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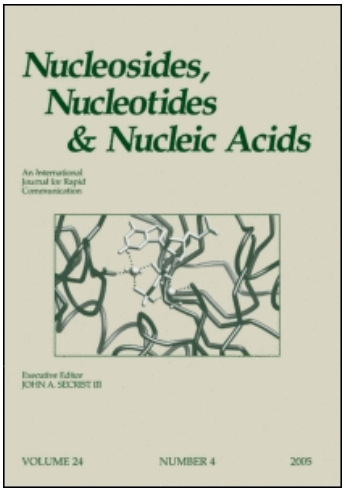

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Synthesis of 2'-Deuterio Tubercidin and Adenosine and the Corresponding *Arabino* Analogs

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NUCLEOSIDES & NUCLEOTIDES, 12(1), 73-82 (1993)

SYNTHESIS OF 2'-DEUTERIO TUBERCIDIN AND ADENOSINE AND THE CORRESPONDING *ARABINO* ANALOGS

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Abstract The 2'-deuterio *arabino* analogs of tubercidin and adenosine have been prepared by Swern oxidation of the 3',5'-TPDS derivatives of tubercidin and adenosine and reduction with $NaBD_4$. Subsequent inversion of stereochemistry at C-2' yielded [2'-^{2}H]tubercidin and [2'-^{2}H]adenosine with 98% deuterium incorporation.

The introduction of deuterium into ribonucleosides in the 2'-position would be expected to simplify conformational studies using measurements of the NOE interactions between the base and H-1' and H-3' if secondary pathways mediated by H-2' compete effectively with the direct interactions. We were interested in applying this approach to studies of the conformation of the inhibitor tubercidin (7-deazaadenosine) (**1a**) bound to the active site of *E. Coli* purine nucleoside phosphorylase[1] using the transferred NOE (TRNOE). Simulations have demonstrated the difficulty of detecting indirect effects in TRNOE experiments, and also indicate the need for a determination of the exchange rate.[2] Deuteriation at C-2' would facilitate exchange rate measurement using T_2 measurements[3], since the H-1' resonance collapses to a singlet. It may also be useful for studying certain metabolic transformations of adenosine and tubercidin, such as the biosynthesis of the antiviral agent 9-ß-D-arabinofuranosyladenine (ara-A) and the introduction of other substituents at C-2'.[4,5]

The reduction of 2'-ketonucleosides with $NaBD_4$ yields primarily the *arabino* isomer, and has been used to prepare 2'-deuteriated *arabino* nucleosides.[6,7] However, the low yield and difficulty of isolation of the minor

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ribo isomer has limited the application of this approach for the preparation of [2'-^{2}H]-labeled ribonucleosides.[8] The low fraction of *ribo* isomer generated also requires that the oxidation reaction which provides the 2'-ketonucleoside must go fully to completion to yield [2'-^{2}H]-labeled ribonucleoside with a high level of deuteriation (e.g. 98% deuteriation requires ca. 99.8% oxidation if reduction yields 10 % *ribo* isomer). Oxidation of protected adenosine with DMSO/Ac_2O followed by $NaBD_4$ reduction has been reported[6] to yield [2'-^{2}H]adenosine with only 50% deuteriation, and we have obtained similar results for tubercidin. Therefore, a synthesis of [2'-^{2}H]tubercidin (**9a**) and [2'-^{2}H]adenosine (**9b**) has been devised which uses inversion of the stereochemistry at C-2' of the isolated [2'-^{2}H]*arabino* reduction product to afford both a high chemical yield and percent isotope incorporation.

Selective protection of **1a** as the 3',5'-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl) (3',5'-*O*-TPDS) derivative **2a**[9,10] (Scheme I) followed by oxidation using DMSO/Ac_2O[6] was found to provide variable yields of 2'-ketotubercidin **3a**. The Dess-Martin[11] 12-I-5 periodinane reagent has

