

Efficient Removal of Sugar *O*-Tosyl Groups and Heterocycle Halogens from Purine Nucleosides with Sodium Naphthalenide¹

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Abstract: Sodium naphthalenide effects removal of 2'-, 3'-, or 5'-*O*-tosyl groups from the sugar, and 2-, 6-, or 8-halogens from purine nucleosides. An improved tosyl protection strategy was developed for the synthesis of 9-(3-deoxy-3-fluoro- β -D-xylofuranosyl)adenine from 2',5'-di-*O*-tosyladenosine. © 1997 Elsevier Science Ltd.

Introduction

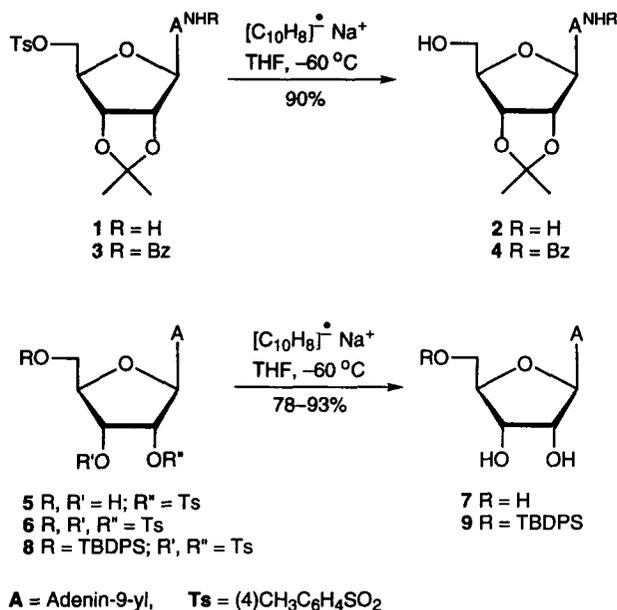
Sodium naphthalenide, an agent with a high reduction potential, has been widely used in organic synthesis.³ Among other applications, it has been employed for cleavage of carbon-halogen bonds⁴ and for regeneration of alcohols⁵ and amines⁶ from *p*-toluenesulfonate esters and *p*-toluenesulfonamides, respectively. Mechanisms are believed to involve single electron transfer (SET) from sodium naphthalenide to the substrate, fragmentation into radical and anionic species, and a second SET to the radical. Protonolysis during workup gives the observed products.⁴⁻⁶ Reductive cleavage of *O*-tosyl carbohydrate derivatives, including 5'-*O*-detosylation (50%) of 2',3'-*O*-isopropylidene-5'-*O*-tosyladenosine, has been described.⁷ We now report expanded applications of sodium naphthalenide for transformations⁸ of the sugar and base moieties of purine nucleosides. This reagent efficiently removes 2'-, 3'- and 5'-*O*-tosyl groups from the sugar moiety of nucleosides, which makes *p*-toluenesulfonyl a viable alternative as a hydroxyl protecting group.⁹ We have developed an improved synthesis of 2',5'-di-*O*-tosyladenosine, and illustrate the *O*-tosyl protection/deprotection methodology in a new synthesis of 9-(3-deoxy-3-fluoro- β -D-xylofuranosyl)adenine. Sodium naphthalenide effects reductive cleavage of bromo or chloro groups from the 2-, 6-, or 8-position of purine nucleosides.

