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Deoxygenative [1,2]-Hydride Shift Rearrangements in Nucleoside and Sugar Chemistry: Analogy with the [1,2]-Electron Shift in the Deoxygenation of Ribonucleotides by Ribonucleotide Reductases[1]

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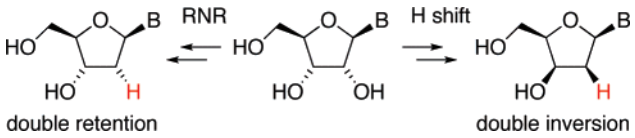

A variant of the semipinacol rearrangement that was observed in our laboratory has been applied to the synthesis of several furanose and pyranose derivatives. The process consists of an "orchestrated" [1,2]-hydride shift with departure of a leaving group from the opposite face. Transient formation of a C═O group is followed by rapid transfer of a hydride-equivalent from the same face from which the leaving group departed, which results in double inversion of stereochemistry at the two vicinal carbon atoms. Treatment of 2′-*O*- and 3′-*O*-tosyladenosine with lithium triethylborohydride in DMSO/THF gave the respective 2′- and 3′-deoxynucleoside analogues with β-D-*threo* configurations. Identical treatment of 5′-*O*-TPS-2′-*O*-tosyladenosine gave 9-(5-*O*-TPS-2-deoxy-β-D-*threo*-pentofuranosyl)adenine. The same [1,2]-hydride shift and stereochemistry with the 5′-OH and 5′-*O*-TPS compounds demonstrated the absence of remote hydroxyl-group participation. Application of this process to other nucleoside 2′-*O*-tosyl derivatives gave the 2′-deoxy-*threo* compounds in good yields. The reaction-rate order was OTs $\approx$ Br $\gg$ Cl for 2′-*O*-tosyladenosine, 2′-bromo-2′-deoxyadenosine, and 2′-chloro-2′-deoxyadenosine (all with β-D-ribo configurations). Analogous results were obtained with mannopyranoside derivatives with either 4,6-*O*-benzylidene protection or a free OH group at C4. Deuterium labeling clearly defined the stereochemical course as a cis-vicinal [1,2]-hydride shift on the face opposite to the original cis OH and OTs groups followed by hydride transfer from the face opposite to the [1,2]-hydride shift. Synthetic and mechanistic considerations are discussed.

Introduction

Deoxygenation of alcohols is employed widely by Nature and in the laboratory. A recent report of reduction of xanthates with trialkyboranes and water as the hydrogen source is intriguingly analogous to reductions with water−metal complexes in biological systems.[2] A number of years ago we reported a deoxygenative [1,2]-hydride shift rearrangement that converted cyclic cis-diol monotosylates into their inverted monohydroxyl analogues.[3] Treatment of 2′-*O*-tosyladenosine with lithium triethylborohydride (LTBH) in DMSO/THF gave 9-[2-deoxy-β-D-*threo*-pentofuranosyl]adenine, and 3′-*O*-tosyladenosine provided the 3′-deoxy-*threo* product in equally high yields.[3] The fully stereoselective process gave access to inverted deoxynucleosides, precursors for anti-HIV agents,[4,5] and other biologically relevant compounds[6] that were difficult to synthesize by available methods.

Baer and co-workers studied reactions of LTBH with several hexopyranoside tosylates.[7] The structures of their products depended on the sugar configurations, the presence or absence

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(1) Nucleic Acid Related Compounds. 146. Paper 145: Robins, M. J.; Nowak, I.; Rajwanshi, V. K.; Miranda, K.; Cannon, J. F.; Peterson, M. A.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *J. Med. Chem.* **2007**, *50*, 3897−3905.

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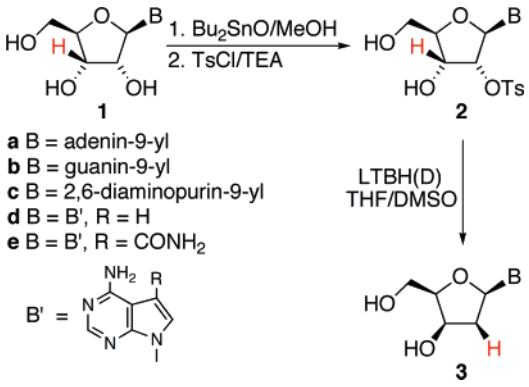
of a 4,6-*O*-benzylidene protecting group, and tosylate group locations. Epoxide formation occurred with trans-diol tosylates,[7a,b] whereas ring contraction,[7c] tosylate displacement by hydride,[7d] and a [1,2]-hydride shift[7d] were observed with other substrates. More recently, deoxygenation of inositol monotosylates with LTBH was found to involve a [1,2]-hydride shift and stereoselective reduction of the derived ketone with retention of configuration.[8]

Kawana and co-workers had investigated reactions of sugar[9] and nucleoside[10] mesylates and tosylates with Grignard reagents and magnesium methoxide/sodium borohydride combinations. Predominant overall inversion at the vicinal carbinol moieties with de(sulfonyl)oxygenative rearrangements was consistent with [1,2]-hydride shifts.[9,10]

