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Regiospecific and Highly Stereoselective Coupling of 6-(Substituted-imidazol-1-yl)purines with 2-Deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl Chloride. Sodium-Salt Glycosylation in Binary Solvent Mixtures: Improved Synthesis of Cladribine[1]

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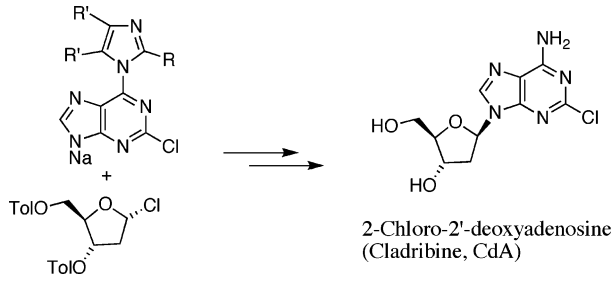

Glycosylation of 6-(substituted-imidazol-1-yl)purine sodium salts with 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl chloride proceeds with regiospecific formation of the N9 isomers. Base substrates with lipophilic substituents on the C6-linked imidazole moiety are more soluble in organic solvents, and the solubility is further increased with binary solvent mixtures. Selective solvation also diminishes the extent of anomerization of the chlorosugar. Stirred reaction mixtures of the modified-purine sodium salts generated in a polar solvent and cooled solutions of the protected 2-deoxysugar chloride in a nonpolar solvent give 2′-deoxynucleoside derivatives with N9 regiochemistry and enhanced β/α configuration ratios. Application of the binary-solvent methodology with 2-chloro-6-(substituted-imidazol-1-yl)purine salts in cold acetonitrile and the chlorosugar in cold dichloromethane gives essentially quantitative yields of the N9 isomers of β-anomeric 2′-deoxynucleoside intermediates. Direct ammonolysis (NH_3/MeOH) of such intermediates or benzylation of the imidazole ring followed by milder ammonolysis of the imidazolium salt gives high yields of the clinical anticancer drug cladribine (2-chloro-2′-deoxyadenosine).

Introduction

The deaminase-resistant drug cladribine[2] (2-chloro-2′-deoxyadenosine, CdA), a close analogue of 2′-deoxyadenosine, is used for treatment of patients with hairy cell leukemia. Complete clinical responses at the 85% level have been reported,[3] and CdA also has been employed for treatment of other neoplasms[4] including acute myelogenous leukemia,[5] chronic lymphatic leukemia,[6] chronic myelogenous leukemia, cutaneous T-cell lymphoma,[7] and non-Hodgkin's lymphoma.[8] Clinical investigations with CdA for treatment of multiple sclerosis, systemic lupus erythematosis-associated glomerulonephritis, and other rheumatoid and immune disorders are in progress.[9]

One approach for the synthesis of CdA involves transformation of natural nucleosides. Chen[10] prepared CdA in eight steps from guanosine (2.8% overall yield). We[11] have reported concise

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syntheses of CdA from 2′-deoxyguanosine (64−75% overall) by conversion of the 6-oxo group to Cl or arylsulfonyloxy, diazotization/chloro-dediazoniation at C2, and ammonolysis at C6 with concomitant deprotection of the sugar moiety. Enzymatic glycosyl transfer methods for the preparation of CdA have been developed.[12]

Several synthetic sequences have employed purine-sugar coupling procedures. A Fischer-Helferich synthesis of 2′-deoxynucleosides reported in 1960[13] included 2-chloro-2′-deoxyadenosine as an intermediate. Ikehara and Tada also employed CdA as an intermediate for the preparation of 2′-deoxyadenosine in a sequence that involved coupling of a mercury salt of 2,8-dichloroadenine with a xylofuranosyl chloride derivative and desulfurization of a late-stage 8,2′-anhydro-9-(β-D-arabinofuranosyl)-2-chloro-8-thioadenine cyclonucleoside.[14]