Results and Discussion

Treatment of 5'-*O*-tosyl derivative **1** with sodium naphthalenide (generated by ultrasound irradiation¹⁰ of sodium and naphthalene in THF) at -60 °C gave 2',3'-*O*-isopropylideneadenosine (**2**, 90%; Scheme 1). This efficient *O*-detosylation (prior yield 50%⁷) might have been enhanced by our addition of sodium naphthalenide to the substrate rather than the prior inverse addition.⁵⁻⁷ Analogous treatment of the 6-*N*-benzoyl derivative **3** also gave efficient 5'-*O*-detosylation, but partial removal of the benzoyl group occurred (during reduction or

workup) to give **2/4** (~1:3, 88%). Treatment of 2'-*O*-tosyladenosine (**5**) or 2',3',5'-tri-*O*-tosyladenosine (**6**) with sodium naphthalenide gave adenosine (**7**). Analogous treatment of 5'-*O*-(*tert*-butyldiphenylsilyl)-2',3'-*O*-tosyladenosine (**8**) gave 5'-*O*-TBDPS-adenosine (**9**, 93%), which demonstrated chemoselectivity relative to the silyl ether function.

Scheme 1

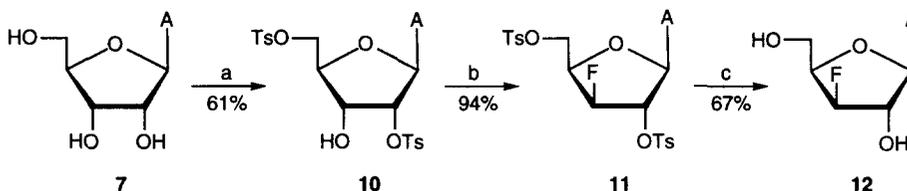


Applications of sodium naphthalenide with uridine derivatives were reported by Philips and Horwitz¹¹ (removal of benzyl from N3 of uridine) and Letsinger and coworkers¹² (removal of methoxytrityl from nucleosides and nucleotides). However, our experiments with *O*-tosyl derivatives of uridine consistently resulted in formation of byproducts. Careful treatment of 2',3'-*O*-isopropylidene-5'-*O*-tosyluridine or 2'-*O*-tosyluridine with sodium naphthalenide (−78 °C, addition stopped with 5–10% of substrate remaining) gave 2',3'-*O*-isopropylideneuridine or uridine, respectively, [80–90% estimated product formation (TLC, ¹H NMR)] but these products were contaminated (5–15%) with byproducts that were not resolved by flash chromatography (or RP-HPLC in the uridine case) and resisted crystallization. Electron transfer to the uracil ring is a likely route to contaminants, and ¹H NMR and HRMS spectra indicated the presence of 5,6-dihydrouracil derivatives.

Moffatt and coworkers demonstrated selective activation of 2'-hydroxyl groups in the 2',3'-diol units of ribonucleosides with dibutyltin oxide¹³ (via 2',3'-*O*-dibutylstannylene intermediates), and activation of the 5'-hydroxyl group with bis(tributyltin)oxide.¹⁴ We treated adenosine (**7**) successively with dibutyltin oxide, bis(tributyltin)oxide, and tosyl chloride and obtained 2',5'-di-*O*-tosyladenosine (**10**, 61% after silica gel column chromatography) (Scheme 2). A prior synthesis of **10** (27%) by treatment of 6-*N*-benzoyladeniosine with tosyl chloride/pyridine (and debenzoylation) required its tedious separation from the 3',5'-di-*O*-tosyl regioisomer and

other products.¹⁵ Treatment of **10** with (diethylamino)sulfur trifluoride (DAST, 2-5 equivalents) at ambient temperature for 6-14 hours gave low to moderate yields of the 3'-fluoro xylo derivative **11** that were solvent dependent [methylene chloride (12%), tetrahydrofuran (25%), dioxane (40%), acetonitrile (51%)]. However, addition of cesium fluoride to a solution of **10** and DAST in dioxane markedly enhanced the yield of the somewhat unstable **11** (94%). Immediate treatment of **11** with sodium naphthalenide in THF at $-78\text{ }^{\circ}\text{C}$ gave 9-(3-deoxy-3-fluoro- β -D-xylofuranosyl)adenine¹⁶ [**12**, complete conversion (TLC); 67% after chromatography and crystallization]. Compound **12** also had been obtained as a rearrangement product of treatment of 6-*N*,5'-*O*-bis(monomethoxytrityl)-3'-*O*-(*tert*-butyldimethylsilyl)adenosine with DAST.¹⁷

