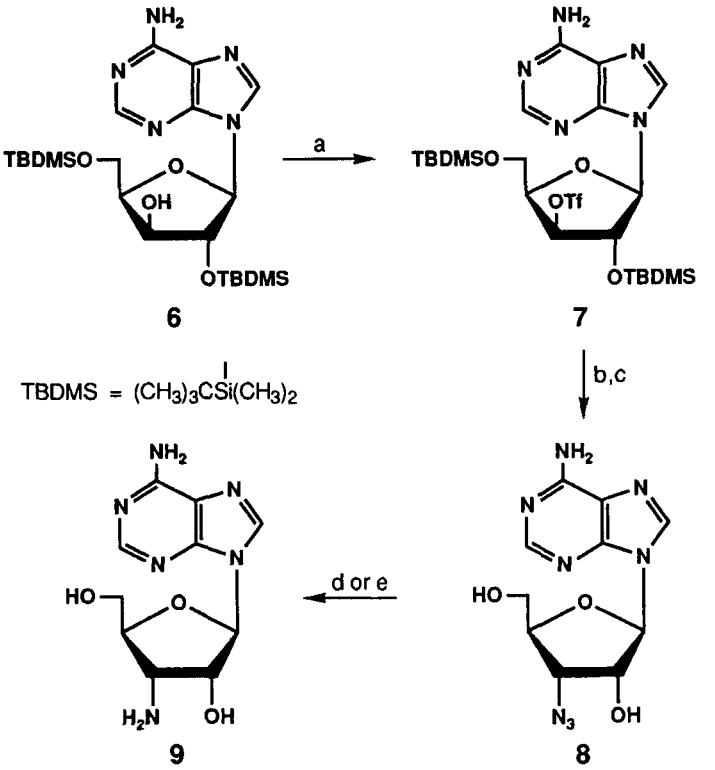
(a) CF_3SO_2Cl/DMAP/CH_2Cl_2/0 °C; (b) LiN_3/DMF/ambient; (c) Bu_4NF/THF/ambient; (d) PPh_3/pyridine/NH_3/MeOH/ambient; (e) Bu_3SnH/AIBN/DMAC/benzene/Δ.

Scheme 1

several hours. Although the resulting azidonucleosides **3a** and **3b** could be isolated and purified, it was more convenient to effect deprotection of the crude extracts with tetrabutylammonium fluoride and isolate 2'-azido-2'-deoxyadenosine (**4b**) and arabino epimer **4a**. Reduction[17] of **4b** and **4a** by Staudinger conditions (triphenylphosphine/pyridine/ammonia/methanol) gave 2'-amino-2'-deoxyadenosine (**5b**) and epimer **5a**. Crude intermediates (workup only) were carried through the sequence to give higher overall yields of **5a** (54%) and **5b** (44%) than reported previously.

In 1981 concomitant reduction of an azido group upon dechlorination of a sugar derivative with tributylstannane/azobis(isobutyronitrile) (AIBN) was reported.[18] That discovery was not included in a recent review of azide chemistry[19] and was overlooked in two recent communications[11,20] that described conversions of azido to aminosugar nucleosides. Treatment of purified **4a** and **4b** with Bu_3SnH/AIBN/benzene/*N*,*N*-dimethylacetamide (DMAC) at reflux, and chromatography of the residues [Dowex 1×2 (OH^-)] gave crystalline **5a** (72%) and **5b** (78%). These reductions proceed cleanly to products plus a small amount of adenine, and higher yields are obtained with larger scale reactions.[11]

We have reported a 9-stage conversion of adenosine into 3'-amino-3'-deoxyadenosine (**9**) (~65%) via 2',3'-anhydro and 3'-*N*-benzyloxazolidinone intermediates.[21] We now describe a 7-stage synthesis via stereoselective inversion (oxidation/reduction) at C3', triflation, azide displacement, and reduction to amine. Oxidation[22] (CrO_3/pyridine/Ac_2O) of 2',5'-bis-*O*-(*tert*-butyldimethylsilyl)adenosine and stereoselective reduction[23] ($NaBH_4$/AcOH) of the protected 3'-ketoadenosine gave the xylo epimer **6**.[23] Crude **6** was triflated efficiently (TfCl/DMAP/CH_2Cl_2) and the xylo triflate **7** underwent substitution (LiN_3/DMF) smoothly at ambient temperature. The crude 3'-azido derivative was deprotected (Bu_4NF/THF) to give 3'-azido-3'-deoxyadenosine (**8**, 79% from **6**). Crystalline **8** was reduced [Bu_3SnH/AIBN/DMAC/benzene/Δ (63%), Ph_3P/pyridine/NH_3/MeOH (90%)] and the residue chromatographed [Dowex 1×2 (OH^-)] to give the antibiotic 3'-amino-3'-deoxyadenosine (**9**). Since the first-stage protection with *tert*-



