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Efficient Syntheses of 2-Chloro-2′-deoxyadenosine (Cladribine) from 2′-Deoxyguanosine[1]

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We report efficient syntheses of the clinical agent cladribine (2-chloro-2′-deoxyadenosine, CldAdo), which is the drug of choice against hairy-cell leukemia and other neoplasms, from 2′-deoxyguanosine. Treatment of 3′,5′-di-*O*-acetyl- or benzoyl-2′-deoxyguanosine (**1**) with 2,4,6-triisopropyl- or 4-methylbenzenesulfonyl chloride gave high yields of the 6-*O*-arylsulfonyl derivatives **2** or **2′b**. Deoxychlorination at C6 of **1** also proceeded to give the 2-amino-6-chloropurine derivative **5** in excellent yields. The nonaqueous diazotization/chloro dediazoniation (acetyl chloride/benzyltriethylammonium nitrite) of **2**, **2′b**, and **5** gave the 2-chloropurine derivatives **3**, **3′b**, and **6**, respectively. The selective ammonolysis at C6 (arylsulfonate with **3** or chloride with **6**) and accompanying deprotection of the sugar moiety gave CldAdo (64−75% overall yield from **1**).

Introduction

The lymphoselective toxicity of 2-chloro-2′-deoxyadenosine (CldAdo, cladribine) and its potential as a chemotherapeutic agent against lymphoid neoplasms were reported by Carson et al.[2] This potent, deaminase-resistant analogue of 2′-deoxyadenosine (dAdo) is currently the drug of choice for hairy-cell leukemia.[3,4] It also shows significant activity against chronic lymphocytic leukemia,[5,6] indolent non-Hodgkin's lymphoma,[7] and Waldenström's macroglobulinemia.[8] Investigations with cladribine treatment of multiple sclerosis,[9] systemic lupus erythematosis-associated glomerulonephritis,[10] and other rheumatoid and immune disorders are in progress. Cladribine is a nucleoside prodrug, which is phosphorylated by deoxycytidine kinase to CldAMP and then sequentially to CldADP and the active CldATP.[2a,11a] Cladribine also is a good substrate for mitochondrial 2′-deoxyguanosine (dGuo) kinase,[11] and induction of programmed cell death by direct effects on mitochondria has been implicated in its potent activity against indolent lymphoid malignancies (via apoptosis) as well as in proliferating cells.[12,13]

Venner reported the Fischer−Helferich syntheses of naturally occurring 2′-deoxynucleosides in 1960[14] and employed CldAdo as an intermediate for 2′-deoxyguanosine and -inosine. Ikehara and Tada also synthesized dAdo with CldAdo as an intermediate [obtained by the desulfurization of 8,2′-anhydro-9-(β-D-arabinofuranosyl)-2-chloro-8-thioadenine].[15]

The syntheses of CldAdo as a target compound have exploited the greater reactivity of leaving groups at C6 relative to those at C2 of the purine ring in S_NAr displacement reactions. Robins and Robins[16] employed the fusion coupling of 2,6-dichloropurine with 1,3,5-tri-*O*-acetyl-2-deoxy-α-D-ribofuranose. The 9-(3,5-di-*O*-acetyl-2-deoxy-α-D-*erythro*-pentofuranosyl)-2,6-dichloropurine anomer was obtained by fractional crystallization. The selective ammonolysis at C6 and accompanying deprotection gave 6-amino-2-chloro-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purine. The pharmacologically active β anomer (cladribine) was prepared by an analogous coupling, chromatographic separation of anomers, and ammonolysis.[17]