There is current interest in mechanisms by which substrate reduction and mechanism-based inhibition of ribonucleotide reductases (RNRs) occur.[11] We described model studies that support a free radical elimination mechanism that might occur during inhibition of RNRs by nucleotides containing an appropriate 2′-substituent.[12] Generation of a free radical at C3′ of a model 2′-chlorohomonucleoside in the presence of (deuterio)tributylstannane resulted in elimination of chlorine (radical) from C2′ followed by a cascade that generated a 3(2*H*)-furanone with no deuterium at C4 (furan numbering, corresponding to C2′ of the homonucleoside).[12b] Parallel treatment of an analogous 2′-*O*-tosylhomonucleoside gave the same 3(2*H*)-furanone with ∼30% deuterium at C4. In that case, generation of a radical at C3′ followed by an assisted [1,2]-electron shift with loss of tosylate from C2′ produced a C2′ radical that underwent deuterium transfer from the stannane followed by stereoselective *β*-elimination of the nucleobase to give the deuterium-containing

SCHEME 1



3(2*H*)-furanone.[12b] Such concerted elimination of tosylate is analogous to our [1,2]-hydride shift rearrangement with LTBH, which converts 2′-*O*-tosyladenosine into 9-(2-deoxy-*β*-D-*threo*-pentofuranosyl)adenine.[3] We now report applications of [1,2]-hydride shift-mediated removal of tosylate from sugar and nucleoside derivatives, extensions to halogen analogues, and mechanistic results with deuterium labeling.

Results and Discussion

Reductive S_N2-type displacements of tosylate by hydride with alkyl tosylates and LTBH have been demonstrated.[13] However, treatment of 2′-*O*-tosyladenosine (**2a**) (Scheme 1) in DMSO with LTBH/THF produced a 2′-deoxynucleoside with NMR spectra that differed from those of 2′-deoxyadenosine (dAdo). Treatment of **2a** with LTBH/THF (10 equiv) in DMSO for 14 h at ambient temperature gave 9-(2-deoxy-*β*-D-*threo*-pentofuranosyl)adenine (**3a**, 98%) with no detected erythro diastereomer, dAdo.[3] Analogous treatment of 2′-*O*-tosylguanosine (**2b**) and 2,6-diamino-9-(*β*-D-ribofuranosyl)purine (**2c**) gave the respective 9-(2-deoxy-*β*-D-*threo*-pentofuranosyl) nucleosides **3b** and **3c**. The nucleoside antibiotic derivatives 2′-*O*-tosyltubercidin (**2d**) and 2′-*O*-tosylsangivamycin (**2e**) underwent [1,2]-hydride shift rearrangement to give the 7-(2-deoxy-*β*-D-*threo*-pentofuranosyl) products **3d** and **3e**. The 2′-*O*-tosyl derivatives **2a**−**e** were prepared by Moffatt's procedure [(i) Bu_2SnO/MeOH, (ii) TsCl/Et_3N/MeOH][14] from nucleosides **1a**−**e**. Accompanying reduction of the nucleobase with LTBH occurred with 2′-*O*-tosyl derivatives of the naturally occurring pyrimidine nucleosides, but this has been circumvented with magnesium salt combinations.[10]

Our X-ray crystal structure of **3a** (Figure 1) shows the furanosyl ring of the sugar moiety with an *S*-range conformation ($_3$E) with a pseudorotational phase angle (*P*) of 196.2° and a maximum puckering amplitude (ν_{max}) of 36.5°. The sugar−base torsion angle (χ) is −94.8° in the anti range. These values in the solid state differ from those based on solution ^{1}H NMR data.[15]

Mechanistic considerations were probed with labeling studies. Treatment of **2a** (L = OTs, X = Y = H) (Figure 2) with LTBD/THF gave 9-(2-deoxy-3-deuterio-*β*-D-*threo*-pentofuranosyl)-adenine (**3a**) (X = Y = H, Z = D). Tosylation of 3′-

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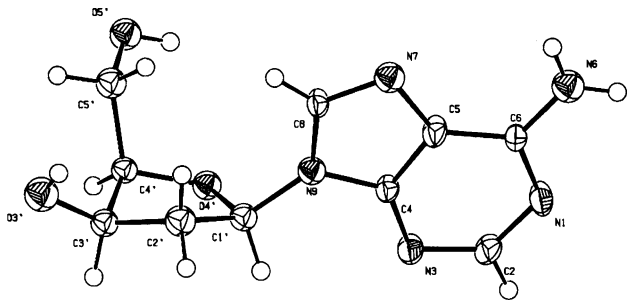


FIGURE 1. X-ray crystal structure of **3a**.

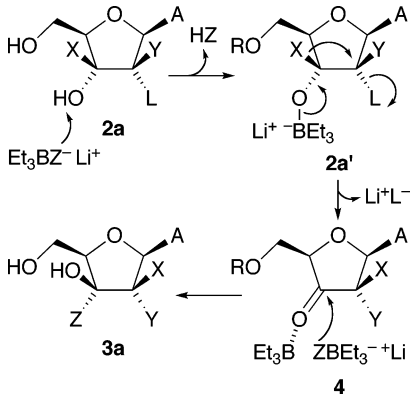
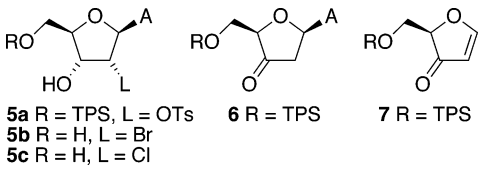


FIGURE 2. Proposed mechanism for conversion of **2a** to **4a**.