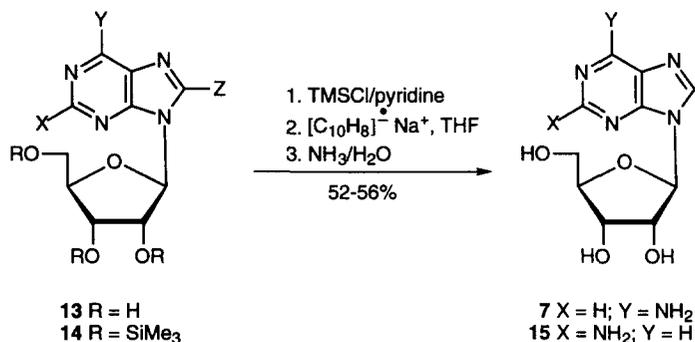
Scheme 2



(a) (i) $\text{Bu}_2\text{SnO}/\text{MeOH}/\Delta$; (ii) $(\text{Bu}_3\text{Sn})_2\text{O}/\text{benzene}/\Delta$; (iii) $\text{TsCl}/\text{pyridine}$; (b) $\text{DAST}/\text{CsF}/\text{dioxane}$; (c) $[\text{C}_{10}\text{H}_8]^{2-} \text{Na}^+/\text{THF}/-78\text{ }^{\circ}\text{C}$.

Nair resorted to photochemical removal of the 6-chloro group¹⁸ for syntheses of 2-aminopurine nucleosides from guanosine owing to experimental problems with catalytic hydrogenolysis of chloride.⁸ We protected 2-amino-6-chloropurine riboside¹⁹ (**13a**, Scheme 3) with trimethylsilyl chloride²⁰ to give **14a**, which was treated with sodium naphthalenide and deprotected with aqueous ammonia to give 2-aminopurine riboside

Scheme 3



13, 14 series: **a** $\text{X} = \text{NH}_2; \text{Y} = \text{Cl}; \text{Z} = \text{H}$
b $\text{X} = \text{Cl}; \text{Y} = \text{NH}_2; \text{Z} = \text{H}$
c $\text{X} = \text{H}; \text{Y} = \text{NH}_2; \text{Z} = \text{Br}$

(**15**, 56% from **13a**). Analogous treatment of the per(trimethylsilyl) derivatives of 2-chloroadenosine (**14b**) and 8-bromoadenosine (**14c**) resulted in smooth dehalogenations to give adenosine (**7**) after deprotection.

In summary, removal of 2'-, 3'-, or 5'-*O*-tosyl groups from adenosine with sodium naphthalenide occurred smoothly. Trimethylsilylation of 2-amino-6-chloro-, 6-amino-8-bromo-, and 6-amino-2-chloropurine ribosides, dehalogenation of protected derivatives with sodium naphthalenide, and deprotection gave moderate yields of the aminopurine nucleosides. In contrast with prior reports, byproducts that were not readily separable from uracil nucleosides were observed upon treatment of uridine derivatives with sodium naphthalenide.