(a) CF_3SO_2Cl/DMAP/CH_2Cl_2/0 °C; (b) LiN_3/DMF/ambient; (c) Bu_4NF/THF/ambient; (d) PPh_3/pyridine/NH_3/MeOH/ambient; (e) Bu_3SnH /AIBN/DMAC/benzene/Δ.

Scheme 2

butyldimethylsilyl chloride gives a mixture of TBDMS ethers,[24] the overall yield of **9** from adenosine by the present route (~31%) is about half that of our 9-stage route (~65%)[21] which proceeds without regioisomer formation. However, this 7-stage route uses convenient procedures and reagents and is as efficient from the readily available 2',5'-bis-*O*-TBDMS-adenosine isomer.

Summary: Selectively protected purine nucleosides react readily with TfCl/DMAP in methylene chloride at ~0 °C to give triflates in high yields. Displacements of triflate at C2' occur smoothly with LiN_3/DMF (and other

Table I. ^{13}C NMR Spectral Data[a,b]

Cmpd	C2	C4	C5	C6	C8	C1'	C2'	C3'	C4'	C5'
4a	152.91	149.51	118.74	156.28	139.45	81.82	67.66	71.70	83.39	59.90
5a	152.59	149.63	118.84	156.21	140.40	84.79[c]	60.73[d]	75.22	84.38[c]	60.73[d]
4b	152.98	149.28	119.42	156.44	139.72	86.38	64.46	71.40	85.50	61.34
5b	152.47	149.40	119.78	156.45	140.54	89.46	57.64	72.13	87.27	62.47
8	152.74	149.16	119.44	156.26	140.25	88.11	73.99	62.32[c]	83.14	61.71[c]
9	152.73	148.90	119.10	155.98	139.68	89.34	74.88	52.37	85.60	61.02

[a]Chemical shifts (Me_2SO-d_6) at 50 MHz. [b]Proton-decoupled singlets. [c]Assignments might be reversed. [d]Peaks were not resolved.

nucleophiles[4,8,12]) at ambient temperature from either the α or β face to give good yields of the ribo or arabino azides. Staudinger reduction (PPh_3/pyridine/NH_3/MeOH) at ambient temperature or radical reduction conditions (Bu_3SnH/AIBN/DMAC/benzene/reflux) gave clean conversions of the azido deoxynucleosides to amino deoxynucleosides. Application of these procedures to 3',5'-*O*-TPDS-adenosine and 2',5'-bis-*O*-TBDMS-xyloA gave the nucleoside antibiotics 2'-amino-2'-deoxyadenosine and 3'-amino-3'-deoxyadenosine in good overall yields.

Experimental Section

Melting points are uncorrected. ^1H NMR spectra (Me_4Si/Me_2SO-d_6 unless otherwise noted) were obtained at 100 or 200 MHz . UV spectra were determined in MeOH solutions unless otherwise noted. Mass spectra were determined on AEI-MS-12 (CI, NH_3) or MS-50 (EI) spectrometers with direct introduction at 150-230 °C. TLC was performed with Merck 5575 silica sheets, preparative TLC with Merck 60-PF_{254} silica, and column

chromatography with MCB SX144-23 silica or Merck Kieselgel 60. LiN_3 (Pfaltz & Bauer) and other chemicals (Aldrich) were used without purification. Solvents were purified, dried, and distilled before use.