deuterioadenosine[16] (3′[^{2}H]**1a**) followed by treatment of the 2′-tosylate **2a** (L = OTs, X = D, Y = H) with LTBH gave 9-[2-deoxy-2(*S*)-deuterio-*β*-D-*threo*-pentofuranosyl]adenine **3a** (X = D, Y = Z = H). Tosylation of 2′-deuterioadenosine[16] (2′[^{2}H]-**1a**) and treatment of **2a** (L = OTs, X = H, Y = D) with LTBH gave 9-[2-deoxy-2(*R*)-deuterio-*β*-D-*threo*-pentofuranosyl]adenine **3a** (X = Z = H, Y = D). The labeling experiments defined the stereochemistry of the rearrangement sequence with inversion of configuration at both C2′ and C3′. The **2a** → **3a** transformations proceeded in high chemical yields with a large excess of LTBH(D). However, significant amounts of adenine were formed (presumably arising by *β*-elimination from a transient base-labile[16] 3′-ketone intermediate) when smaller quantities of super hydride were used (stoichiometric to ∼5 equiv). Yu and Spencer used stoichiometric LBTH with a more stable 2-deoxy-*myo*-inositol tosylate, and reduction of their intermediate ketone also occurred from the less-hindered face.[8] We assume that LTBH(D) executed a rapid acid−base reaction with the hydroxyl group at C3′ (and presumably also at C5′) to give a boronate complex **2a′** (Figure 2). Rate-determining cleavage of the C2′−L (leaving group) bond with an accompanying [1,2]-hydride shift from C3′ to C2′ and flow of electron density from the boron−O3′ bond to form an O═C3′ bond would generate a boron-complexed intermediate **4**. Hydride (deuteride) transfer to C3′ of **4** followed by aqueous workup would produce the 2′-deoxy-*threo* nucleoside **3a**.

We had observed highly stereoselective hydride transfer from borohydride reagents at the α-face of nucleoside 3′-ketones protected at both O2′ and O5′ with bulky silyl groups.[16] Therefore, it was not surprising that Lewis acid-complexed 3′-ketones would be reduced with complete stereoselectivity from



5a R = TPS, L = OTs
5b R = H, L = Br
5c R = H, L = Cl

6 R = TPS **7** R = TPS

FIGURE 3. Precursor and possible product structures.

the α-face of nucleoside intermediates such as **4** with bulky groups at C1′ and C4′ on the *β*-face (and hydrogens at C1′, C2′, and C4′ on the α-face). The putative O5′ boronate complex **4** has no hydride equivalent for tethered transfer[16] at the *β*-face. We probed this aspect with *tert*-butyldiphenylsilyl (TPS) protection at O5′ of **2a**. Treatment of 5′-*O*-TPS-2′-*O*-tosyladenosine (**5a**) (Figure 3) with LTBH/THF (10 equiv) for 3 h at ambient temperature gave 5′-*O*-TPS-**3a**, which was deprotected (TBAF/THF) to give **3a** (85% overall). Diminished amounts of LTBH gave lower yields of 5′-*O*-TPS-**3a** (plus adenine), but attempts to isolate[17] or identify 5′-*O*-TPS-3′-ketone intermediate **6** or a 3(2*H*)-furanone decomposition product[12b] **7** were unsuccessful. Treatment of **5a** with NaOMe (or NaOEt) in alcohol/benzene mixtures did not produce **6** or **7** [elimination products of the (pent-1-enofuranosyl)-type[18] were detected]. Difficulties have been noted with larger scale applications of our original procedure,[3] and protection strategies have been employed.[4,19] However, we have not experienced difficulties and have obtained reasonable to excellent yields with complete reduction stereoselectivity when purified solvents and *fresh* LTBH(D)/THF reagents[20] were used. Our present results with **1c** → **3c** followed by treatment of **3c** with adenosine deaminase[21] might be an efficient alternative for the guanine[19] analogue.

We also probed the [1,2]-hydride shift rearrangement with halide instead of tosylate at C2′. Treatment of 2′-bromo-2′-deoxyadenosine[22] (**5b**) in DMSO with LTBH/THF (10 equiv) resulted in the formation of **3a** at a rate comparable to that of **2a** → **3a**. In marked contrast, treatment of 2′-chloro-2′-deoxyadenosine[10a,23] (**5c**) for 18 h at ambient temperature resulted in a mixture of **3a**/**5c** (3:7). Extension of the time to 24 h and elevation of the temperature to 50 °C caused complete conversion of **5c** → **3a** (90% isolated). Parallel experiments revealed that the process with **5c** was ∼90-fold slower than those with **2a** or **5b** (Figure 4). It is noteworthy that attempted S_N2-type reduction of cyclohexyl chloride with LTBH did not occur at 25 °C, whereas secondary bromides and iodides (as well as primary alkyl halides) underwent reduction.[24] None of the 2′-deoxy-*erythro* diastereomer (dAdo) was detected upon treatment of **5b** or **5c** with LTBH/THF/DMSO (the same as with treatment of **2a**), and only the *threo* product of [1,2]-hydride transfer from C3′ to C2′ was obtained. Cleavage of the C2′−L bond in the

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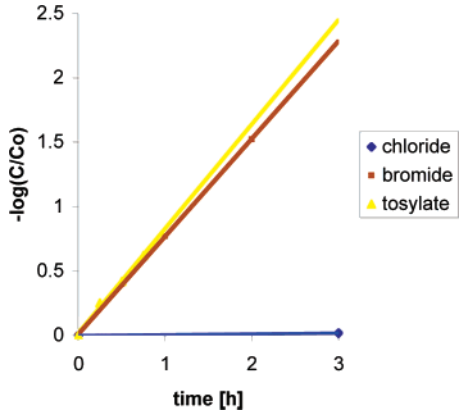

FIGURE 4. Pseudo-first-order plots for conversions of **2a**, **5b**, and **5c** into **3a**.