Experimental

^1H (Me_4Si) NMR spectra were determined at 200 or 500 MHz, ^{13}C (Me_4Si) at 125.1 MHz, and ^{19}F (CCl_3F) at 470.3 MHz on Varian Gemini 200 or VXR 500S spectrometers with solutions in CDCl_3 unless otherwise noted. Mass spectra (MS and HRMS) were obtained by electron impact (EI, 20 eV), chemical ionization (CI, CH_4), or fast atom bombardment (FAB, thioglycerol matrix) techniques with a Jeol SX 102A spectrometer. A NEY 300 Ultrasonik laboratory cleaning bath was used for ultrasonic irradiation. Reagent grade chemicals were used and solvents were distilled prior to use. Pyridine was dried by reflux over and distillation from CaH_2 . THF was refluxed over and distilled from LiAlH_4 and then distilled from potassium benzophenone ketyl. Sodium naphthalenide (0.3–0.5 M) was prepared from Na and naphthalene in dry THF under argon with ultrasonic irradiation and protection from oxygen as described.¹⁰ TLC was performed on Merck kieselgel 60-F₂₅₄ with S₁ ($\text{EtOAc}/i\text{-PrOH}/\text{H}_2\text{O}$, 4:1:2; upper layer) and S₂ ($\text{MeOH}/\text{CHCl}_3$, 1:9) with visual detection under 254 nm light. Merck kieselgel 60 (230–400 mesh) was used for column chromatography and Dowex 1 × 2 (OH^-) resin was used for anion exchange chromatography. Preparative RP-HPLC was performed with a Spectra Physisc SP 8800 ternary pump system and a Dynamx C₁₈ Column. Solid products were dried *in vacuo* over P_4O_{10} at elevated temperatures. Starting **13b** and **13c** were commercial samples, and **1**,²¹ **3**,²² **5**,¹³ **6**¹⁵ [71%; TsCl (4 equiv)/pyridine/3 °C/60 h], **13a**,¹⁹ 2',3'-*O*-isopropylidene-5'-*O*-tosyluridine²³ and 2'-*O*-tosyluridine¹³ were prepared as described.

5'-*O*-(*tert*-Butyldiphenylsilyl)-2',3'-di-*O*-(*p*-toluenesulfonyl)adenosine (8). TsCl (477 mg, 2.5 mmol) was added to a solution of 5'-*O*-TBDPS-adenosine²⁴ (**9**; 505 mg, 1 mmol) in dried pyridine (10 mL) under N_2 at ~ 0 °C (ice-bath), and stirring was continued for 72 h (TLC, S₂). Ice-cold saturated $\text{NaHCO}_3/\text{H}_2\text{O}$ (5 mL) was added, stirring was continued for 30 min, and volatiles were evaporated. The residue was partitioned ($\text{H}_2\text{O}/\text{CHCl}_3$) and the organic layer was washed ($\text{HCl}/\text{H}_2\text{O}$, $\text{NaHCO}_3/\text{H}_2\text{O}$, brine), dried (MgSO_4), and evaporated. Column chromatography ($\text{CHCl}_3 \rightarrow 2\% \text{ MeOH}/\text{CHCl}_3$) of the yellow glass gave a colorless foam (715 mg, 88%) that was crystallized (MeOH) to give **8**: mp 144–145 °C; ^1H NMR δ 1.07 (s, 9 H, *t*-Bu), 2.30, 2.45 (2s, 2 × 3 H, 2 × Me), 3.77 (dd, 1 H, $J = 3.4, 11.6$ Hz, H5''), 3.92 (dd, 1 H, $J = 3.7, 11.6$ Hz, H5'), 4.45–4.50 (m, 1 H, H4'), 5.42 (dd, 1 H, $J = 2.6, 5.5$ Hz, H3'), 5.55 (br s, 2 H, NH_2), 5.69 (dd, 1 H, $J = 5.5, 6.8$ Hz, H2'), 6.08 (d, 1 H, $J = 6.8$ Hz, H1'), 6.92–7.84 (m, 18 H, aromatic), 7.70 (s, 1 H, H2), 7.99 (s, 1 H, H8); MS (EI) m/z 756 ($\text{M}^+ - t\text{-Bu}$, 100), 449 (78), 199 (72), 135 (BH_2 , 48); HRMS (CI) m/z calc. for $\text{C}_{40}\text{H}_{43}\text{N}_5\text{O}_8\text{S}_2\text{Si}$ (MH^+): 814.2401; found 814.2402.