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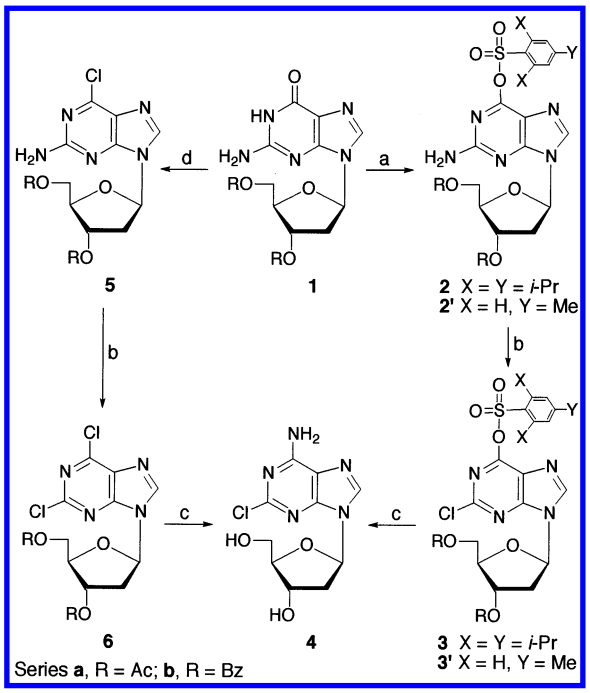
The stereoselective glycosylation of the sodium salts of halopurines and analogues with 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl chloride gave *β*-nucleoside anomers via predominantly Walden inversion,[18,19] and ammonolysis/deprotection gave CldAdo.[20] Although the sodium salt glycosylation procedure usually gave good anomeric stereoselectivity, minor quantities of α anomers and >10% of the N7 regioisomers were usually formed.[21,22] This requires separations and results in diminished yields of the desired N9 product. Carson et al.[2] had reported an enzymatic transfer of the 2-deoxy sugar from thymidine to 2-chloroadenine (ClAde). Holý and co-workers noted that cells of a strain of *Escherichia coli* performed glycosyl transfer from 2′-deoxyuridine to 2-chloro-6-[(dimethylaminomethylene)amino]purine to give a derivative of CldAdo.[23] Very recently Barai and co-workers[24] described an *E. coli*-mediated glycosyl transfer synthesis of 2,6-diamino-9-(3-deoxy-*β*-D-*erythro*-pentofuranosyl)purine[25] and its enzymatic deamination to 3′-deoxyguanosine.[25] They reported glycosyl transfer from 2′-deoxyguanosine to ClAde and claimed an 81% yield of CldAdo (on the basis of ClAde).[26] However, a 3:1 ratio of dGuo/ClAde was employed, so the yield of CldAdo was <27% on the basis of dGuo.

Our chemical approach for the synthesis of regio- and stereochemically pure CldAdo, which avoids the separation of mixtures with fusion and sodium salt glycosylation procedures, employs the transformation of naturally occurring nucleosides.[27] The conversion of the 6-oxo function of dGuo into the appropriate leaving groups, diazotization/chloro dediazoniation of the 2-amino function, and selective C6 ammonolysis of 2-chloro-6-(substituted)purine derivatives provide a route from dGuo to CldAdo with the retention of both *β*-anomeric stereochemistry and N9-isomeric purity.

We have recently reported improved methods for the replacement of an amino group on purine nucleoside derivatives with chlorine, bromine, or iodine under nonaqueous conditions.[1,28] These mild diazotization/halo dediazoniation methods were found to be applicable at C6 of dAdo derivatives as well as at C2 of 2-amino-6-chloropurine nucleosides. We now describe the efficient syntheses of CldAdo, which employ acetyl chloride and benzyltriethylammonium nitrite (BTEA-NO_2)-mediated chloro dediazoniation of 6-*O*-2,4,6-triisopropylbenzenesulfonyl (TiPBS) or 6-chloro derivatives that are readily obtained from dGuo.

SCHEME 1[a]



[a] (a) TiPBS−Cl/Et_3N/DMAP/$CHCl_3$. (b) AcCl/BTEA-NO_2/CH_2Cl_2, −5 to 0 °C. (c) NH_3/MeOH/CH_2Cl_2/Δ. (d) $POCl_3$/BTEA-Cl/*N*,*N*-dimethylaniline/MeCN/Δ.

Results and Discussion

Our projected synthesis of CldAdo (**4**; Scheme 1) from dGuo required the efficient transformation of the 6-oxo function into good leaving groups without protection of the 2-amino moiety, chloro dediazoniation at C2, and selective ammonolysis at C6 with accompanying sugar deprotection. Two approaches we evaluated for functionalization at C6 were arylsulfonylation of O6 and chlorodeoxygenation at C6.