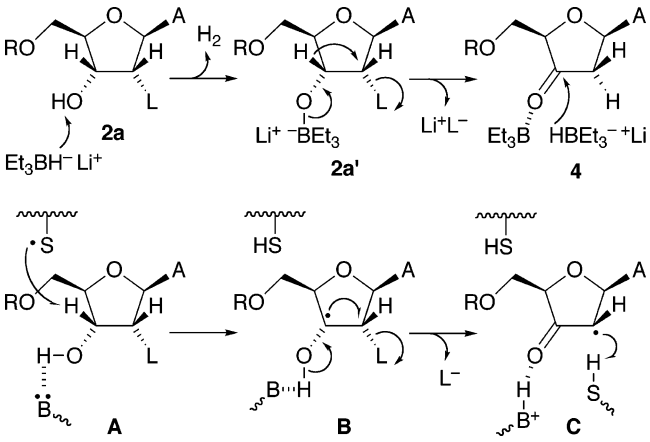

FIGURE 5. Comparison of [1,2]-hydride shift and [1,2]-electron shift (RNR) mechanisms.

step(s) from **2a′** to **4** (Figure 5) appears to be rate-determining in harmony with S_N2-type mechanisms.

Our studies with 5′-homonucleoside analogues clearly demonstrated that relay generation of free radical species at C3′ can result in loss of a chlorine atom (enol formation by radical elimination with no incorporation of deuterium from tributyltin deuteride) or a tosylate anion (abstraction of deuterium from the stannane by the resulting C2′ radical).[12] The present [1,2]-hydride shift undoubtedly produces the same type of ketone intermediate **4** (Figure 5), which is reduced at the α-face by the large excess of LTBH(D) to give the inverted 2′-deoxy-*threo* product **3a**.

In our model studies,[12] and probably at the active site of ribonucleotide reductases (RNRs), such nucleos(t)ide 3′-ketones are labile (in the absence of stabilizing interactions) and undergo *β*-elimination of the nucleobase to produce an intermediate enone **7** (R = H, Figure 3).[11d] Radical-shift-induced loss of tosylate from C2′ (**B** → **C**) followed by hydrogen atom transfer at the α-face of the resulting C2′ radical (**C**)[12b] is analogous to the hydride-shift-induced loss of tosylate from **2a′** followed by hydride transfer from LTBH at the α-face of C3′. In both cases of induced loss of tosylate, electron density is shifted from C3′ to C2′ to generate the more electron-deficient 3′-carbonyl carbon (with enhanced polarity alternation[25] in the furanose ring compared to the **2a**-type starting materials). That and formation

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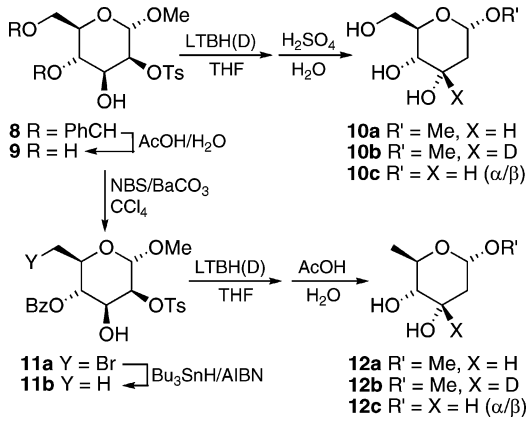
SCHEME 2



of the ketone double bond at C3′ apparently provide adequate driving force for expulsion of the leaving group from C2′. The relatively unstable 3′-ketone complex **4** is reduced with inversion by excess LTBH(D) to produce **3**. A more complicated radical-mediated reduction of C3′ at the stereodirected active site of RNRs produces the diastereomeric 2′-deoxy-*erythro* nucleosides (or *β*-elimination can occur in model systems—and also at the active site of RNRs upon incubation with mechanism-based inhibitory 2′-deoxynucleotide analogues).[11d] Our model[12b] and RNR-mediated[11] [1,2]-electron shifts, as well as [1,2]-hydride shifts,[3] are mechanistically related to semipinacol rearrangements of halohydrins[26] that also proceed via intermediate ketones. Metal hydrides, hydroxides, and Grignard reagents have been shown to promote [1,2]-(alkyl and hydride) shifts with halohydrins derived from cycloalkanes.[27]

As noted, Baer and co-workers had found that treatment of methyl 4,6-*O*-benzylidene-2-*O*-tosyl-α-D-mannopyranoside[28] (**8**) with LTBH gave a 2-deoxy product with inversion of configuration at C3, consistent with a [1,2]-hydride shift and reduction of an intermediate 3-ketone.[7d] Other diastereomers of **8** underwent desulfonylation,[7d] deoxygenation via epoxide intermediates,[7a,b] and [1,2]-alkyl shifts.[7c]