Our first synthesis of cladribine for biological activity evaluations involved fusion coupling of 2,6-dichloropurine with 1,3,5-tri-*O*-acetyl-2-deoxy-α-D-*erythro*-pentofuranose.[2a] Ammonolysis of the anomeric mixture resulted in regiospecific replacement of the chloride at C6 and concomitant cleavage of the sugar esters to give CdA and its α-isomer. Reacylation of that mixture with *p*-toluoyl chloride, chromatographic separation of the anomers, and deprotection gave CdA (16% overall).[2b] Fusion of 2,6-dichloropurine and methyl 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-D-*erythro*-pentofuranoside gave a mixture of anomers that was processed to give CdA (8% overall).[2b]

The purine sodium-salt glycosylation method for industrial production of CdA was devised by Robins et al.[15] It gives good β/α anomeric stereoselectivity but variable selectivity for the N9 versus N7 purine regioisomers. The resulting mixtures of four regio- and diastereoisomers with similar chromatographic mobilities can be difficult to separate, which can diminish the yields of pure CdA. In the original procedure,[15a] the sodium salt of 2,6-dichloropurine and 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl chloride were coupled in acetonitrile to give β anomers of the N9 (59%) and N7 (13%) regioisomers (yields of the α anomers were not reported). Hildebrand and Wright[16] reported yields of 9-β- (50%), 9-α- (1.5%), and 7-β- (15%). The ambident character of purine sodium salts (N9 and N7 of the imidazole ring and sometimes N3 of the pyrimidine) results in formation of regioisomers in the absence of demanding steric and/or electronic effects. Chromatographic separation followed by heating the protected 9-β isomer in methanolic ammonia at 100 °C gave CdA in 42% overall yield.

Gupta and Munk[17] prepared CdA by coupling the potassium salt of 2-chloro-6-*N*-(heptanoyl)adenine and the 2-deoxy chlorosugar derivative in THF, which reduced the amount of N7 regioisomer and enhanced β-anomer formation. Kazimierczuk and Kaminski[18] examined couplings of 2-chloro-6-substituted (e.g., alkoxy, halo, alkylthio) purine derivatives with 2-deoxy-3,5-di-*O*-aroyl-α-D-*erythro*-pentofuranosyl chlorides in the presence of alkali metal hydrides or hydroxides and phase-transfer catalysts, but formation of N7 regioisomers persisted. Gerszberg and Alonso[19] used the sodium-salt method with acetone as solvent, and high stereoselectivity was achieved by careful control of reaction times. The overall yield of CdA was low (30% based on 2-chloroadenine), which can be attributed to the meager solubility of purine sodium salts in acetone. It might be possible that the noted regioselectivity enhancement was augmented by hydrogen bonding of acetone with the purine 6-amino group to create steric congestion in the space proximal to N7. A clear need exists for cost-effective and selective methods for the preparation of CdA.

We reasoned that improvements in the regioselectivity for N9 isomer formation as well as enhancements of β anomeric stereoselectivity might be achieved by alteration of the lipophilic properties of the purine bases and selective solvation of reactants in mixed-solvent reaction media. We recently reported methods for the preparation of 6-(substituted-imidazol-1-yl)purines from readily available purines and purine nucleosides;[20] such purine acceptors undergo regiospecific N9 glycosylation with furanosyl and pyranosyl sugar donors.[21] We now report improved coupling methodology that gives N9 regiospecific glycosylation of 6-(substituted-imidazol-1-yl)purines with 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl chloride in binary solvent mixtures. We show that solvent combinations exert a powerful influence on the stereoselectivity of glycosylation with an activated sugar derivative that does not have a participating group adjacent to the anomeric center and describe examples of efficient coupling syntheses of cladribine.

Results and Discussion

Lewis acid catalyzed glycosylations with peracylated sugars are believed to occur via S_N1-related mechanisms with accompanying anchimeric assistance by a neighboring acyl group at C2. Stepwise or concerted formation of a bicyclo[*n*.3.0] cationic bridge involving the C1−C2 bond of the sugar ring directs the approach of incoming nucleophiles from the side opposite to the fused acyloxonium ring, which usually results