Several acyl-protected 6-*O*-sulfonyl derivatives of dGuo are readily available.[29−31] The treatment of 3′,5′-di-*O*-acetyl-2′-deoxyguanosine[32] (**1a**) or its 3′,5′-di-*O*-benzoyl analogue **1b**[32] with TiPBS−Cl/Et_3N/DMAP/$CHCl_3$ by a modification of the method of Hata et al.[30] gave the 6-*O*-TiPBS derivatives **2a**[33] (91%) or **2b** (86%), respectively. The similar treatment of **1b** with TsCl/Et_3N/DMAP/$CHCl_3$ gave the 6-*O*-Ts derivative **2′b** (89%). Efficient displacement of sulfonate from C6 required a sterically hindered arylsulfonyl derivative. Our attempts with a more economical 6-*O*-Ts derivative gave poor yields at

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the final stage owing to attack of ammonia at both the sulfonyl sulfur and C6 (**3′b** gave **4** in 43% yield). By contrast, ammonolysis of the 6-*O*-TiPBS derivatives proceeded efficiently at C6 with minimal attack at the hindered sulfur atom. Both types of the arylsulfonate derivatives, and especially the 6-*O*-Ts, underwent increased nucleophilic attack at the sulfur with lower temperatures (−20 to 0 °C) to give 6-oxopurine derivatives. However, treatment of the 6-*O*-TiPBS compounds with NH_3/MeOH/CH_2Cl_2 in a pressure tube at 80 °C strongly favored nucleophilic attack at C6 to give good yields of CldAdo. This suggests a crossover of the activation-energy profiles for nucleophilic attack at the sulfonyl sulfur versus C6 between 0 and 80 °C.

Chlorine has been the most frequently used leaving group at C6 of purine nucleosides. Original studies on deoxychlorination of guanosine[34] (Guo) and dGuo[35] derivatives with $POCl_3$ gave moderate (Guo) to poor (dGuo) yields of 2-amino-6-chloropurine products, and improved procedures have been reported.[27a,36,37] We effected deoxychlorination of the acid-labile 2′-deoxy derivatives **1** with $POCl_3$/*N*,*N*-dimethylaniline/BTEA-Cl/MeCN/Δ[27a,37] and obtained the 6-chloro derivatives **5a** (90%) and **5b** (85%) in high yields under carefully controlled conditions. Our modified procedure for nonaqueous diazotization/chloro dediazoniation[1,28] (AcCl/BTEA-NO_2/CH_2Cl_2, −5 to 0 °C) worked well for the replacement of the 2-amino group of **2**, **2′b**, and **5** with chlorine to give **3a** (89%), **3b** (90%), **3′b** (87%), **6a** (95%), and **6b** (91%).

The displacement of the hindered arylsulfonate (from **3**) or chloride (from **6**) at C6 with the accompanying cleavage of the sugar esters was effected at 80 °C with NH_3/MeOH/CH_2Cl_2. CldAdo was obtained in high yields from **3a** (81%), **3b** (83%), **6a** (87%), and **6b** (94%) but only in moderate yield from the 6-*O*-Ts derivative **3′b** (43%).

In summary, syntheses of the clinical drug cladribine were accomplished in three steps from the readily available **1a** or its dibenzoyl analogue **1b**. The replacement of the 2-amino group proceeded in high yields by diazotization/chloro dediazoniation with AcCl/BTEA-NO_2. The selective ammonolysis of **3a** and **3b** (6-*O*-TiPBS) or **6** (6-Cl), with accompanying deacylation, gave **4** (64−75% overall yield). The ammonolysis of **3′b** (6-*O*-Ts) was problematic and gave **4** in poor overall yield (33%). The routes that employed the deoxychlorination of **1** were ∼10% more efficient overall than those which involved 6-*O*-TiPBS intermediates.