We briefly examined mannopyranose derivatives without the conformational constraints of a 4,6-*O*-acetal. Debenzylidenation of **8**[28] and treatment of **9**[28,29] with excess LTBH gave the C3-inverted methyl 2-deoxy-α-D-*ribo*-hexopyranoside[30] (**10a**) (Scheme 2), which was treated with aqueous sulfuric acid to give 2-deoxy-D-*ribo*-hexopyranose[30] (2-deoxy-D-allose) (**10c**). LTBD/THF converted **9** into methyl 2-deoxy-3-deuterio-α-D-*ribo*-hexopyranoside (**10b**), consistent with a [1,2]-hydride shift and reduction of an intermediate 3-ketone at the *β*-face. Treatment of **8** with NBS[31] gave the 6-bromo compound **11a** that underwent debromination (Bu_3SnH/AIBN) to give 4-*O*-benzoyl-6-deoxy-2-*O*-tosyl-α-D-mannopyranoside (**11b**). Treatment of **11b** with LTBH gave methyl 2,6-dideoxy-α-D-*ribo*-

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hexopyranoside[32] (**12a**) (91%), and hydrolysis gave 2,6-dideoxy-α-D-*ribo*-hexopyranose[32,33] (digitoxose) (**12c**). Treatment of **11b** with LTBD gave methyl 2,6-dideoxy-3-deuterio-α-D-*ribo*-hexopyranoside (**12b**). The same stereochemical outcome in the presence or absence of protection at O4 and O6 precludes participation or directive effects by the hydroxyl groups. Hydride attack occurred at the less hindered β-face.

Summary and Conclusions

We have demonstrated that a completely stereoselective and chemically efficient deoxygenative [1,2]-hydride shift rearrangement occurred upon treatment of several ribonucleoside and mannopyranoside *cis*-vicinal diol monotosylates with LTBH(D). Deuterium labeling showed that the process occurred with inversion of stereochemistry at both carbinol carbons. This is consistent with abstraction of the hydroxyl proton by hydride, generation of a carbonyl group with a concomitant [1,2]-hydride shift to the backside of the vicinal carbon, and displacement of the tosylate group. Attack of borohydride at the less hindered face generated the inverted alcohol. The process also occurred with bromide and chloride leaving groups with an S_N2-like rate order of OTs ≈ Br ≫ Cl for these semipinacol rearrangements. The nucleobase and sugar substituents had negligible effects. Mechanistic similarities exist between the [1,2]-hydride shift process of the semipinacol rearrangements and the [1,2]-electron shift that occurs during reduction of ribonucleotides to 2′-deoxynucleotides at the active site of ribonucleotide reductases (RNRs). Radical-induced deoxygenations catalyzed by RNRs result in double retention of stereochemistry at C2′ and C3′, in contrast with the doubly inverted semipinacol products. Analogous results with mannopyranoside tosylates provide ready access to deoxyallose and digitoxose sugars.

Experimental Section[34]

General Procedure A: Preparation of 2′-*O*-Tosylnucleosides[14] **(2).** The nucleoside **1** (1.0 mmol) was stirred under reflux in absolute MeOH (25 mL) with Bu_2SnO (275 mg, 1.1 mmol) until the suspension became a clear solution [**1c**,**d** (∼45 min); **1a**,**e** (∼1 h); **1b** (∼2 h)]. The solution was cooled to ambient temperature, and Et_3N (2.1 mL, 1.52 g, 15 mmol) and then TsCl (2.85 g, 15 mmol) were added. Stirring was continued until tosylation was virtually complete (TLC) [**1c** (∼5 min); **1b**,**d** (∼10 min); **1a** (∼15 min); **1e** (∼45 min)]. Volatiles were evaporated, and the residue was partitioned [Et_2O (50 mL)/H_2O (50 mL)]. Volatiles were evaporated from the aqueous phase, and the residue was recrystallized to give **2a**[14] (73%), **2b**[4c] (52%), **2c**[5] (79%), **2d** (67%), and **2e** (52%).

2d: ^{1}H NMR δ 2.29 (s, 3H), 3.59 (m, 2H), 4.01 (m, 1H), 4.29 (t, *J* = 5.0 Hz, 1H), 5.38 (dd, *J* = 7.5, 5.0 Hz, 1H), 5.77 (t, *J* = 5.0 Hz, 1H), 5.94 (d, *J* = 5.0 Hz, 1H), 6.08 (d, *J* = 7.5 Hz, 1H), 6.43 (d, *J* = 3.5 Hz, 1H), 7.14 (br s, 2H), 7.16 (d, *J* = 3.5 Hz, 1H), 7.91 (s, 1H). Anal. Calcd for $C_{18}H_{20}N_4O_6S$ (420.4): C, 51.42; H, 4.79; N, 13.33. Found: C, 51.35; H, 4.85; N, 13.32.

2e: ^{1}H NMR δ 2.27 (s, 3H), 3.60 (m, 2H), 4.02 (m, 1H), 4.31 (m, 1H), 5.23 (dd, *J* = 7.5, 5.0 Hz, 1H), 6.07 (d, *J* = 7.5 Hz, 1H), 5.70 (br s, 2H), 7.36, 7.86 (2 × s, 2 × 1H), 7.40 (br s, 2H), 7.96, 8.32 (2 × s, 2 × 1H). Anal. Calcd for $C_{19}H_{21}N_5O_7S$ (463.5): C, 49.24; H, 4.57; N, 15.11. Found: C, 49.23; H, 4.53; N, 15.03.