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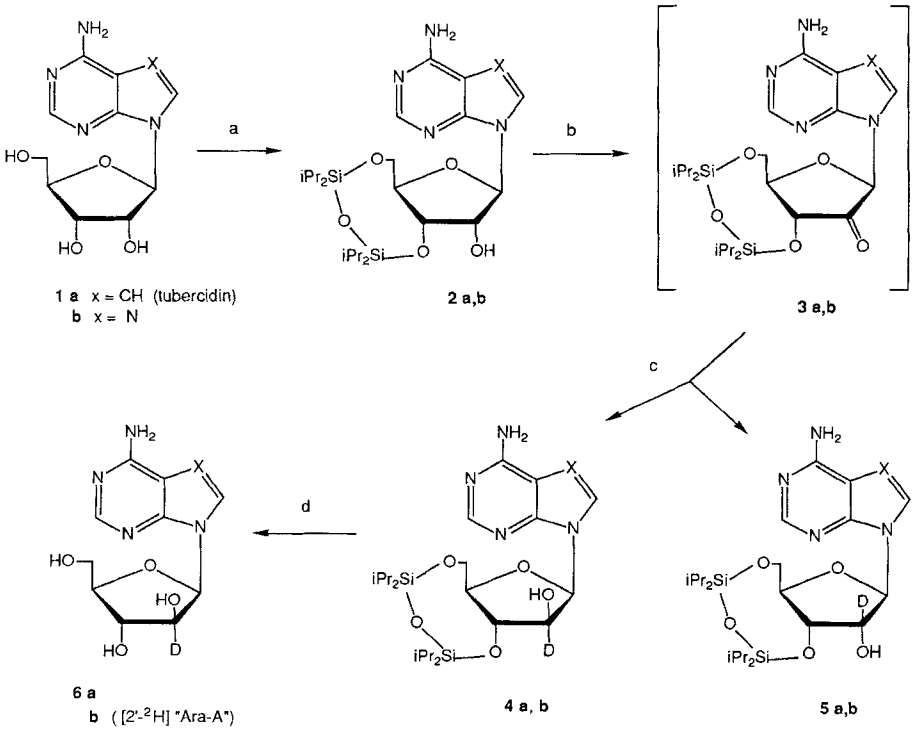
Scheme I



(a) TIPDSCl$_2$/pyridine; (b) i. oxalyl chloride/DMSO/CH_2Cl_2 / -78°C, ii. Et_3N; (c) $NaBD_4$/EtOH; (d) Bu_4NF/THF.

been reported to oxidize 3',5'-bis-*O*-(*tert*-butyldimethylsilyl)adenosine cleanly,[12] but treatment of **2a** with this reagent resulted in a complex mixture, although reaction with **2b** did yield **3b.** The Swern modification of the Moffatt oxidation,[13] which has been employed for oxidation of pyrimidine nucleosides,[14] was found to efficiently convert **2a** to 3',5'-*O*-TPDS-2'-ketotubercidin (**3a**). Compound **3a** was then , without isolation, reduced with $NaBD_4$ to provide an 85:15 mixture of completely 2'-deuteriated *arabino* epimer **4a** and partially 2'-deuteriated *ribo* epimer **5a**. Pure **4a** was isolated by silica gel chromatography in 45 % yield from **1a**, and was then deprotected to yield the 2'-deuterio *arabino* analog of tubercidin **6a**. Starting with 3',5'-*O*-TPDS-adenosine (**2b**), the reduction products **4b** and **5b** were obtained in a similar manner in a 75:25 ratio. Purification and deprotection of **4b** yielded the 2'-deuterio *arabino* analog of adenosine **6b** ([2'-^{2}H]ara-A).