Sodium Naphthalenide (Stock Solution). A mixture of sodium spheres (1.18 g, 51.3 mmol) and naphthalene (2.2 g, 17.2 mmol) in dried, deoxygenated (Ar, 30 min) THF (50 mL) was subjected to ultrasonic irradiation under Ar for 30 min at ambient temperature. The resulting stock solution was stored in a sealed flask at $-20\text{ }^{\circ}\text{C}$.

2',3'-*O*-Isopropylideneadenosine (2). **Typical *O*-Detosylation Procedure.** A precooled ($-10\text{ }^{\circ}\text{C}$) aliquot ($\sim 3\text{ mL}$) of the stock solution of sodium naphthalenide ($\sim 0.34\text{ M}$) was added dropwise (canula, $\sim 5\text{ min}$) into a stirred solution of **1**²¹ (115 mg, 0.25 mmol) in dried, deoxygenated (Ar, 15 min) THF (8 mL) at $-60\text{ }^{\circ}\text{C}$ until the green color of the anion radical persisted. The reaction was quenched (saturated $\text{NH}_4\text{Cl}/\text{H}_2\text{O}$) after $\sim 5\text{ min}$ [TLC (S_2) showed no starting material]. Volatiles were evaporated and the residue was partitioned ($\text{CHCl}_3/\text{H}_2\text{O}$). The aqueous layer was extracted with CHCl_3 (2 \times) and the combined organic phase was washed ($\text{NaHCO}_3/\text{H}_2\text{O}$, brine), dried (Na_2SO_4), and evaporated. Column chromatography ($\text{CHCl}_3 \rightarrow 4\%\text{ MeOH}/\text{CHCl}_3$) gave **2** (69 mg, 90%) with data identical to those of commercial **2**. Analogous treatment of **1** with the stock solution of sodium naphthalenide stored at $-20\text{ }^{\circ}\text{C}$ for 3 weeks gave **2** (88%).

6-*N*-Benzoyl-2',3'-*O*-isopropylideneadenosine (4). Compound **3**²² (141 mg, 0.25 mmol) was treated with sodium naphthalenide as described for **2** and the product was column chromatographed ($\text{CHCl}_3 \rightarrow 3\%\text{ MeOH}/\text{CHCl}_3$) to give **4**²⁵ (68 mg, 66%) and **2** (17 mg, 22%; identical to the above sample).

Adenosine (7) From *O*-Tosyladenosines. Method A. A solution of **5**¹³ (211 mg, 0.5 mmol) in DMF/THF (1:2, 15 ml) was treated with sodium naphthalenide as described for **2** ($-78\text{ }^{\circ}\text{C}$). The reaction was quenched (saturated $\text{NH}_4\text{Cl}/\text{H}_2\text{O}$), the mixture was evaporated, and the residue was partitioned ($\text{H}_2\text{O}/\text{CH}_2\text{Cl}_2$). The aqueous layer was concentrated and applied to a Dowex 1 \times 2 (OH^-) column (H_2O). Elution with $\text{MeOH}/\text{H}_2\text{O}$ (1:1) gave **7** (109 mg, 82%; data identical to those of a commercial sample of **7**).

Method B. Treatment of **6**¹⁵ (109 mg, 0.15 mmol) with sodium naphthalenide as described for **2** and workup and purification as described in method A gave **7** (31 mg, 78%).