Experimental Section

The melting points for **4** were determined with a hot-stage apparatus. UV spectra were recorded with solutions in MeOH. ^{1}H NMR spectra were recorded at 300 MHz with solutions in $CDCl_3$ unless otherwise indicated. "Apparent" peak shapes are in quotation marks when the first-order splitting should be more complex or when the peaks were poorly resolved. Mass spectra were determined with FAB (glycerol) unless otherwise indicated. The chemicals and solvents were of reagent quality. CH_2Cl_2 and MeCN were dried by reflux over and distillation from CaH_2. $CHCl_3$ was dried over P_2O_5 and distilled. AcCl, $POCl_3$, and *N*,*N*-dimethylaniline were freshly distilled before use. BTEA-NO_2 was prepared from BTEA-Cl by ion exchange [Dowex 1X2 (NO_2^-)]. Column chromatography (silica gel, 230−400 mesh) was performed with CH_2Cl_2/MeOH. Compounds **1a** and **1b** were prepared as described.[32]

Method 1 (nucleoside/TiPBS−Cl/DMAP/Et_3N/$CHCl_3$) is described for **1a** → **2a**, method 2 (nucleoside/AcCl/BTEA-NO_2/CH_2Cl_2) for **2a** → **3a**, method 3 (nucleoside/*N*,*N*-dimethylaniline/$POCl_3$/BTEA-Cl/MeCN) for **1a** → **5a**, and method 4 (nucleoside/NH_3/MeOH/CH_2Cl_2/Δ) for **3a** → **4**. Analogous reactions with equivalent molar proportions of other nucleosides gave the indicated products and quantities.

9-(3,5-Di-*O*-acetyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl)-2-amino-6-*O*-(2,4,6-triisopropylbenzenesulfonyl)purine (2a). Method 1. Et_3N (1.25 mL, 910 mg, 9.0 mmol) was added to a stirred solution of **1a** (1.67 g, 4.8 mmol), TiPBS−Cl (2.73 g, 9.0 mmol), and DMAP (72 mg, 0.6 mmol) in dried $CHCl_3$ (70 mL) under N_2. Stirring was continued for 24 h, and volatiles were evaporated. The orange residue was chromatographed (CH_2Cl_2/MeOH) to give **2a**[33] (2.67 g, 91%) as a slightly yellow foam: UV λ_{max} 238, 291 nm, λ_{min} 264 nm; ^{1}H NMR (500 MHz) δ 1.26−1.32 (m, 18H), 2.08 (s, 3H), 2.14 (s, 3H), 2.54 (ddd, J = 4.7, 9.0, 14.0 Hz, 1H), 2.91−2.99 (m, 2H), 4.22−4.37 (m, 3H), 4.43−4.47 (m, 2H), 4.97 (br s, 2H), 5.41−5.42 ("d", 1H), 6.26−6.29 (m, 1H), 7.21 (s, 2H), 7.84 (s, 1H); LRMS *m*/*z* 618 (MH^+ [$C_{29}H_{40}N_5O_8S$] = 618); HRMS *m*/*z* 640.2413 (MNa^+ [$C_{29}H_{39}N_5O_8SNa$] = 640.2417).

2-Amino-9-(3,5-di-*O*-benzoyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl)-6-*O*-(2,4,6-triisopropylbenzenesulfonyl)purine (2b). Treatment of **1b** (950 mg, 2.0 mmol) by method 1 gave **2b** (1.27 g, 86%) as a white solid foam: UV λ_{max} 289 nm, λ_{min} 264 nm; ^{1}H NMR δ 1.29−1.32 (m, 18H), 2.76 (ddd, J = 2.1, 6.0, 14.3 Hz, 1H), 2.96 ("quint", J = 6.8 Hz, 1H), 3.15−3.25 (m, 1H), 4.34 ("quint", J = 6.8 Hz, 2H), 4.65−4.74 (m, 2H), 4.85−4.90 (m, 1H), 5.00 (br s, 2H), 5.84−5.86 ("d", 1H), 6.38−6.43 (m, 1H), 7.30 (s, 2H), 7.44−7.55 (m, 4H), 7.58−7.69 (m, 2H), 7.85 (s, 1H), 8.04 (d, J = 7.1 Hz, 2H), 8.11 (d, J = 7.1 Hz, 2H); LRMS *m*/*z* 742 (MH^+ [$C_{39}H_{44}N_5O_8S$] = 742), 764 (MNa^+ [$C_{39}H_{43}N_5O_8SNa$] = 764); HRMS *m*/*z* 764.2730 (MNa^+ [$C_{39}H_{43}N_5O_8SNa$] = 764.2730).