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in highly stereoselective diastereomer formation. However, the absence of a stereodirecting group at C2 allows formation of α/β anomeric mixtures, which are obtained in syntheses of 2′-deoxynucleosides unless stereocontrol is achieved by other means. A partial solution to the problem was realized by the discovery[22] that 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl chloride crystallized selectively from anomeric mixtures of the glycosyl halide. Displacements of the S_N2-type resulting from treatment of the α-chloro sugar with the sodium salt of certain purines or silyl ethers of some pyrimidines give the β-anomer of 2′-deoxynucleosides with high stereoselectivity. However, the selectivity varies markedly with the nature of the heterocyclic base, the countercation, and reaction conditions (e.g., solvent, temperature, time), and solvent polarity is a major factor. Hubbard et al.[23] evaluated changes in the anomeric composition of the noted 2-deoxysugar chloride in different solvents at various times and temperatures. They observed that nonpolar solvents decreased rates of anomerization and decomposition of the chlorosugar, whereas solutions in polar solvents (such as DMF) underwent rapid anomerization, even at reduced temperatures. Also, the rates of glycosylation with the β-anomer of the chlorosugar are higher. Unfortunately, purine sodium salts are virtually insoluble in nonpolar solvents. Miniscule purine-salt concentrations severely limit the rates of S_N2 glycosylation in two-phase solution/salt mixtures; anomerization of the chlorosugar becomes increasingly problematic with time. Purine salts have slightly increased solubility in the more polar acetone, but yields were low to moderate;[19,24] stereoselective glycosylations of 7-deazapurines with 5-deoxy-2,3-*O*-isopropylidene-α-D-ribofuranosyl chloride in toluene were effected with phase transfer catalysis.[25]

We first mixed a purine sodium salt in DMF or acetonitrile (ACN) with a solution of 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl chloride in DMF or ACN. Nearly equal amounts of α- and β-anomers were formed, in harmony with prior studies. Changes in temperature, reactant structure, and reaction media were examined to evaluate effects on yields and anomeric compositions. Lower temperatures decreased the chlorosugar anomerization rate and gave slightly higher β/α coupling ratios. Purine-salt solubility in nonpolar solvents was increased by introduction of lipophilic substituents.[20] Binary solvent combinations were used to fine-tune the average dielectric constant of reaction media and promote preferential solvation of the reactants[26] (a nonpolar chlorosugar and a polar purine salt).

The highly polar 6-(1,2,4-triazol-4-yl)purine (**1a**) (Scheme 1) was virtually insoluble in solvents other than DMF (and ACN to a smaller extent). Suspensions of the sodium salt of **1a** (generated with NaH in DMF or ACN) were mixed with solutions of the chlorosugar **2**, and the reaction mixtures were stirred at ambient temperature [lower temperatures gave minor increases in β/α anomer (**3a**/**4a**) ratios]. Isolated yields of (**3a** + **4a**) were about 50%, with exclusive formation of N9 regioisomers but little β-anomer stereoselectivity (Table 1, entries 1−3). Coupling of the sodium salt of 6-(imidazol-1-yl)-purine (**1b**) and **2** in polar solvents gave similar results (entries 4−6), but >5:1 β/α stereoselectivity was observed with the sodium salt of **1b** in ACN and **2** in toluene (entry 7). Glycosylation of the sodium salt of the more lipophilic 6-(2-propylimidazol-1-yl)purine[20] (**1c**) in DMF with **2** in DMF gave **3c** and **4c** with the α-anomer formed in excess (entry 8). A parallel reaction with ACN as solvent for both components gave **3c**/**4c** (∼4:1) (entry 9), whereas the salt of **1c** in ACN and **2** in toluene gave **3c** and **4c** with >30:1 β/α stereoselectivity (entry 10). Mixing the sodium salt of **1c** in ACN and **2** in DCM (both at 0 °C) gave the N9-linked β anomer **3c** as the only product detected (^{1}H NMR before chromatography). Thus, the composition of the binary mixture with a nonpolar solvent for the chlorosugar was the most important factor, followed by solubility enhancement with more lipophilic[20] purine salts. Only minor variations in yields and anomeric ratios of the glycosylation products were observed with the sodium salts of 6-(2-propyl-, butyl-, or pentylimidazol-1-yl)purines under our standard conditions. However, remarkably inferior results were obtained with the 6-(2-hexyl- and dodecylimidazol-1-yl)purines. It might be possible that analogues with longer alkyl side-chains undergo self-association that impedes coupling processes. However, regiospecific N9 glycosylation occurred with the longer-chain analogues as well as with the more favorable purine substrates.