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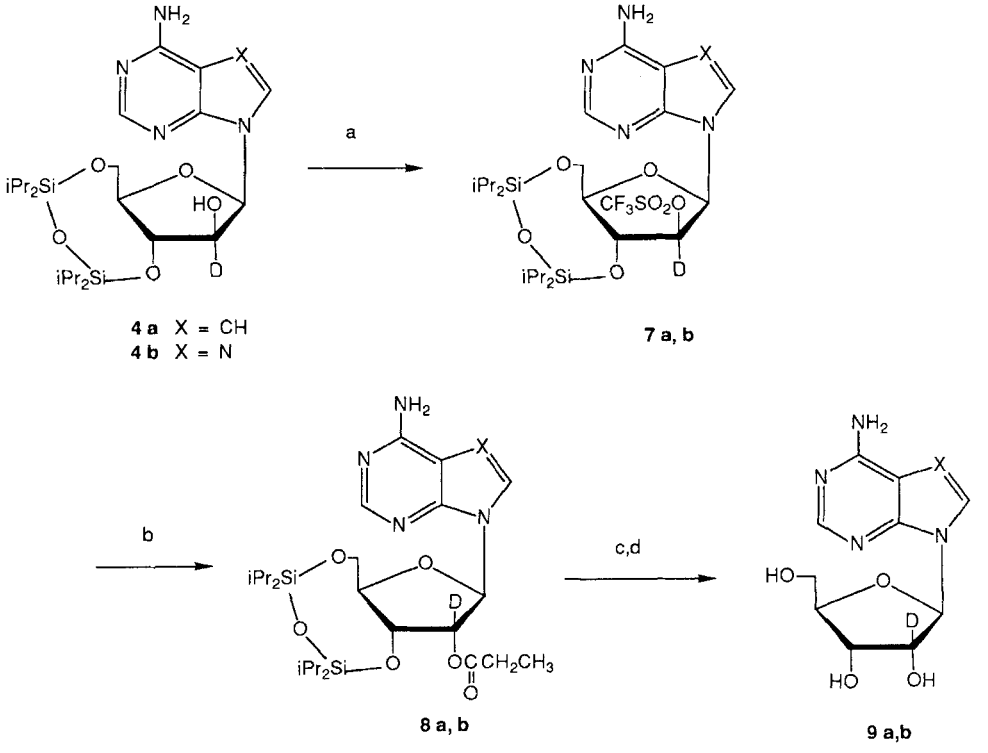
Scheme II



4 a X = CH
4 b X = N

7 a, b

8 a, b

9 a,b

(a) $(CF_3SO_2)_2O$, DMAP/Pyr/CH_2Cl_2; (b) EtCOOCs, DMPU; (c) Bu_4NF/THF; (d)NH_3/MeOH/H_2O.

The subsequent inversion of configuration at C-2' (Scheme II) was based on the procedure reported for adenosine.[15] Thus, the 2'-*O*- triflate **7a** was prepared from **4a** using trifluoromethanesulfonic anhydride in the presence of DMAP. The subsequent displacement reaction of **7a** with cesium propionate was performed using the HMPA substitute DMPU (1,3-dimethyl-2-oxohexahydropyrimidine)[16] as the solvent. Complete conversion to propionate ester **8a** was achieved after one day at room temperature, whereas in DMF complete reaction could not be obtained even after several days. After removal of protecting groups and ion exchange chromatography,[6] [2'-^{2}H]tubercidin (**9a**) was obtained in 8% yield from **1a**. Using the same sequence of reactions, **4b** was converted to [2'-^{2}H]adenosine (**9b**).

Confirmation of 2'-deuteriation was provided by the 500 MHz ^{1}H NMR spectra of **6a**,**6b**,**9a**, and **9b** in ^2H_2O, in which the resonance for H-1' appears as a singlet instead of a doublet, only a trace of the signal for H-2' remains, and the multiplet for H-3' is now a doublet. Integration of the residual H-2' multiplet at ca. 4.5-4.7 ppm indicates that 98% deuteriation was achieved in each case. This level of deuteriation was confirmed by mass spectrometry for **9a**. Recently, a synthesis of **9b** has been reported which is based on achieving a reversal of the stereoselectivity of reduction of 2'-ketonucleosides.[17] The synthesis of **9b** *via* the *arabino* isomer **4b** has the advantage of the isotopic purity of the product being independent of the yield of the oxidation reaction.

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EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a GN-500 (General Electric) spectrometer. Chemical shifts are reported downfield from tetramethylsilane or 3-(trimethylsilyl)propionic acid as an internal standard. High resolution mass spectra were determined on a Kratos Concept ISQ in the electron impact mode using per-trimethylsilylated samples.[18] Elemental analyses were performed by Galbraith Laboratories (Knoxville, TN). Column chromatography on silica gel (Merck, 230-400 mesh) was conducted under medium pressure (flash chromatography). Ion exchange chromatography was performed with a 1 X 30 cm column of Dowex 1-X2 (OH^-; 200-400 mesh) (Bio-Rad), eluting successively with H_2O, 25%, 50% and 75% MeOH. High performance liquid chromatography was conducted on a Waters μPorasil

column (3.9 mm x 30 cm) on an ISCO system using UV detection (254 nm) and heptane:ethanol (2:1) as the mobile phase. Solvents were dried by storage over activated molecular sieves.