5'-*O*-(*tert*-Butyldiphenylsilyl)adenosine (9). Compound **8** (162 mg, 0.2 mmol) was treated with sodium naphthalenide ($-70\text{ }^{\circ}\text{C}$), purified as described for **2**, and crystallized (EtOH) to give **9** (94 mg, 93%): mp $190\text{--}191\text{ }^{\circ}\text{C}$ and other data as reported.²⁴

2',5'-*Di-O*-(*p*-toluenesulfonyl)adenosine (10). A mixture of adenosine (**7**; 267 mg, 1 mmol) and dibutyltin oxide (249 mg, 1 mmol) in MeOH (30 mL) was refluxed for 30 min and evaporated to dryness. The white residue was coevaporated with benzene (3 \times 10 mL), suspended in dried benzene (50 mL), and bis(tributyltin)oxide (1.53 mL, 1.79 g, 3 mmol) was added. The reaction mixture was refluxed under Ar for 2 h and the resulting solution was cooled in an ice-bath. Pyridine (5 mL) and TsCl (419 mg, 2.2 mmol) were added and the reaction mixture was stored at $5\text{ }^{\circ}\text{C}$ for 24 h [additional TsCl (191 mg, 1 mmol) was added and the mixture was stored at $5\text{ }^{\circ}\text{C}$ for an additional 24 h]. Water (5 mL) was added and the mixture was stirred for 30

min at ambient temperature and evaporated. The residue was coevaporated with toluene (3 ×) and partitioned [H₂O/AcOH (9:1)/CHCl₃]. The organic layer was washed (H₂O, NaHCO₃/H₂O, brine), dried (Na₂SO₄), and column chromatographed (CH₂Cl₂ → 4% EtOH/CH₂Cl₂) to give **10** (350 mg, 61%) as a white foam with data as reported.¹⁵

9-[3-Deoxy-3-fluoro-2,5-di-O-(*p*-toluenesulfonyl)-β-D-xylofuranosyl]adenine (11). Dried CsF (1.45 g, 9.51 mmol) was added to a solution of **10** (1.21 g, 2.09 mmol) in dried dioxane (120 mL) and the suspension was subjected to ultrasonic irradiation for 30 min under anhydrous conditions. DAST (1.39 mL, 1.69 g, 10.5 mmol) was added and stirring was continued for 48 h at ambient temperature. NaHCO₃/H₂O was added, volatiles were evaporated, and the residue was partitioned (NaHCO₃/H₂O/CHCl₃). The organic layer was washed (NaHCO₃/H₂O, brine), dried (Na₂SO₄), evaporated, and the residue was column chromatographed (CH₂Cl₂ → 3% EtOH/CH₂Cl₂) to give **11** (1.135 g, 94%) as a somewhat unstable white foam: ¹H NMR (acetone-*d*₆) δ 2.32, 2.39 (2s, 2 × 3 H, 2 × Me), 4.36 (ddd, 1 H, *J* = 1.0, 7.7, 11 Hz, H5'), 4.45 (ddd, 1 H, *J* = 1.0, 3.5, 11 Hz, H5''), 4.72 (dddd, 1 H, *J* = 3.0, 5.5, 8.0, 21 Hz, H4'), 5.63 (ddd, 1 H, *J* = 3.0, 5.5, 52 Hz, H3'), 6.03 (d, 1 H, *J* = 6.0 Hz, H1'), 6.04 (ddd, 1 H, *J* = 3.0, 6.0, 22 Hz, H2'), 6.69 (br s, 2 H, NH₂), 7.10, 7.34, 7.52, 7.74 (4d, 4 × 2 H, *J* = 8 Hz, aromatic), 7.95 (s, 1 H, H2), 8.02 (s, 1 H, H8); ¹⁹F NMR (acetone-*d*₆): δ -201.89 (dt, *J* = 21, 52 Hz, F3'); ¹³C NMR (acetone-*d*₆) δ 21.58, 21.64 (2 × CH₃), 68.11 (d, *J* = 13.0 Hz, C5'), 77.98 (d, *J* = 19.6 Hz, C2'), 82.99 (d, *J* = 28.8 Hz, C4'), 86.25 (d, *J* = 5.7 Hz, C1'), 95.24 (d, *J* = 190 Hz, C3'), 128.47, 128.86, 130.66, 130.85, 132.52, 133.59, 146.28, 146.85, (aromatic), 120.63 (C5), 140.38 (C8), 150.17 (C4), 153.80 (C2), 157.21 (C6); HRMS (FAB) *m/z* calc. for C₂₄H₂₅FN₅O₇S₂ (MH⁺): 578.1179; found 578.1183.