A polar solute interacts differently with each component of a solvent mixture, and solvent compositions in the immediate vicinity of a solute differ from the bulk solvent composition. Wilson[27] proposed a local composition (LC) model to describe microscopic solution structures, and the LC model has been used

SCHEME 1. Sodium Salt Glycosylations of 6-(Heteroaryl)purines with 2

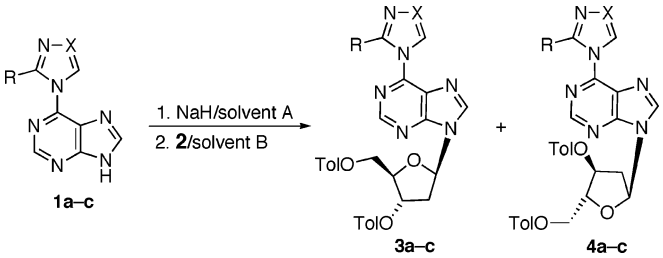

TABLE 1. Glycosylation Stereoselectivity[a]

entry[b]	solvents[c]	X	R	(**3**:**4**)[d]
1 (**1a**)	DMF/DMF	N	H	∼1:1
2 (**1a**)	ACN/ACN	N	H	<1:1
3 (**1a**)	DMF/ACN	N	H	∼2.5:1
4 (**1b**)	DMF/DMF	CH	H	<1:1
5 (**1b**)	ACN/ACN	CH	H	<1:1
6 (**1b**)	DMF/ACN	CH	H	∼1:1
7 (**1b**)	ACN/toluene	CH	H	>5:1
8 (**1c**)	DMF/DMF	CH	Pr	<1:1
9 (**1c**)	ACN/ACN	CH	Pr	∼4:1
10 (**1c**)	ACN/toluene	CH	Pr	>30:1
11 (**1c**)	ACN/DCM	CH	Pr	*e*

[a] See Experimental Section for details. [b] Starting material in parentheses. [c] Solvents (A/B); ACN = acetonitrile, DCM = dichloromethane. [d] By ^{1}H NMR. [e] Only β-anomer was detected (solutions of both **1c** and **2** were at 0 °C).

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SCHEME 2. Glycosylation of Purine Sodium Salts with 2

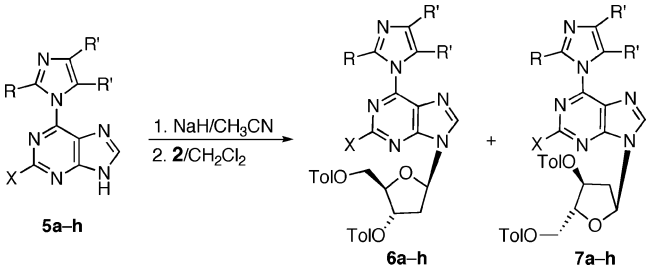


TABLE 2. Glycosylation Stereoselectivity and Yield[a]

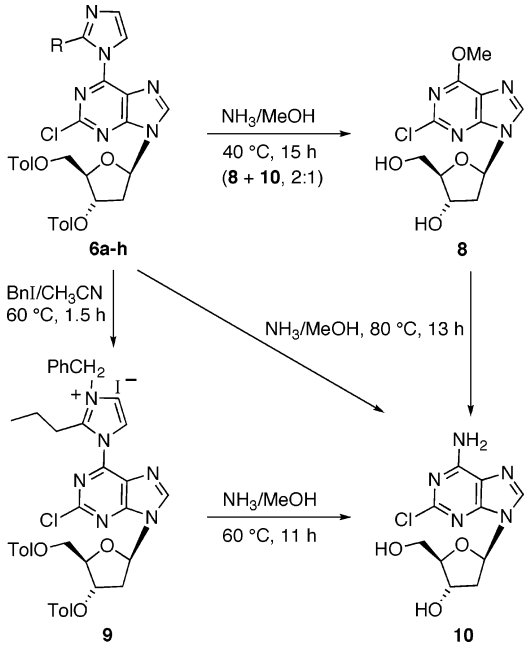
entry[b]	X	R	R′	(**6**:**7**)[c]	(**6** + **7**)[d]
1 (**5a**)	Cl	H	H	65:35	71
2 (**1c**)	H	Pr	H	*e*,*f*	57[f]
3 (**5b**)	Cl	Pr	H	*e*	95
4 (**5c**)	Cl	^{i}Pr	H	98:2	∼100
5 (**5d**)	Cl	Bu	H	96:4	86
6 (**5e**)	Cl	Pent	H	98:2	∼100
7 (**5f**)	Cl	2-PhPr	H	98:2	∼99
8 (**5g**)	Cl	$PhCH_2$	H	98:2	85
9 (**5h**)	Cl	H	Ph	*e*	∼100