2'-*O*-(Trifluoromethanesulfonyl)-3',5'-*O*-(1,1,3,3,-tetraisopropyl-1,3-disiloxanyl)adenosine (2a). Trifluoromethanesulfonyl chloride (202 mg, 1.20 mmol) was added to a cold (0 °C) stirred solution of **1a**[14] (509 mg, 1.00 mmol) and DMAP (366 mg, 3.00 mmol) in anhydrous CH_2Cl_2 (5mL). The yellow solution was stirred for 10 min and partitioned between ice-cold AcOH/H_2O (1:99, 150 mL) and CH_2Cl_2 (2 x 75mL). The combined organic phase was washed with ice-cold saturated $NaHCO_3$/H_2O (150 mL), brine (150 mL), and dried (Na_2SO_4), filtered, and evaporated. The residue (619 mg) was crystallized ($CHCl_3$/hexanes, 1:2) to give **2a** (422 mg). An additional 54 mg was obtained by preparative TLC ($CHCl_3$/MeOH, 19:1) of the concentrated mother liquor to give **2a** (476 mg, 74%) as a colorless solid: mp 152-154 °C dec; UV max 258 nm (ε 16 000), min 224 nm (ε 2100); ^{1}H NMR δ 0.8-1.3 (m, 28, 4 × iPr), 4.01 (m, 3, H4',5',5''), 5.36 (m, 1, H3'), 6.06 (d, $J_{2'-3'}$ = 4.6 Hz, 1, H2'), 6.44 (s, 1, H1'), 7.40 (br s, 2, NH_2), 8.03 (s, 1, H2), 8.25 (s, 1, H8); MS *m/z* 641.1985 (1.7, $M^+[C_{23}H_{38}F_3N_5O_7SSi_2]$ = 641.1983). Anal. Calcd for $C_{23}H_{38}F_3N_5O_7SSi_2$ (641.8): C, 43.04; H, 5.97; N, 10.91. Found: C, 42.74; H, 5.95; N, 10.80.

9-[2-*O*-(Trifluoromethanesulfonyl)-3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanyl)-β-D-arabinofuranosyl]adenine (2b). The triflation of **1b**[14] (509 mg, 1.00 mmol) to **2b** was performed as described for **2a**. Silica column chromatography (EtOAc/hexanes, 1:1) of the residue (688 mg) gave **2b** (558 mg, 87%) as an amorphous solid: mp 77-82 °C; UV max 257 nm (ε 16 100), min 223 nm (ε 2500); ^{1}H NMR δ 0.8-1.3 (m, 28, 4 × iPr), 3.80-4.40 (m, 3, H4',5',5''), 5.68 (m, $J_{3'-2'}$ = 3.8 Hz, 1, H3'), 6.05 (m, 1, H2'), 6.43 (d, $J_{1'-2'}$ = 3.5 Hz, 1, H1'), 7.42 (br s, 2, NH_2), 8.10 (s, 1, H2), 8.39 (s, 1, H8); MS *m/z* 641.1986 (25, $M^+[C_{23}H_{38}F_3N_5O_7SSi_2]$ = 641.1983). Anal. Calcd for $C_{23}H_{38}F_3N_5O_7SSi_2$ (641.8): C, 43.04; H, 5.97; N, 10.91. Found: C, 43.06; H, 6.07; N, 10.65.

2'-*O*-(Trifluoromethanesulfonyl)-3',5'-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanyl)guanosine (2c). The triflation of **1c**[14] (525 mg, 1.00 mmol) to **2c** was performed as described for **2a**. Crystallization of the residue (98% EtOH, 2 crops) afforded **2c** (447 mg, 68%) as a colorless solid: mp 198-199 °C dec; UV max 255 nm (ε 15 800), min 222 nm (ε 2700); ^{1}H NMR δ 1.06 (m, 28, 4 × iPr), 4.05 (br s, 3, H4',5',5"), 4.76 (m, 1, H3'), 5.94 (m, 1, H2'), 6.13 (d, $J_{1'-2'}$= 1.6 Hz, 1, H1'), 6.32 (br s, 2, NH_2), 8.92 (s, 1, H8), 10.75 (s, 1, NH). Anal. Calcd for $C_{23}H_{38}F_3N_5O_8SSi_2$ (657.8): C, 42.00; H, 5.82; N, 10.65. Found: C, 42.10; H, 5.90; N, 10.74. The filtrate from the second crop was concentrated and purified on a silica column ($CHCl_3$) to give **2d** (129 mg, 16%) as a white solid foam. Attempted crystallization of this material resulted in decomposition. Amorphous **2d**: UV (MeOH) max 305, 247 nm, (HCl/H_2O/MeOH, pH ~2) max 305, 247 nm, (NaOH/H_2O/MeOH, pH ~12) 265 sh, 256 nm; ^{1}H NMR δ 1.00 (m, 28, 4 × iPr), 3.87 (br s, 2, H5',5"), 4.28 (br s, 1, H4'), 4.88 (br s, 1, H3'), 5.98 (m, 1, H2'), 6.32 (d, $J_{1'-2'}$ = 5.5 Hz, 1, H1'), 7.28 (br s, 2, NH_2), 8.50 (s, 1, H8).