General Procedure B: Deoxygenative [1,2]-Hydride Shift Rearrangement. LTBH (1 M in THF; 15 mL, 15 mmol) [**Note**[20]] was added by syringe into a stirred solution of **2a** (421 mg, 1.00 mmol) in dried DMSO (15 mL) under N_2 at ambient temperature, and stirring was continued for 18 h. H_2O (5 mL) was added **cautiously**, and the solution was concentrated. The residue was chromatographed [(Dowex 1 × 2 (OH^-), H_2O] and recrystallized (MeOH) to give **9-(2-deoxy-β-D-*threo*-pentofuranosyl)adenine**[3,6a] (**3a**) (247 mg, 98%): mp 220−221 °C [**Note**[35]] (lit.[6a] mp 218−220 °C); ^{1}H NMR δ 2.26 (d, *J* = 14.6 Hz, 1H), 2.75−2.82 (m, 1H), 3.58−3.63 (m, 1H), 3.71−3.76 (m, 1H), 3.88−3.92 (m, 1H), 4.31−4.36 (m, 1H), 4.70 (t, *J* = 5.4 Hz, 1H), 5.99 (d, *J* = 5.4 Hz, 1H), 6.26 (d, *J* = 8.3 Hz, 1H), 7.36 (br s, 2H), 8.15, 8.35 (2 × s, 2 × 1H); ^{13}C NMR δ 40.7, 59.9, 69.2, 82.4, 85.2, 119.0, 140.0, 148.5, 152.2, 156.1; FAB-MS *m*/*z* 252 ([M + H$^+$], 10), 157 (100); HRMS ($C_{10}H_{14}N_5O_3$) calcd 252.1091, found 252.1090.

Deuterium Labeling. Treatment of **2a** with LTBD[20] according to general procedure B gave 3′[^{2}H]**3a**: ^{1}H NMR δ 2.26 (d, *J* = 14.6 Hz, 1H), 2.79 (dd, *J* = 8.8, 14.6 Hz, 1H), 3.58−3.64 (m, 1H), 3.71−3.76 (m, 1H), 3.88−3.92 (m, 1H), 4.71 (t, *J* = 5.6 Hz, 1H), 5.98 (s, 1H), 6.26 (d, *J* = 8.8 Hz, 1H), 7.38 (br s, 2H), 8.16, 8.36 (2 × s, 2 × 1H); ^{13}C NMR δ 40.7, 60.0, 68.9 (reduced intensity), 82.5, 85.2, 119.0, 140.1, 148.5, 152.3, 156.1; FAB-MS *m*/*z* 253 ([M + H$^+$], 100); HRMS ($C_{10}H_{13}DN_5O_3$) calcd 253.1154, found 253.1155.

Tosylation of 2′[^{2}H]**1a**[16] at O2′ by general procedure A followed by treatment of 2′[^{2}H]**2a** with LTBH[20] according to general procedure B gave 2′(*R*)[^{2}H]**3a**: ^{1}H NMR δ 2.26 (d, *J* = 2.0 Hz, 1H), 3.55−3.63 (m, 1H), 3.71−3.76 (m, 1H), 3.87−3.91 (m, 1H), 4.31−4.36 (m, 1H), 4.64 (t, *J* = 5.4 Hz, 1H), 5.93 (d, *J* = 5.0 Hz, 1H), 6.25 (d, *J* = 1.9 Hz, 1H), 7.31 (br s, 2H), 8.14, 8.34 (2 × s, 2 × 1H); ^{13}C NMR δ 40.4 (reduced intensity), 59.9, 69.2, 82.4, 85.2, 118.9, 140.0, 148.5, 152.2, 156.1; FAB-MS *m*/*z* 253 ([M + H$^+$], 10), 141 (100); HRMS ($C_{10}H_{13}DN_5O_3$) calcd 253.1154, found 253.1152.

Tosylation of 3′[^{2}H]**1a**[16] at O2′ by general procedure A followed by treatment of 3′[^{2}H]**2a** with LTBH[20] according to general procedure B gave 2′(*S*)[^{2}H]**3a**: ^{1}H NMR δ 2.77 (dd, *J* = 5.9, 8.8 Hz, 1H), 3.57−3.63 (m, 1H), 3.71−3.76 (m, 1H), 3.88−3.91 (m, 1H), 4.33 (dt, *J* = 3.4, 5.4 Hz, 1H), 4.70 (t, *J* = 5.6 Hz, 1H), 5.98 (d, *J* = 5.9 Hz, 1H), 6.25 (d, *J* = 8.3 Hz, 1H), 7.35 (br s, 2H), 8.15, 8.35 (2 × s, 2 × 1H); ^{13}C NMR δ 40.4 (reduced intensity), 59.9, 69.2, 82.5, 85.2, 119.0, 140.1, 148.6, 152.3, 156.1; FAB-MS *m*/*z* 253 ([M + H$^+$], 100); HRMS ($C_{10}H_{13}DN_5O_3$) calcd 253.1154, found 253.1153.

Treatment of **2b**−**e** gave **3b** [70% (H_2O); Dowex 1 × 2 (OH^-), 50 mM aqueous $Et_3NH{\cdot}HCO_3$ with data as reported[4c]], **3c** [74%; Dowex 1 × 2 (OH^-) H_2O → 30% MeOH/H_2O; with data as reported[5]], **3d** [82% (diffusion crystallization MeOH/Et_2O)], and **3e** [71%; Dowex 1 × 2 (OH^-), H_2O → H_2O/MeOH, 1:1], respectively.