[a] See Experimental Section for details. [b] Starting materials in parentheses. [c] By ^{1}H NMR. [d] Isolated % yield (relative to **1** or **5**). [e] Only β-anomer detected. [f] Product was **3c**.

extensively to correlate vapor−liquid equilibrium data for binary and multicomponent mixtures. Deng et al.[28] reported correlations of ^{1}H NMR chemical shifts of binary mixtures with compositions based on the LC model. Preferential solvation of reaction species can result in altered free energies of activation,[29] which can change the ratios of two competitive pathways. Preferential solvation can increase the solubility of a polar solute, and such "cosolvent effects" have been demonstrated most dramatically in supercritical binary mixtures.[30]

We reasoned that the use of appropriate solvent mixtures might result in enhanced LC solvation of polar regions of our purine sodium salts by a polar solvent and preferential solvation of lipophilic regions of the purine substituent, as well as the chlorosugar, by less polar LC environments in binary solvent mixtures. Although the dielectric constant of toluene is lower than that of DCM,[31] the dipolarity/polarizability and hydrogen-bond-donor acidity of DCM are significantly greater than those of toluene.[32] DCM is a better solvent than toluene for purine salts as well as for the chlorosugar **2**, and it is easily evaporated. Therefore, DCM was chosen as the low polarity solvent for **2**, and ACN was used for sodium salt glycosylations with the 2-chloro-6-(substituted-imidazol-1-yl)purines (**5**) (Scheme 2, Table 2) that might provide convenient access to cladribine. After completion of our solvent-effect studies,[33] Bauta et al. reported empirical combinations of additives, bases, and solvents for an improved synthesis of clofarabine [6-amino-2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)purine].[34]

SCHEME 3. Transformation of Intermediates 6 into 10



Highly stereoselective coupling was observed with the purine acceptors with lipophilic substituents on the appended imidazole ring (entries 2−9). The poor β/α coupling stereoselectivity (∼1.9:1, entry 1) observed with 2-chloro-6-(imidazol-1-yl)purine (**5a**) might result from the decreased solubility of the sodium salt of **5a** and/or a less favorable LC environment. Glycosylation of **1c** (entry 2) (no 2-chloro substituent on the purine ring) was highly stereoselective and the reaction was complete (TLC), although a moderate isolated yield of **3c** was obtained. Exclusive formation of N9 regioisomers was observed with all of the coupling products (^{1}H NMR) in agreement with our prior results.[21] It is noteworthy that the β-anomeric N9-regioisomer **6h** was the only coupling product detected in the glycosylation of **5h** with **2**. The X-ray crystal structure of a nucleoside derivative of **5h** showed a dihedral projection angle of ∼57° between the planes of the C6-linked-purine and imidazole rings,[20] and alkylation of **5h** with iodoethane gave a minor amount of the N7 regioisomer in addition to the major 9-ethyl product.[33]

We next turned our attention to transformations of the intermediates **6** into cladribine. We have previously noted that treatment of 6-(imidazol-1-yl)purine nucleosides with NH_3/MeOH at ambient temperature resulted in retention of the imidazoyl group.[21] Heating such solutions at 100 °C (pressure vessel) effected slow displacement of imidazole with accompanying formation of 6-methoxypurine derivatives. The more electrophilic 2-chloropurine analogue **6b** underwent S_NAr displacements with NH_3/MeOH at 40 °C (15 h) to give the 2-chloro-6-methoxypurine nucleoside **8** plus cladribine (**10**) (∼2:1, respectively) (Scheme 3). Heating **6b** with NH_3/MeOH at 80 °C gave **10** plus 2-propylimidazole (1:1), which were not readily separated by chromatography. Higher reaction temperatures (≥100 °C) caused loss of 2-chloroadenine from **10**. Thus, the 2-propylimidazole group at C6 is replaced more readily by a methoxyl group,[21] which undergoes ammonolysis. Such a