2'-Azido-2'-deoxy-3',5'-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanyl)adenosine (3b). A solution of crude **2b** (688 mg) and LiN_3 (245 mg, 5.0 mmol) in anhydrous DMF (10mL) was stirred at ambient temperature for 2 h. H_2O (50mL) was added and the mixture extracted (EtOAc, 2 x 100 mL). The combined organic phase was washed with brine (100 mL) and dried (Na_2SO_4) and evaporated. Crystallization (98% EtOH) of the resulting solid foam (607 mg) gave **3b** (350 mg, 2 crops; 66% from **1b**) of **3b** as colorless rods: mp 175-177 °C; UV 258 nm (ε 16 300), min 225 nm (ε 4300); ^{1}H NMR δ 0.9-1.2 (m, 28, 4 × iPr), 3.98 (br s, 3, H4',5',5"), 5.00 (m 1, H2'), 5.44 (t, $J_{3'-2'}$ = 5.8 Hz, 1, H3'), 5.83 (d, $J_{1'-2'}$ = 1.5 Hz, 1, H1'), 7.34 (br s, 2, NH_2), 8.06 (s, 1, H2), 8.22 (s, 1, H8); MS *m/z* 534.2563 (2.7, $M^+[C_{22}H_{38}N_8O_4Si_2]$ = 534.2555). Anal. Calcd for $C_{22}H_{38}N_8O_4Si_2$ (534.8): C, 49.41; H, 7.16; N, 20.95. Found: C, 49.30; H, 7.20; N, 20.78.

9-[2-Azido-2-deoxy-3,5-*O*-(1,1,3,3-tetraisopropyl-1,3-disiloxanyl)-β-D-arabinofuranosyl]adenine (3a). The preparation of **3a**

from **2a** (619 mg of crude solid foam) was performed as described for **3b** with stirring for 16 h. The residue was crystallized (CH_3CN) to give **3a** (369 mg, 69% from **1a**) as a colorless solid: mp 168-169 °C; UV max 259 nm (ε 15 000), min 228 nm (ε 2500); ^{1}H NMR δ 1.09 (s, 28, 4 × iPr), 4.14 (m, 3, H4',5',5''), 4.65 (dd, $J_{2'-3'}$ = 5.5 Hz, 1, H2'), 5.21 (m, 1, H3'), 5.81 (d, $J_{1'-2'}$ = 1.0 Hz, 1, H1'), 5.96 (br s, 2, NH_2), 8.05 (s, 1, H2), 8.37 (s, 1, H8); MS *m/z* 534.2557 (2, $M^+[C_{22}H_{38}N_8O_4Si_2]$ = 534.2555). Anal. Calcd for $C_{22}H_{38}N_8O_4Si_2$ (534.8): C, 49.41; H, 7.16; N, 20.95. Found: C, 49.18; H, 7.14; N, 20.92.