4-Amino-7-(2-deuterio-3,5-*O*-TPDS-ß-D-arabinofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (4a). Dimethylsulfoxide (0.37 mL, 5.2 mmol) was added dropwise over 2 min. to a solution of oxalyl chloride (0.305 g, 0.21 mL, 2.4 mmol) in anhydrous CH_2Cl_2 (4 mL) at -78°C. Then a solution of **2a**[9] (0.814 g, 1.6 mmol) in CH_2Cl_2 (6 mL) was added dropwise over 20 min. and the reaction was stirred at - 65 to -75°C for 2 h. Triethylamine (1.56 mL, 11.2 mmol) was then added rapidly, and the mixture was stirred for an additional 1 h. The cooling bath was removed and the reaction was allowed to reach room temperature. The mixture was then washed with water (10 mL) and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), evaporated, and dissolved in absolute EtOH and re-evaporated. Analysis by HPLC showed that at least 90% oxidation of **2a** to **3a** had occurred.

To a stirred solution of ketone **3a** in absolute EtOH (8 mL) at 0°C was added $NaBD_4$ (200 mg, 4.8 mmol) (minimum 98% ^2H). The mixture was stirred for 1 h, and then additional $NaBD_4$ (100 mg, 2.4 mmol) was added and the reaction was stirred for 1 h at room temperature. The mixture was added to brine (50 mL) and extracted with EtOAc. The organic layers were washed with H_2O, brine, dried (Na_2SO_4), and evaporated. The residue was dissolved in toluene and evaporated to dryness. It was then chromatographed on silica gel with $CHCl_3$/MeOH (25:1), and rechromatographed with hexane/EtOAc (1:3) to remove a compound that co-elutes with the product in the first system. Evaporation provided 0.365 g (45%) of **4a** as a foam, which was crystallized (CH_3CN): mp 87-89°C; ^1H NMR (DMSO-d_6) δ 3.72 (m, 1 H, H-4'), 3.92 (dd, 1 H, H-5", $J_{4'-5"}$ = 2.79 Hz, $J_{5'-5"}$ = 12.70 Hz), 3.98 (dd, 1 H, H-5', $J_{4'-5'}$ = 3.59 Hz), 4.42 (d, 1 H, H-3', $J_{3'-4'}$ = 8.20 Hz), 5.59 (s, 1 H, 2'-OH), 6.34 (s, 1 H, H-1'), 6.54 (d, 1 H, H-7, J_{7-8} = 3.63 Hz), 6.97 (s, 2 H, NH_2), 7.15 (d, 1 H, H-8), 8.03 (s, 1 H, H-2). Anal. Calcd for $C_{23}H_{39}DN_4O_5Si_2$: C, 54.19; H/D, 7.91; N, 10.99. Found:C, 54.12; H/D, 8.20; N, 10.83.

9-(2-Deuterio-3,5-*O*-TPDS-ß-D-arabinofuranosyl)adenine (4b). This compound was prepared from **2b** (Aldrich) using the above method for the synthesis of **4a**, omitting the second chromatography step, to provide 0.400 g (49 %) of **4b**, which was recrystallized (CH_3CN): mp 105-107°C (Lit.

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[15] 115-117° for [3'-^{18}O]-labeled analog); ^{1}H NMR (DMSO-d_6) δ 3.78 (m, 1 H, H-4'), 3.91 (dd, 1 H, H-5", $J_{4'-5"}$ = 2.59 Hz, $J_{5'-5"}$ = 12.55 Hz), 4.09 (dd, 1 H, H-5', $J_{4'-5'}$ = 4.23 Hz), 4.55 (d, 1 H, H-3', $J_{3'-4'}$ = 8.23 Hz), 5.74 (s, 1 H, 2'-OH), 6.18 (s, 1 H, H-1'), 7.26 (s, 2 H, NH_2), 8.02 (s, 1 H, H-8), 8.09 (d, 1 H, H-2). Anal. Calcd for $C_{22}H_{38}DN_5O_5Si_2$: C, 51.73; H/D, 7.70; N, 13.71. Found:C, 51.69; H/D, 7.90; N, 13.46.