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2-chloro-6-methoxypurine → 6-amino-2-chloropurine transformation had been reported with a riboside derivative.[35] Neither selective crystallization of **10** nor extraction of 2-propylimidazole into an organic phase was successful. However, quantitative ammonolysis of **6e** (TLC), evaporation of volatiles, and extraction of the more lipophilic 2-pentylimidazole into DCM gave **10** (70%) as a colorless powder. Additional **10** (15%) was recovered from the DCM extract by chromatography/extraction.

Although quantitative ammonolysis of the 2-chloro-6-(substituted-imidazol-1-yl)purine intermediates (TLC) completed our successful synthesis of cladribine, this step remained problematic with analogues lacking the 2-chloro substituent. Imidazolium (pK_a ~7) is known to be far superior to imidazole (pK_a ~14.5) as a leaving group;[36] we reasoned that activation of a 6-(imidazol-1-yl) group by alkylation would both increase the S_NAr ammonolysis rate and produce an organic-soluble byproduct. Methylation of the imidazole moiety did not proceed to completion, but treatment of 9-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)-2-chloro-6-(2-propylimidazol-1-yl)purine[20] with benzyl iodide (generated in situ with $PhCH_2Cl$ and NaI in ACN) gave the 3-benzyl-2-propylimidazolium iodide. Ammonolysis of that salt (NH_3/MeOH, 60 °C, 4 h) gave 2-chloroadenosine (50% after chromatography and recrystallization).

The activation strategy also was successful for syntheses of **10**. In situ benzylation of **6** → **9** was complete, except with **6c** and **6h** (darkening and some decomposition occurred with **6a**). Ammonolysis of **9** liberated 1-benzyl-2-propylimidazole and cleaved the toluoyl esters to give **10** (optimization of **5b** → **6b** → **9** → **10** gave purified cladribine in >90% yield). Chromatography was used routinely for purification of **10**, but polarity differences for extraction workup are much greater with the 2-alkyl-1-benzylimidazoles than with the 2-alkylimidazole byproducts.

Summary and Conclusions

We have described new 6-(substituted-imidazol-1-yl)purines that undergo regiospecific glycosylation at N9. An approach to highly stereoselective glycosylation of 6-(substituted-imidazol-1-yl)purine sodium salts with 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl chloride in binary solvent mixtures (purine salt/acetonitrile and chlorosugar/dichloromethane) gives *β*-anomeric N9 regioisomers in good to high yields. Ammonolysis (NH_3/MeOH) produces the nucleosides directly. Benzylation of the imidazole moiety at C6 followed by ammonolysis of the resulting imidazolium salt permits S_NAr displacement of the 2-alkyl-1-benzylimidazole leaving groups under milder conditions. Application of these procedures to the synthesis of cladribine (2-chloro-2′-deoxyadenosine) provides the purified clinical anticancer drug in >90% overall yields.

Experimental Section[37]

The starting 6-(substituted-imidazol-1-yl)purines were prepared and characterized as described.[20]

General Method 1. Glycosylation of 1a−1c with 2-Deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl Chloride (2) (Table 1). A mixture of the 6-(heteroaryl)purine **1a−1c** (1.0 mmol) and NaH (60 mg, 60% w/w dispersion, 1.5 mmol) in a dried polar solvent A was stirred at ambient temperature under a positive pressure of N_2 for 2 h. A solution of **2** (700 mg, 1.8 mmol) in a dried less-polar solvent B was added with a syringe, and the mixture was stirred for 22 h. Volatiles were evaporated in vacuo, and the composition of the residue was evaluated (^{1}H NMR). Some of the residues were chromatographed and isolated yields were determined.