4-Amino-7-(2-deoxy-β-D-*threo*-pentofuranosyl)pyrrolo[2,3-*d*]-pyrimidine (3d). Mp 202−203 °C; UV max 272 nm (ε 11 900), min 239 nm (ε 2300); ^{1}H NMR δ 2.14 (dd, *J* = 14.6, 2.9 Hz, 1H), 2.72−2.77 (ddd, *J* = 14.6, 8.8, 5.9 Hz, 1H), 3.56−3.82 (m, 3H), 4.29−4.32 (m, 1H), 4.62 (t, *J* = 5.6 Hz, 1H), 5.98 (d, *J* = 5.9 Hz, 1H), 6.32 (dd, *J* = 8.7, 3.4 Hz, 1H), 6.56 (d, *J* = 3.9 Hz, 1H), 7.05 (br s, 2H), 7.46 (d, *J* = 3.4 Hz 1H), 8.06 (s, 1H); ^{13}C NMR δ 157.5, 151.3, 149.0, 123.1, 102.9, 99.2, 84.2, 82.5, 69.4, 60.0, 40.8; HRMS ($C_{11}H_{14}N_4O_3$) calcd 250.1066, found 250.1074. Anal. Calcd for $C_{11}H_{14}N_4O_3{\cdot}0.25H_2O$ (254.7): C, 51.86; H, 5.74; N, 21.99. Found: C, 51.74; H, 5.42; N, 21.65.

4-Amino-5-carboxamido-7-(2-deoxy-β-D-*threo*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine (3e). Mp 236−237 °C; UV max 280

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(35) X-ray quality crystals of **3a** were obtained by diluting a concentrated solution of **3a** in DMSO with MeOH and allowing the resulting solution to stand overnight. Large crystals of **3a** that formed were separated, washed with MeOH, and dried under vacuum.

nm (ϵ 14 800), min 221 nm (ϵ 1200); ^{1}H NMR δ 2.15−2.18 (m, 1H), 2.70−2.76 (ddd, J = 14.2, 7.8, 6.3 Hz, 1H), 3.67−3.82 (2 × m, 2 × 1H), 3.86−3.90 (m, 1H), 4.30−4.35 (m, 1H), 4.61 (t, J = 5.6 Hz, 1H), 5.66 (d, J = 5.4 Hz, 1H), 6.29 (dd, J = 8.3, 2.9 Hz, 1H), 7.30, 7.99 (2 × br s, 2 × 1H); 8.08, 8.16 (2 × s, 2 × 1H); ^{13}C NMR δ 166.6, 158.1, 152.4, 149.6, 126.5, 110.1, 101.2, 84.7, 83.3, 69.2, 59.9, 40.9; HRMS ($C_{12}H_{15}N_5O_4$) calcd 293.1124, found 293.1129. Anal. Calcd for $C_{12}H_{15}N_5O_4 \cdot 0.25H_2O$ (297.8): C, 48.40; H, 5.25, N, 23.52. Found: C, 48.89; H, 5.25; N, 23.50.

2′-Chloro-2′-deoxyadenosine (5c). Tf_2O (0.35 mL, 0.55 g, 3.29 mmol) was added to a cold (0 °C) stirred solution of 9-(3,5-di-*O*-TBS-β-D-arabinofuranosyl)adenine[36] (1.4 g, 2.74 mmol) and DMAP (1.0 g, 8.22 mmol) in CH_2Cl_2 (10 mL). Stirring was continued for 25 min, volatiles were evaporated, and the residue was chromatographed (EtOAc/hexanes, 1:1 → 2:1) to give 9-(3,5-di-*O*-TBS-2-*O*-triflyl-β-D-arabinofuranosyl)adenine (1.34 g, 78%) as a colorless oil. A solution of this material (1.34 g, 2.14 mmol) and LiCl (1.0 g, 23.5 mmol) in dry DMF (10 mL) was heated at 90 °C for 1.5 h, and the cooled reaction mixture was partitioned (H_2O/CH_2Cl_2). The aqueous phase was extracted (CH_2Cl_2, 3×), and volatiles were evaporated from the combined organic phase to give an oil that was chromatographed (EtOAc/hexanes, 1:1 → 2:1) to give 3′,5′-di-*O*-TBS-2′-chloro-2′-deoxyadenosine (1.34 g, 92%). A solution of this material (3.0 g, 5.86 mmol) and NH_4F (1.08 g, 29.3 mmol) in MeOH (70 mL) was heated at reflux overnight. Volatiles were evaporated, and the residue was chromatographed (EtOAc → EtOAc/MeOH, 3:1) to give **5c**[10a,23] (1.65 g, 99%): ^{1}H NMR δ 3.57−3.63 (m, 1H), 3.67−3.72 (m, 1H), 4.06−4.09 (m, 1H), 4.36−4.40 (m, 1H), 5.13 (dd, J = 6.8 Hz, 4.9, 1H), 5.44 (t, J = 5.9 Hz, 1H), 6.00 (d, J = 5.4 Hz, 1H), 6.16 (d, J = 7.3 Hz, 1H), 7.44 (br s, 2H), 8.16, 8.43 (2 × s, 2 × 1H); ^{13}C NMR δ 61.0, 61.2, 70.3, 86.4, 87.8, 119.2, 139.6, 149.1, 152.7, 156.2; FAB-MS *m*/*z* 286 ([M + H$^+$], 100); HRMS ($C_{10}H_{13}ClN_5O_3$) calcd 286.0707, found 286.0719.