2'-Azido-2'-deoxyadenosine (4b). Bu_4NF/THF (1 M; 2 mL, 2 mmol) was added to a solution of **3b** (607 mg of crude solid foam) in THF (5 mL) and stirring was continued at ambient temperature for 16 h. The solution was diluted with H_2O (25 mL), concentrated, and chromatographed [Dowex 1×2 (OH^-); MeOH/H_2O (1:9 - 1:4)]. Crystallization (MeOH) of the residue gave **4b** (217 mg, 2 crops; 74%) as a white solid: mp 217-219 °C dec (lit.[6a] 221-222.5 °C); UV max 259 nm (ε 15 700), min 227 nm (ε 2900); ^{1}H NMR δ 3.65 (m, 2, H5',5''), 4.00 (m, 1, H4'), 4.56 (m, 2, H2',3'), 5.29 (t, $J_{OH-5',5''}$ = 6.0 Hz, OH5'), 5.98 (d, $J_{OH-3'}$ = 5.5 Hz, 1, OH3'), 6.04 (d, $J_{1'-2'}$ = 5.2 Hz, 1, H1'), 7.37 (br s, 2, NH_2), 8.16 (s, 1, H2), 8.39 (s, 1, H8); MS *m/z* 292.1034 (3.4, $M^+[C_{10}H_{12}N_8O_3]$ = 292.1032). Anal. Calcd for $C_{10}H_{12}N_8O_3$ (292.3): C, 41.10; H, 4.14; N, 38.34. Found: C, 40.82; H, 4.16; N, 38.73.

9-(2-Azido-2-deoxy-β-D-arabinofuranosyl)adenine (4a). The preparation of **4a** from **3a** (crude foam from 1 mmol of **1a**) was performed as described for **4b**. After work up, the residue was crystallized (H_2O) to give **4a** (232 mg, 79%) as a white solid: mp 198-199 °C (lit.[7a] 198-200 °C dec); UV max 260 nm (ε 15 700), min 229 nm (ε 2500); ^{1}H NMR δ 3.60-3.90 (m, 3, H4',5',5''), 4.44 (m, 1, H3'), 4.62 (m, 1, H2'), 5.23 (t, $J_{OH-5',5''}$ = 6 Hz, 1, OH5'), 6.02 (d, $J_{OH-3'}$ = 5 Hz, 1, OH3'), 6.43 (d, $J_{1'-2'}$ = 7.0 Hz, 1, H1'), 7.35 (br s, 2, NH_2), 8.17 (s, 1, H2), 8.35 (s, 1, H8); MS *m/z* 292.1029 (6.4, $M^+[C_{10}H_{12}N_8O_3]$ = 292.1032). Anal. Calcd for $C_{10}H_{12}N_8O_3$ (292.3): C, 41.10; H, 4.14; N, 38.34. Found: C, 40.81; H, 4.22; N, 38.10.

2'-Amino-2'-deoxyadenosine (5b). *Method A.* Ph_3P (655 mg, 2.50 mmol) was added to a solution of **4b** (crude solid from 1 mmol of **1b**) in pyridine (8 mL) and saturated (0 °C) NH_3/MeOH (8 mL), and stirring was continued in a sealed pressure bottle at ambient temperature for 16 h. The solution was evaporated, benzene (50 mL) added, and the mixture extracted (H_2O, 2 x 100 mL). The combined aqueous extract was evaporated and the residue was dissolved (H_2O/THF, 1:1; 10 mL), chromatographed [Dowex 1×2 (OH^-), H_2O], and crystallized (Et_2O/MeOH) to give **5b** (118 mg, 44%) as a colorless solid: mp 195-197 °C (lit.[6a] mp 197-198 °C); UV (H_2O) max 259 nm (ε 15 800), min 227 nm (ε 2400); (0.1 M HCl/H_2O) max 255 nm (ε 15 400), min 225 nm (ε 2700); (0.1 M NaOH/H_2O) max 258 nm (ε 15 800), min 229 nm (ε 3700); ^{1}H NMR δ 1.68 (br s, 2, 2'-NH_2), 3.65 (m, 2, H5',5''), 3.99 (m, 3, H2',3',4'), 5.52 (m, 2, OH3',5'), 5.69 (d, $J_{1'-2'}$ = 8.0 Hz, 1, H1'), 7.37 (br s, 2, 6-NH_2), 8.14 (s, 1, H2), 8.32 (s, 1, H8); MS *m/z* 266.1123 (1, $M^+[C_{10}H_{14}N_6O_3]$ = 266.1127). Anal. Calcd for $C_{10}H_{14}N_6O_3$ (266.3): C, 45.11; H, 5.30; N, 31.56. Found: C, 45.05; H, 5.30; N, 31.38.