4-Amino-7-(2-deuterio-ß-D-arabinofuranosyl)pyrrolo[2,3-*d*]pyrimidine (6a). To a solution of **4a** (76 mg, 0.15 mmol) in anhydrous THF (2 mL) was added 1 M tetrabutylammonium fluoride (TBAF) in THF (0.35mL, 0.35 mmol), and the mixture was stirred overnight at room temperature. The mixture was evaporated and the residue was partitioned between $CHCl_3$ and H_2O, and the aqueous layer was washed with $CHCl_3$. The aqueous layer was concentrated and subjected to ion exchange chromatography. The product was eluted with 50-75% MeOH in H_2O and the solvent evaporated to yield 37 mg of **6a** as a white solid (92 %): mp 122-124 °C (Lit.[19] 125-126°C for unlabeled compound). ^{1}H NMR (^2H_2O) δ 3.87 (dd, 1 H, H-5", $J_{4'-5"}$ = 4.91 Hz, $J_{5'-5"}$ = 12.65 Hz), 3.96 (dd, 1 H, H-5', $J_{4'-5'}$ = 2.73 Hz), 4.01 (m, 1 H, H-4'), 4.34 (d, 1 H, H-3', $J_{3'-4'}$ = 7.08 Hz), 6.52 (s, 1 H, H-1'), 6.65 (d, 1 H, H-7, J_{7-8} = 3.69 Hz), 7.41 (d, 1 H, H-8), 8.14 (s, 1 H, H-2); NMR spectrum in DMSO-d_6 was identical to that reported for the unlabeled compound[6] except for effects of deuteriation. Anal. Calcd for $C_{11}H_{13}DN_4O_4 \cdot 1/4\ H_2O$: C, 48.62; H/D, 5.38; N, 20.62. Found:C, 48.30; H/D, 5.55; N, 20.19.

9-(2-Deuterio-ß-D-arabinofuranosyl)adenine (6b). In a manner similar to that described for the synthesis of **6a**, **4b** was treated with TBAF. Crystallization occurred in the aqueous layer during the extraction and additional product was obtained by concentration of the filtrate to provide a total of 19.5 mg (73 %) of **6b**: mp 250-251°C (Lit.[21] 257°C): ^{1}H NMR (^2H_2O) δ 3.89 (dd, 1 H, H-5", $J_{4'-5"}$ = 4.63 Hz, $J_{5'-5"}$ = 12.75 Hz), 3.97 (dd, 1 H, H-5', $J_{4'-5'}$ = 2.15 Hz), 4.08 (m, 1 H, H-4'), 4.37 (d, 1 H, H-3', $J_{3'-4'}$ = 6.55 Hz), 6.43 (s, 1 H, H-1'), 8.25 (s, 1 H, H-2), 8.37 (s, 1 H, H-8). Anal. Calcd for $C_{10}H_{12}DN_5O_4 \cdot 3/4\ H_2O$: C, 42.63; H/D, 5.19; N, 24.86. Found:C, 42.52; H/D, 4.80; N, 24.82.

4-Amino-7-[2-deuterio-3,5-*O*-TPDS-2-*O*-(trifluoromethanesulfonyl)-ß-D-arabinofuranosyl]pyrrolo[2,3-*d*]pyrimidine (7a). Trifluoromethanesulfonic anhydride (0.54 g, 0.32 mL, 1.92 mmol) was added dropwise over 5 min. to a stirred solution of **4a** (0.571 g, 1.12 mmol), 4-(dimethylamino)pyridine (0.88 g, 7.2 mmol), and pyridine (2.51 mL, 31 mmoL) in anhydrous CH_2Cl_2 (30 mL) at 0°C. After being stirring for another 1.5 h at 0 to