General Method 2. Glycosylation of 1c, 5a−5h with 2-Deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl Chloride (2) (Table 2). A mixture of **1c** or the 2-chloro-6-(substituted-imidazol-1-yl)-purine **5a−5h** (1.0 mmol) and NaH (60 mg, 60% w/w dispersion, 1.5 mmol) in dried CH_3CN (10 mL) was stirred under N_2 at ambient temperature for 8 h, and the solution was cooled to 0 °C. A solution of **2** (700 mg, 1.8 mmol) in cold, dried CH_2Cl_2 (0 °C, 10 mL) was then added with a syringe. The reaction mixture was stirred for 22 h with gradual warming to ambient temperature. Volatiles were evaporated in vacuo, and the residue was chromatographed (25 g of silica gel; MeOH/CH_2Cl_2, 1:30).

2-Chloro-9-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α/*β*-D-*erythro*-pentofuranosyl]-6-(imidazol-1-yl)purine (6a/7a). ^{1}H NMR (300 MHz) *δ* 6.66 (dd, *J* = 5.8, 1.8 Hz, 1H, H1′ of the α anomer), 6.58 ("t", *J* = 6.8 Hz, 1H, H1′ of the *β* anomer).

2-Chloro-9-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-*β*-D-*erythro*-pentofuranosyl]-6-(2-propylimidazol-1-yl)purine (6b). Yield 83%; analytical sample (recrystallized from EtOAc): mp 192−193 °C; UV max 220, 239, 287 nm (*ϵ* 40 700, 38 300, 16 700), min 231, 265 nm (*ϵ* 35 900, 10 300); ^{1}H NMR (500 MHz) *δ* 8.52 (s, 1H), 8.27 (s, 1H), 8.00 (d, *J* = 7.8 Hz, 2H), 7.86 (d, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.28 (d, *J* = 7.8 Hz, 2H), 7.20 (s, 1H), 6.61 (t, *J* = 7.1 Hz, 1H), 5.82−5.83 (m, 1H), 4.68−4.84 (m, 3H), 3.29 (t, *J* = 7.8 Hz, 2H), 2.98−3.01 (m, 2H), 2.47 (s, 3H), 2.38 (s, 3H), 1.86 (sext, *J* = 7.5 Hz, 2H), 1.07 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz) *δ* 166.3, 166.2, 154.4, 153.4, 151.5, 148.2, 145.0, 144.7, 142.4, 130.1, 129.8, 129.61, 129.56, 129.2, 126.6, 126.4, 123.0, 120.6, 85.5, 83.8, 75.2, 64.1, 38.9, 33.1, 22.0, 21.9, 21.6, 14.3; HRMS *m/z* 637.1940 (MNa^+ [$C_{32}H_{31}ClN_6O_5Na$ = 637.1942]). Anal. Calcd for $C_{32}H_{31}ClN_6O_5$: C, 62.49; H, 5.08; N, 13.66. Found: C, 62.44; H, 5.18; N, 13.72.

A larger scale reaction with the sodium salt of **5b** (1.54 g, 5.87 mmol) in dried CH_3CN (100 mL) and **2** (3.74 g, 9.62 mmol) in dried CH_2Cl_2 (general method 2) for 5 h (complete by TLC) gave **6b** (3.42 g, 95%).

2-Chloro-9-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-*β*-D-*erythro*-pentofuranosyl]-6-(2-isopropylimidazol-1-yl)purine (6c). UV max 223, 241, 285 nm (*ϵ* 32 100, 35 400, 14 800), min 230, 265 nm (*ϵ* 30 300, 9200); ^{1}H NMR (500 MHz) *δ* 8.42 (d, *J* = 1.0 Hz, 1H), 8.26 (s, 1H), 7.99 (d, *J* = 7.8 Hz, 2H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 2H), 7.11 (d, *J* = 1.0 Hz, 1H), 6.60 (t, *J* = 6.8 Hz, 1H), 5.81 (br s, 1H), 4.78−4.83 (m, 1H), 4.67−4.71 (m, 2H), 4.08 (sept, *J* = 6.8 Hz, 1H), 2.97−3.01 (m, 2H), 2.46 (s, 3H), 2.37 (s, 3H), 1.43 (d, *J* = 6.8 Hz, 3H), 1.41 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz) *δ* 166.1, 166.0, 156.2, 154.2, 153.2, 148.2, 144.7, 144.4, 142.3, 129.9, 129.6, 129.4, 129.3, 128.8, 126.4, 126.3, 123.0, 120.4, 85.2, 83.6, 74.9, 63.9, 38.6, 28.8, 21.8, 21.6; HRMS *m/z* 637.1931 (MNa^+ [$C_{32}H_{31}ClN_6O_5Na$ = 637.1942]).