2-Amino-9-(3,5-di-*O*-benzoyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl)-6-*O*-(4-methylbenzenesulfonyl)purine (2′b). Et_3N (700 μL, 506 mg, 5.0 mmol) was added to a stirred solution of **1b** (1.43 g, 3.0 mmol), TsCl (858 mg, 4.5 mmol), and DMAP (36 mg, 0.3 mmol) in dried $CHCl_3$ (45 mL) under N_2. Stirring was continued for 15 h, and volatiles were evaporated. The slightly yellow residue was chromatographed (CH_2Cl_2/MeOH) to give **2′b** (1.68 g, 89%) as a white solid foam: UV λ_{max} 300 nm; ^{1}H NMR (DMSO-d_6) δ 2.43 (s, 3H), 2.73 (ddd, J = 2.1, 8.4, 14.4 Hz, 1H), 3.17−3.27 ("quint", J = 7.2 Hz, 1H), 4.52−4.65 (m, 3H), 5.76−5.78 ("d", 1H), 6.37−6.41 (m, 1H), 6.95 (br s, 2H), 7.47−7.73 (m, 8H), 7.95 (d, J = 7.8 Hz, 2H), 8.03−8.11 (m, 4H), 8.30 (s, 1H); LRMS *m*/*z* 630 (MH^+ [$C_{31}H_{28}N_5O_8S$] = 630), 652 (MNa^+ [$C_{31}H_{27}N_5O_8SNa$] = 652); HRMS *m*/*z* 652.1467 (MNa^+ [$C_{31}H_{27}N_5O_8SNa$] = 652.1478).

9-(3,5-Di-*O*-acetyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl)-2-chloro-6-*O*-(2,4,6-triisopropylbenzenesulfonyl)purine (3a). Method 2. A solution of AcCl (200 μL, 220 mg, 2.8 mmol) in dried CH_2Cl_2 (12 mL) under N_2 was chilled in a NaCl/ice/H_2O bath (−5 to 0 °C) for 15 min. BTEA-NO_2 (520 mg, 2.2 mmol) was dissolved in dried CH_2Cl_2 (8 mL), and this solution was immediately added dropwise to the cold, stirred solution of AcCl/CH_2Cl_2. A solution of **2a** (288 mg, 0.5 mmol) in dried CH_2Cl_2 (5 mL) was then added dropwise to the cold solution and stirring was continued for 5 min (TLC, 95:5 CH_2Cl_2/MeOH, showed complete conversion of **2a** into a single product). The reaction mixture was added dropwise at a rapid rate to a cold (ice/H_2O bath), vigorously stirred mixture of saturated $NaHCO_3$/

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H_2O (100 mL)//CH_2Cl_2 (100 mL). The layers were separated, and the organic phase was washed with cold (0 °C) H_2O (2 × 100 mL) and dried ($MgSO_4$) for 1 h. Volatiles were evaporated, and the residue was chromatographed (CH_2Cl_2/MeOH) to give **3a** (267 mg, 89%) as a white solid foam: UV λ_{max} 240, 266 nm, λ_{min} 255 nm; ^{1}H NMR (500 MHz) δ 1.24−1.31 (m, 18H), 2.08 (s, 3H), 2.13 (s, 3H), 2.67 (ddd, J = 2.5, 7.0, 15.5 Hz, 1H), 2.76−2.81 (m, 1H), 2.90−2.96 ("quint", J = 7.0 Hz, 1H), 4.28−4.33 ("quint", J = 7.0 Hz, 2H), 4.35−4.39 (m, 3H), 5.38−5.39 ("d", 1H), 6.42−6.45 (m, 1H), 7.22 (s, 2H), 8.23 (s, 1H); LRMS m/z 637 (MH^+ [$C_{29}H_{38}ClN_4O_8S$] = 637); HRMS m/z 659.1902 (MNa^+ [$C_{29}H_{37}ClN_4O_8SNa$] = 659.1918).