Method B. A solution of **4b** (21 mg, 0.072 mmol) in dry DMAC (0.3 mL) and dry benzene (1 mL) was deoxygenated (Ar, 30 min). Bu_3SnH (50 μL, 54 mg, 0.18 mmol) was added, deoxygenation continued for 15 min, and AIBN (2 mg) added. The solution was refluxed for 1 h (TLC showed a polar product and adenine), evaporated, and the residue partitioned [EtOAc (5 mL)/H_2O (3 mL)]. Concentration (~1 mL) and chromatography [Dowex 1×2 (OH^-); H_2O (100 mL), MeOH/H_2O (1:3, 100 mL)], of the aqueous layer and crystallization (Et_2O/MeOH) gave **5b** (15 mg, 78%) with identical physical data.

9-(2-Amino-2-deoxy-β-D-arabinofuranosyl)adenine (5a). *Method A.* Preparation of **5a** from crude **4a** (from 1 mmol of **1a**) was performed as described for **5b** (method A). The residue was dissolved (DMF/H_2O, 1:1; 50 mL) and the solution stirred at 60 °C for 16 h, evaporated, and the residue subjected to ion exchange chromatography and recrystallization to give **5a** (145 mg, 54%) as a colorless solid: mp 228-231 °C dec (lit.[7a] 224-228 °C); UV (H_2O) max 255 nm (ε 15 300), min 226 nm (ε

2700); (0.1 M HCl/H_2O) max 255 nm (ε 15 400), min 225 nm (ε 2800); (0.1 M NaOH/H_2O) max 258 nm (ε 15 600), min 231 nm (ε 4000); ^1H NMR δ 1.52 (br s, 2, 2'-NH_2), 3.45-3.80 (m, 4, H2',4',5',5''), 4.10 (m, 1, H3'), 5.15 (br s, 1, OH5'), 5.44 (d, $J_{OH-3'}$ = 5.0 Hz, 1, OH3'), 6.22 (d, $J_{1'-2'}$ = 7.1 Hz, 1, H1'), 7.24 (br s, 2, 6-NH_2), 8.14 (s, 1, H2), 8.32 (s, 1, H8); MS *m/z* 266.1109 (1, $M^+[C_{10}H_{14}N_6O_3]$ = 266.1127). Anal. Calcd for $C_{10}H_{14}N_6O_3$ (266.3): C, 45.11; H, 5.30; N, 31.56. Found: C, 45.07; H, 5.42; N, 31.37.

Method B. Reduction of **4a** (20 mg, 0.068 mmol) with Bu_3SnH (48 μL, 52 mg, 0.17 mmol) as described for **5b** (method B) gave **5a** (13 mg, 72%) with identical physical data.

9-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-*O*-(trifluoromethanesulfonyl)-β-D-xylofuranosyl)adenine (7). Triflyl chloride (0.28 mL, 445 mg, 2.64 mmol) was added dropwise to a cold (ice bath) solution of 9-[2,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-xylofuranosyl]adenine[23] (**6**; 1.09 g, 2.2 mmol) and DMAP (815 mg, 6.7 mmol) in anhydrous CH_2Cl_2 (11 mL) and stirring was continued for 30 min. Workup as described for **2a** gave crude **7** (1.35 g, 98%) of sufficient purity (TLC, ^1H NMR) for use in the next step. Chromatography (silica; EtOAc/hexanes, 3:7 - 3:2) gave **7** (1.12 g, 81%) as a white solid: mp 111-114 °C; ^1H NMR ($CDCl_3$) δ -0.04, 0.04, 0.06 (s,s,s; 3,3,6; SiMe's), 0.88, 0.92 (s,s; 9,9; $SiCMe_3$'s), 3.95-4.03 (m, 2, H5',5''), 4.49-4.56 (m, 1, H4'), 4.92 (dd, $J_{2'-1'}$ = 2.2 Hz, $J_{2'-3'}$ = 2.4 Hz, 1, H2'), 5.17 (dd, $J_{3'-4'}$ = 3.8 Hz, 1, H3'), 5.79 (br s, 2, NH_2), 6.04 (d, 1, H1'), 8.02 (s, 1, H2), 8.31 (s, 1, H8); MS *m/z* 570 (95, M^+ - CMe_3), 267 (100).