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5°C, the mixture was poured into ice-cold, saturated $NaHCO_3$ (75 mL) with vigorous stirring, the layers were separated, and the aqueous layer washed with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), evaporated, and twice dissolved in toluene and re-evaporated. The residue was chromatographed on silica gel (30 g) with hexane/THF (3:2) as eluent. After evaporation, dissolving in toluene and re-evaporation, 0.528 g (74%) of **7a** was obtained as a foam that was used immediately for the preparation of **8a**: ^1H NMR ($CDCl_3$) δ 3.93 (m, 1 H, H-4'), 4.12 (m, 2 H, H-5',5"), 4.98 (d, 1 H, H-3', $J_{3'-4'}$ = 7.60 Hz), 6.64 (s, 1 H, H-1'), 6.78 (d, 1 H, H-7, J_{7-8} = 3.06 Hz), 7.22 (s, 2 H, NH_2), 7.36 (d, 1 H, H-8), 8.23 (s, 1 H, H-2).

9-[2-Deuterio-3,5-*O*-TPDS-2-*O*-(trifluoromethanesulfonyl)-ß-D-arabinofuranosyl]adenine (7b). This compound was prepared from **4b** using the procedure described for the synthesis of **7a** to yield 0.648 g (90%) of **7b**, which was homogenous by TLC and possessed a ^1H NMR spectrum identical to that of the unlabeled analog,[15] except for the effects of 2'-deuteriation ; ^1H NMR ($CDCl_3$) δ 3.98 (m, 1 H, H-4'), 4.10 (dd, 1 H, H-5", $J_{4'-5"}$ = 3.12 Hz, $J_{5'-5"}$ = 12.79 Hz), 4.20 (dd, 1 H, H-5', $J_{4'-5'}$ = 4.79 Hz), 5.20 (d, 1 H, H-3', $J_{3'-4'}$ = 7.75 Hz), 6.42 (s, 1 H, H-1'), 7.20 (s, 2 H, NH_2), 8.15 (d, 1 H, H-8), 8.33 (s, 1 H, H-2).

4-Amino-7-[2-deuterio-2-*O*-(1'-propanoyl)-3,5-*O*-TPDS-ß-D-arabinofuranosyl]pyrrolo[2,3-*d*]pyrimidine (8a). To a solution of **7a** (0.508 g, 0.793 mmol) in anhydrous DMPU (4.5 mL) was added dry cesium propionate[20] (1.15 g, 5.56 mmol), and the suspension was stirred at room temperature for 16 h. The reaction mixture was added to H_2O (30 mL), extracted with ether, and the extracts were dried ($MgSO_4$), evaporated, dissolved in toluene and re-evaporated. The residue was chromatographed twice on silica gel, first using elution with hexane/EtOAc (1:1) to remove residual DMPU, and then with $CHCl_3$/MeOH (25:1) to yield 0.286 g (64%) of **8a** as white crystals: mp 146-148°C; ^1H NMR (DMSO-d_6) δ ca. 1.0-1.1 (CH_3, under $(CH_3)_2CH$), 2.39 (m, 2 H, CH_2C=O), 3.87 (m, 1 H, H-4'), 3.92 (dd, 1 H, H-5", $J_{4'-5"}$ = 2.05 Hz, $J_{5'-5"}$ = 12.67 Hz), 3.98 (dd, 1 H, H-5', $J_{4'-5'}$ = 3.71Hz), 5.06 (d, 1 H, H-3', $J_{3'-4'}$ = 8.25 Hz), 6.04 (s, 1 H, H-1'), 6.58 (d, 1 H, H-7, J_{7-8} = 3.23 Hz), 7.10 (s, 2 H, NH_2), 7.26 (d, 1 H, H-8), 7.98 (s, 1 H, H-2). Anal. Calcd for $C_{26}H_{43}DN_4O_6Si_2$: C, 55.19; H/D, 7.84; N, 9.90. Found: C, 55.07; H/D, 8.05; N, 9.69.