9-(3,5-Di-*O*-benzoyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl)-2-chloro-6-*O*-(2,4,6-triisopropylbenzenesulfonyl)purine (3b). The treatment of **2b** (1.20 g, 1.6 mmol) by method 2 gave **3b** (1.10 g, 90%) as a yellow solid foam: UV λ_{max} 230, 266 nm, λ_{min} 255 nm; ^{1}H NMR δ 1.22−1.34 (m, 18H), 2.92−3.00 (m, 3H), 4.30−4.34 (m, 2H), 4.68−4.77 (m, 3H), 5.80−5.82 ("d", 1H), 6.54−6.57 (m, 1H), 7.42−7.64 (m, 8H), 8.00 (d, J = 8.4 Hz, 2H), 8.10 (d, J = 8.4 Hz, 2H), 8.26 (s, 1H); HRMS m/z 783.2224 (MNa^+ [$C_{39}H_{41}ClN_4O_8SNa$] = 783.2231).

9-(3,5-Di-*O*-benzoyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl)-2-chloro-6-*O*-(4-methylbenzenesulfonyl)purine (3′b). Treatment of **2′b** (1.45 g, 2.3 mmol) by method 2 gave **3′b** (1.30 g, 87%) as a slightly yellow foam: UV λ_{max} 267 nm, λ_{min} 255 nm; ^{1}H NMR (DMSO-d_6) δ 2.45 (s, 3H), 2.86 (ddd, J = 3.4, 6.2, 14.0 Hz, 1H), 3.21−3.30 ("quint", J = 7.0 Hz, 1H), 4.55−4.67 (m, 3H), 5.82−5.84 (m, 1H), 6.56−6.61 (m, 1H), 7.42−7.72 (m, 8H), 7.88 (d, J = 7.8 Hz, 2H), 8.04−8.07 (m, 4H), 8.88 (s, 1H); HRMS m/z 671.0983 (MNa^+ [$C_{31}H_{25}ClN_4O_8SNa$] = 671.0979).

9-(3,5-Di-*O*-acetyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl)-2-amino-6-chloropurine (5a). Method 3. A mixture of **1a** (540 mg, 1.54 mmol), BTEA-Cl (710 mg, 3.1 mmol), *N*,*N*-dimethylaniline (215 μL, 206 mg, 1.7 mmol), and $POCl_3$ (720 μL, 1.2 g, 7.7 mmol) in MeCN (6 mL) was stirred in a preheated oil bath (85 °C) for 10 min. Volatiles were flash evaporated immediately (in vacuo), and the yellow foam was dissolved ($CHCl_3$, 15 mL) and stirred vigorously with crushed ice for 15 min. The layers were separated, and the aqueous phase was extracted ($CHCl_3$, 3 × 5 mL). Crushed ice was frequently added to the combined organic phase, which was washed [ice/H_2O (3 × 5 mL), 5% $NaHCO_3$/H_2O (to pH ∼7)] and dried ($MgSO_4$). Volatiles were evaporated, and the residue was chromatographed (CH_2Cl_2/MeOH) to give **5a**[36,37] (517 mg, 90%) as a white solid foam: UV λ_{max} 248, 310 nm, λ_{min} 268 nm; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.02 (s, 3H), 2.08 (s, 3H), 2.49−2.52 (m, 1H), 3.04−3.06 (m, 1H), 4.20−4.29 (m, 3H), 5.32−5.34 ("d", 1H), 6.23−6.26 (m, 1H); 7.03 (br s, 2H), 8.35 (s, 1H); ^{1}H NMR δ 2.03 (s, 3H), 2.08 (s, 3H), 2.51 (ddd, J = 2.7, 5.9, 14.2 Hz, 1H), 2.85−2.94 ("quint", J = 7.1 Hz, 1H), 4.28−4.42 (m, 3H), 5.35−5.37 (m, 1H), 6.21−6.26 (m, 1H), 7.89 (s, 1H); HRMS (EI) m/z 369.0844 (M^+ [$C_{14}H_{16}ClN_5O_5$] = 369.0840).