2′-Bromo-2′-deoxyadenosine (5b). An analogous reaction sequence with LiBr gave **5b**[22] (85%): ^{1}H NMR δ 3.56−3.62 (m, 1H), 3.67−3.72 (m, 1H), 4.06−4.09 (m, 1H), 4.29−4.31 (m, 1H), 5.16 (dd, J = 7.8 Hz, 4.9, 1H), 5.43 (dd, J = 6.8 Hz, 4.9, 1H), 6.06 (d, J = 4.9 Hz, 1H), 6.24 (d, J = 7.3 Hz, 1H), 7.43 (br s, 2H), 8.15, 8.41 (2 × s, 2 × 1H); ^{13}C NMR δ 52.9, 61.3, 70.3, 86.6, 88.2, 119.2, 139.7, 149.1, 152.8, 156.3; FAB-MS *m*/*z* 330 ([M + H$^+$], 100); HRMS ($C_{10}H_{13}BrN_5O_3$) calcd 330.0202, found 330.0192.

Treatment of 5b with LTBH. LTBH (1 M in THF; 2.72 mL, 2.72 mmol) was added to a solution of **5b** (60 mg, 0.18 mmol) in dried DMSO (2.72 mL) and the reaction mixture was stirred for 21 h at ambient temperature. H_2O (1.0 mL) was added, volatiles were evaporated in vacuo, and the residue was chromatographed [(Dowex 1 × 2 (OH$^-$), H_2O → H_2O/MeOH, 1:1] to give **3a** (40 mg, 88%) with identical spectral data to those from **2a** → **3a**.

Treatment of 5c with LTBH. LTBH (1 M in THF; 5.25 mL, 5.25 mmol) was added to a solution of **5c** (100 mg, 0.35 mmol) in dried DMSO (5.3 mL) and the reaction mixture was stirred for 24 h at 50 °C. H_2O (1.5 mL) was added, volatiles were evaporated in vacuo, and the residue was chromatographed [(Dowex 1 × 2 (OH$^-$), H_2O → H_2O/MeOH, 1:1] to give **3a** (79 mg, 90%) with identical spectral data to those from **2a** → **3a**.

Comparison of Reaction Rates of 2a, 5b, and 5c with LTBH. Independent solutions of 0.17 mmol samples of **2a**, **5b**, and **5c** in DMSO/THF (1:1) were treated with 15 molar equiv of LTBH/THF (1 M) at 22 °C. Aliquots of the individual reaction mixtures were quenched (H_2O) and subjected to ion-exchange chromatography [(Dowex 1 × 2 (OH$^-$), H_2O → MeOH], and the **3a**/starting material ratios were analyzed (^{1}H NMR). The determinations were conducted under pseudo-first-order conditions:

$$k_1 t = -2.303 \log(C/C_o) + a \quad (1)$$

where C/C_o is the ratio of the concentration of starting material **2a**, **5b**, or **5c** in the mixture at time t to the initial concentration of starting material. Values of the term [$-\log(C/C_o)$] were plotted against [t(min)k(s^{-1}) = k_1(min^{-1})/3600]. The plots in Figure 4 are results from single determinations.

Synthesis of 3a from 2a via 5a. TPS-Cl (0.35 mL, 370 mg, 1.35 mmol) was added to a stirred solution of **2a**[12a,14] (421 mg, 1 mmol) in dried pyridine (10 mL), stirring was continued for 18 h at ambient temperature, and volatiles were evaporated. The residue was partitioned (HCl/H_2O//EtOAc), and the organic layer was washed ($NaHCO_3/H_2O$, brine) and dried ($MgSO_4$). Volatiles were evaporated, and the residue was chromatographed (MeOH/EtOAc, 1:50 → 1:15) to give 5′-*O*-(*tert*-butyldiphenylsilyl)-2′-*O*-tosyladenosine (**5a**) (560 mg, 85%): ^{1}H NMR ($CDCl_3$) δ 1.02 (s, 9H), 2.30 (s, 3H), 3.82 (dd, J = 11.6, 4.0 Hz, 1H), 4.01 (dd, J = 11.6, 4.4 Hz, 1H), 4.25 (m, 1H), 4.79 (m, 1H), 5.59 (t, J = 6.0 Hz, 1H), 5.92 (br s, 3H), 6.18 (d, J = 6.5 Hz, 1H), 6.95−7.70 (m, 14H), 7.85, 8.11 (2 × s, 2 × 1H); HRMS $C_{33}H_{38}N_5O_6SSi$ calcd 660.2312, found 660.2332. A solution of **5a** (132 mg, 0.200 mmol) in dried THF (5 mL) was treated with LTBH/THF (1 M; 2 mL, 2 mmol) by general procedure B (THF rather than DMSO as solvent). H_2O (2 mL) was added after 3 h, volatiles were evaporated, and the residue was partitioned ($NaHCO_3/H_2O$//$CHCl_3$). The organic layer was washed (brine) and dried ($MgSO_4$), and volatiles were evaporated. The residue was chromatographed (EtOAc → MeOH/EtOAc, 1:15) to give 9-(5-*O*-TPS-2-deoxy-β-D-*threo*-pentofuranosyl)adenine (5′-*O*-TPS-**3a**) (86 mg, 88%): HRMS [$C_{26}H_{32}N_5O_3Si$] calcd 490.2274, found 490.2287. TBAF/THF (1 M; 0.3 mL, 0.3 mmol) was added to a solution of 5′-*O*-TPS-**3a** in THF (5 mL) and the solution was stirred for 4 h at ambient temperature. Volatiles were evaporated, and the residue was chromatographed [(Dowex 1 × 2 (OH$^-$), H_2O] to give **3a** (50 mg, 85% from **5a**) with identical spectral data as those for **3a** from **2a**.

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Supporting Information Available: General experimental details, experimental procedures and data for **8**−**12**, NMR spectra, and X-ray CIF data for **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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