2'-Deuterio-2'-*O*-(1-propanoyl)-3',5'-*O*-TPDS-adenosine (8b). The procedure for **8a** was followed for the preparation of **8b** with an altered reaction work-up. When the reaction mixture was poured into H_2O, the product

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crystallized and was filtered and washed with H_2O to provide a powder that was free of DMPU. Chromatography on silica gel with $CHCl_3$/MeOH (30:1) as eluent yielded 0.234 g (52%) of **8b** as white crystals: mp 179-181°C (Lit. [15] 166-168 °C for [3'-^{18}O] labeled analog). ^{1}H NMR (DMSO-d_6) δ ca. 1.0-1.1 (CH_3, under $(CH_3)_2CH$), 2.41 (m, 2 H, CH_2C=O), 3.90 (m, 1 H, H-4'), 3.94 (dd, 1 H, H-5", $J_{4'-5"}$ = 2.57 Hz, $J_{5'-5"}$ = 12.36 Hz), 4.00 (dd, 1 H, H-5', $J_{4'-5'}$ = 3.72 Hz), 5.26 (d, 1 H, H-3', $J_{3'-4'}$ = 8.37 Hz), 6.09 (s, 1 H, H-1'), 7.37 (s, 1 H, NH_2), 8.05 (d, 1 H, H-2), 8.24 (s, 1 H, H-8). Anal. Calcd for $C_{25}H_{42}DN_5O_6Si_2$: C, 52.97; H/D, 7.65; N, 12.36. Found: C, 53.30; H/D, 8.01; N, 12.15.

4-Amino-7-(2-deuterio-ß-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (2'-deuteriotubercidin) (9a). To a solution of **8a** (141 mg, 0.25 mmol) in THF (5 mL) was added 1 M TBAF in THF (0.575 mL, 0.575 mmol), and the mixture was stirred at reflux for 1 h. The solvent was evaporated, and the residue was suspended in MeOH (5 mL). After addition of NH_3/H_2O (5 mL), the reaction flask was sealed and the contents stirred overnight at room temperature. The solution was then concentrated and washed with $CHCl_3$. Ion exchange chromatography with the product eluting with 50% MeOH and crystallization from H_2O yielded 28 mg (42 %) of **9a:** mp 246-248 °C (Lit.[22] 246-248°C for **1a**); ^{1}H NMR (^2H_2O) δ 3.81 (dd, 1 H, H-5", $J_{4'-5"}$ = 3.73 Hz, $J_{5'-5"}$ = 12.74 Hz), 3.86 (dd, 1 H, H-5', $J_{4'-5'}$ = 2.94 Hz), 4.24 (m, 1 H, H-4'), 4.38 (d, 1 H, H-3', $J_{3'-4'}$ = 2.57 Hz), 6.14 (s, 1 H, H-1'), 6.68 (d, 1 H, H-7, J_{7-8} = 3.68), 7.38 (d, 1 H, H-8), 8.16 (s, 1 H, H-2). MS(EI): calcd for $C_{23}H_{45}DN_4O_4Si_4$ 555.2660, found 555.2649. Anal. Calcd for $C_{11}H_{13}DN_4O_4$: C, 49.44; H/D, 5.28; N, 20.96. Found: C, 49.48; H/D, 5.35; N, 20.68.

2'-Deuterioadenosine (9b). The procedure for the synthesis of **9a** was utilized to prepare **9b** from **8b**. The product was crystallized from the reaction mixture after extraction with $CHCl_3$ and additional material was obtained from the mother liquor by ion exchange chromatography using 25% MeOH to elute the product to provide a total of 45 mg (67 %) of **9b** as white crystals: mp 230-231°C (Lit.[23] 234-235°C for **1b**); ^{1}H NMR (^2H_2O) δ 3.84 (dd, 1 H, H-5", $J_{4'-5"}$ = 3.30 Hz, $J_{5'-5"}$ = 12.98 Hz), 3.92 (dd, 1 H, H-5', $J_{4'-5'}$ = 2.17 Hz), 4.30 (m, 1 H, H-4'), 4.43 (d, 1 H, H-3', $J_{3'-4'}$ = 2.88 Hz), 6.07 (s, 1 H, H-1'), 8.24 (s, 1 H, H-2), 8.33 (s, 1 H, H-8). Anal. Calcd for $C_{10}H_{12}DN_5O_4 \cdot 1/2\ H_2O$: C, 43.32; H/D, 5.09; N, 25.26. Found:C, 43.23; H/D, 5.10; N, 25.30.

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