9-(3-Deoxy-3-fluoro-β-D-xylofuranosyl)adenine (12). Compound **11** (238 mg, 0.412 mmol) was treated with a precooled (-30 °C) aliquot of the stock solution of sodium naphthalenide as described for **2** (-78 °C). The reaction was quenched [AcOH (0.5 mL)], neutralized (NH₃/MeOH), evaporated, absorbed on silica as a solution in MeOH, dried and column chromatographed (EtOAc → 3% MeOH/EtOAc) to give **12** (74 mg, 67%) as a white microcrystalline powder with ¹H and ¹⁹F NMR data as reported:¹⁶ mp 214 °C (MeOH), mp 212-213 °C (EtOH) (lit.¹⁶ mp 212-214 °C); ¹³C NMR (Me₂SO-*d*₆) δ 58.25 (d, *J* = 10.3 Hz, C5'), 77.57 (d, *J* = 26.3 Hz, C2'), 81.92 (d, *J* = 19.8 Hz, C4'), 88.73 (C1'), 95.66 (d, *J* = 184 Hz, C3'), 118.87 (C5), 138.52 (C8), 149.31 (C4), 152.94 (C2), 156.210 (C6).

2-Amino-9-(β-D-ribofuranosyl)purine (15). **Typical Dehalogenation Procedure.** TMSCl (0.21 mL, 180 mg; 1.65 mmol) was added to a solution of **13a**¹⁹ (100 mg, 0.33 mmol) in pyridine (10 mL) and stirring was continued for 30 min at ambient temperature. Volatiles were evaporated and the residue was coevaporated with toluene (2 × 5 mL) and dissolved [ice-cold CHCl₃ (10 mL)]. The solution was washed [ice-cold saturated NaHCO₃/H₂O (2 × 5 mL), brine (5 mL)], dried (Na₂SO₄) and evaporated. The solidified residue

(crude **14a**) was dried *in vacuo* for 10 h and dissolved in dried THF (5 mL). The solution was deoxygenated (Ar, 30 min), cooled ($-60\text{ }^{\circ}\text{C}$) and treated with sodium naphthalenide as described in **2** until TLC (S_1) indicated complete conversion to the more polar product. The reaction was quenched (saturated $\text{NH}_4\text{Cl}/\text{H}_2\text{O}$), volatiles were evaporated, and the residue was dissolved in EtOAc (10 mL). The solution was washed [brine (5 mL)], dried (Na_2SO_4), and evaporated. The residue was dissolved [MeOH (5 mL)], $\text{NH}_3/\text{H}_2\text{O}$ (28%, 4 mL) was added, and stirring was continued for 30 min. Volatiles were evaporated and the residue was partitioned [Et_2O (8 mL)/ H_2O (4 mL)]. The organic phase was washed [H_2O (3 mL)] and the combined aqueous layer was concentrated and applied to a Dowex 1×2 (OH^-) column. Elution ($\text{H}_2\text{O} \rightarrow 90\% \text{ MeOH}/\text{H}_2\text{O}$) and evaporation gave white crystals of **15** (49 mg, 56% from **13a**) with data as reported.¹⁸

Adenosine (7) From Dehalogenation.

Method A. Transient protection and treatment of 6-amino-2-chloropurine riboside (2-chloroadenosine) (**13c**; 100 mg, 0.33 mmol) as described for **15** gave **7** (46 mg, 52%) with data identical to those of a commercial sample.

Method B. Treatment of 6-amino-8-bromopurine riboside (8-bromoadenosine) (**13d**; 100 mg, 0.29 mmol) by the procedure described for **15** gave **7** (43 mg, 56%) with data identical to those of a commercial sample.

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