2-Amino-9-(3,5-di-*O*-benzoyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl)-6-chloropurine (5b). Treatment of **1b** (2.38 g, 5 mmol) by method 3 gave **5b** (2.10 g, 85%) as a slightly yellow solid foam: UV λ_{max} 310 nm; ^{1}H NMR (DMSO-d_6) δ 2.69−2.78 ("ddd", 1H), 3.20−3.24 ("quint", J = 7.2 Hz, 1H), 4.56−4.67 (m, 3H), 5.77−5.79 ("d", 1H), 6.39−6.44 (m, 1H), 7.02 (br s, 2H), 7.48−7.71 (m, 6H), 7.96 (d, J = 8.4 Hz, 2H), 8.06 (d, J = 8.7 Hz, 2H), 8.37 (s, 1H); LRMS m/z 494 (MH^+ [$C_{24}H_{21}ClN_5O_5$] = 494); HRMS m/z 516.1042 (MNa^+ [$C_{24}H_{20}ClN_5O_5Na$] = 516.1051).

9-(3,5-Di-*O*-acetyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl)-2,6-dichloropurine (6a). Treatment of **5a** (265 mg, 0.7 mmol) by method 2 gave **6a**[38] (266 mg, 95%) as a white solid foam: UV λ_{max} 274 nm, λ_{min} 232 nm; ^{1}H NMR (500 MHz) δ 2.12 (s, 3H), 2.15 (s, 3H), 2.73 (ddd, J = 2.4, 5.9, 14.2 Hz, 1H), 2.83−2.86 (m, 1H), 4.38−4.39 (m, 3H), 5.41−5.42 ("d", 1H), 6.45−6.50 (m, 1H), 8.33 (s, 1H); HRMS m/z 411.0230 (MNa^+ [$C_{14}H_{14}Cl_2N_4O_5Na$] = 411.0239).

9-(3,5-Di-*O*-benzoyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl)-2,6-dichloropurine (6b). Treatment of **5b** (407 mg, 0.8 mmol) by method 2 gave **6b** (386 mg, 91%) as a slightly yellow solid foam: UV λ_{max} 274 nm, λ_{min} 257 nm; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.87 (ddd, J = 3.5, 8.0, 17.5 Hz, 1H), 3.25−3.31 (m, 1H), 4.57−4.71 (m, 3H), 5.83−5.85 ("d", 1H), 6.59−6.62 (m, 1H), 7.46−7.72 (m, 6H), 7.91 (d, J = 7.5 Hz, 2H), 8.09 (d, J = 7.5 Hz, 2H), 8.96 (s, 1H); HRMS m/z 535.0562 (MNa^+ [$C_{24}H_{18}Cl_2N_4O_5Na$] = 535.0552).

2-Chloro-2′-deoxyadenosine (Cladribine, 4). Method 4. NH_3/MeOH (12 mL, saturated at 0 °C) was added to a solution of **3a** (159 mg, 0.25 mmol) in CH_2Cl_2 (8 mL) in a pressure tube. The tube was sealed and immediately immersed in an oil bath preheated to 80 °C. Heating (80 °C) was continued for 7 h, and volatiles were evaporated. The residue was dissolved (H_2O, 2 mL), the solution was applied to a column of Dowex 1X2 (OH^-, 20 mL), and the flask was rinsed (H_2O, 5 mL) and applied to the column. The column was washed (H_2O) until the pH of the eluate was neutral and then MeOH/H_2O (1:1) was applied. UV-absorbing fractions were pooled, and volatiles were evaporated. EtOH (3 × 10 mL) was added and evaporated, and the residue was dried (in vacuo) to give **4** (58 mg, 81%). The white powder was recrystallized from MeOH to give **4** (2 crops, 84% recovery) with a mp > 300 °C (crystals slowly became brown at ∼220 °C) or from H_2O (2 crops, 72% recovery) with a mp > 300 °C (lit. softening at 210−215 °C[17] and then dec; >300 °C;[19,22] 232 °C[23]); UV, ^{1}H NMR, and MS data were in agreement with published values.[22,23] Anal. Calcd for $C_{10}H_{12}ClN_5O_3$: C, 42.04; H, 4.23; N, 24.51. Found: C, 41.85; H, 4.40; N, 24.46.

Treatment of **3b** (83%), **3′b** (43%), **6a** (87%), or **6b** (94%) by method 4 gave **4** as white, TLC-homogeneous powders with identical spectral data.

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Supporting Information Available: ^{1}H NMR spectra of compounds **2a**, **2b**, **2′b**, **3a**, **3b**, **3′b**, **5b**, and **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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