3'-Azido-3'-deoxyadenosine (8). A solution of crude **7** (242 mg, 0.385 mmol) and LiN_3 (96 mg, 1.92 mmol) in anhydrous DMF (4 mL) was stirred at ambient temperature for 7 h and evaporated. The residue was partitioned (EtOAc//saturated $NaHCO_3/H_2O$) and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give crude 3'-azido-2',5'-bis-*O*-(*tert*-butyldimethylsilyl)-3'-deoxyadenosine (191 mg, 95%): ^1H NMR ($CDCl_3$) δ -0.04, 0.08, 0.13 (s,s,s; 3,3,6; SiMe's), 0.82, 0.91 (s,s; 9,9; $SiCMe_3$'s), 3.84 (dd, $J_{5''-5'}$ = 11.7 Hz, $J_{5''-4'}$ = 2.7 Hz, 1, H5''), 4.02-4.13 (m, 2, H5',3'), 4.20-4.26 (m, 1, H4'), 4.87 (dd, $J_{2'-1'}$ = 4.0 Hz, $J_{2'-3'}$ = 4.7 Hz, 1,

H2'), 5.64 (br s, 2, NH_2), 6.03 (d, 1, H1'), 8.17 (s, 1, H2), 8.35 (s, 1, H8); MS *m/z* 505 (20, $M^+ - CH_3$), 464 (100), 463 (60), 292 (86). Bu_4NF/THF (1 M; 1 mL, 1 mmol) was added to a solution of crude product (191 mg) in anhydrous THF and stirring was continued at ambient temperature for 6 h. The solution was evaporated and the residue was diluted with H_2O (2 mL), chromatographed [Dowex 1×2 (OH^-); H_2O, MeOH/H_2O, and MeOH], and crystallized (MeOH) to give **8** (91 mg, 2 crops; 81% from **7**): mp 214-215 °C dec (lit.[5] mp 218-220 °C); ^1H NMR δ 3.56 (ddd, $J_{5''-5'}$ = 12.3 Hz, $J_{5''-4'}$ = 3.3 Hz, $J_{5''-OH}$ = 6.6 Hz, 1, H5''), 3.69 (ddd, $J_{5'-4'}$ = 3.5 Hz, $J_{5'-OH}$ = 5.1 Hz, 1, H5'), 4.00 (ddd, $J_{4'-3'}$ = 3.6 Hz, 1, H4'), 4.34 (dd, $J_{3'-2'}$ = 5.6 Hz, 1, H3'), 5.01 (br s, dd after D_2O, $J_{2'-1'}$ = 5.9 Hz, 1, H2'), 5.63 (dd, 1, OH5'), 5.91 (d, 1, H1'), 6.25 (br s, 1, OH2'), 7.41 (br s, 2, NH_2), 8.17 (s, 1, H2), 8.39 (s, 1, H8).

3'-Amino-3'-deoxyadenosine (9). *Method A.* Reduction of **8** (50 mg, 0.17 mmol) as described for **5b** (method A) and "diffusion crystallization"[25] (MeOH/Et_2O) gave **9** (41 mg, 90%): mp 255-260 °C dec (lit.[5] mp 260 °C); ^1H NMR δ 1.75 (br s, 2, 3'-NH_2), 3.42 - 3.86 (m, 4, H3',4',5',5''), 4.30 (br s, dd after D_2O, $J_{2'-3'}$ = 5.0 Hz, $J_{2'-1'}$ = 3.0 Hz, 1, H2'), 5.20 (br s, 1, OH5'), 5.92 (d, 1, H1'), 6.00 (br s, 1, OH2'), 7.36 (br s, 2, 6-NH_2), 8.15 (s, 1, H2), 8.40 (s, 1, H8).

Method B. Treatment of **8** (115 mg, 0.39 mmol) with Bu_3SnH (0.27 mL, 292 mg, 1.00 mmol) as described for **5b** (method B) and "diffusion crystallization"[25] (MeOH/Et_2O) gave **9** (65 mg, 63%): mp 247-250 °C dec. Adenine was formed as a significant by-product in this reduction.

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