6-(2-Butylimidazol-1-yl)-2-chloro-9-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-*β*-D-*erythro*-pentofuranosyl]purine (6d). UV max 223, 241, 287 nm (*ϵ* 29 900, 33 400, 13 200), min 230, 265 nm (*ϵ* 28 100, 7500); ^{1}H NMR (500 MHz) *δ* 8.51 (s, 1H), 8.26 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.09 (s, 1H), 6.60 (t, *J* = 6.9 Hz, 1H), 5.80 (br s, 1H), 4.78−4.81 (m, 1H), 4.66−4.70 (m, 2H), 3.31 (t, *J* = 7.8 Hz, 2H), 2.97−3.00 (m, 2H), 2.46 (s, 3H), 2.37 (s, 3H), 1.80 (quint, *J* = 7.4 Hz, 2H), 1.50 (sext, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz) *δ* 166.1, 165.0, 154.1, 153.2, 151.4, 147.9, 144.7, 144.4, 142.2, 129.9, 129.5, 129.4, 129.3, 128.9, 126.4, 126.2, 122.7, 120.3, 85.2, 83.6, 74.9, 63.9, 38.6, 30.7, 30.1,

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(37) General experimental items are in Supporting Information.

22.6, 21.8, 21.7, 13.9; HRMS *m*/*z* 629.2270 (MH^+ [$C_{33}H_{34}ClN_6O_5$ = 629.2279]).

6-(2-Butylimidazol-1-yl)-2-chloro-9-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl]purine (7d). ^{1}H NMR (500 MHz) δ 8.59 (s, 1H), 8.41 (s, 1H), 7.97 (d, J = 8.3 Hz, 2H), 7.57 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.13−7.14 (m, 3H), 6.67 (dd, J = 6.4, 1.8 Hz, 1H), 5.72−5.73 (m, 1H), 4.96−4.97 (m, 1H), 4.62−4.70 (m, 2H), 3.31 (t, J = 7.8 Hz, 2H), 3.06−3.15 (m, 2H), 2.46 (s, 3H), 2.14 (s, 3H), 1.80 (quint, J = 7.4 Hz, 2H), 1.50 (sext, J = 7.4 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H).

2-Chloro-9-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl]-6-(2-pentylimidazol-1-yl)purine (6e). UV max 223, 241, 287 nm (ϵ 32 100, 34 700, 15 000), min 231, 265 nm (ϵ 30 000, 9300); ^{1}H NMR (500 MHz) δ 8.50 (s, 1H), 8.26 (s, 1H), 7.98 (d, J = 8.2 Hz, 2H), 7.84 (d, J = 7.9 Hz, 2H), 7.30 (d, J = 7.9 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 7.09 (s, 1H), 6.60 (t, J = 7.0 Hz, 1H), 5.80 (br s, 1H), 4.80−4.81 (m, 1H), 4.67−4.69 (m, 2H), 3.28−3.29 (m, 2H), 2.98−3.03 (m, 2H), 2.46 (s, 3H), 2.37 (s, 3H), 1.82 (quint, J = 7.6 Hz, 2H), 1.36−1.48 (m, 4H), 0.93 (t, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz) δ 166.04, 165.99, 154.1, 153.2, 151.5, 148.0, 144.7, 144.4, 142.2, 129.9, 129.5, 129.4, 129.3, 128.9, 126.4, 126.2, 122.7, 120.3, 85.2, 83.6, 75.0, 63.9, 38.6, 31.8, 31.0, 27.7, 22.5, 21.8, 21.7, 14.1; HRMS *m*/*z* 643.2426 (MH^+ [$C_{34}H_{36}ClN_6O_5$ = 643.2436]).

2-Chloro-9-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl]-6-{2-[2(*R*/*S*)-phenylpropyl]imidazol-1-yl}purine (6f). UV max 241, 285 nm (ϵ 33 300, 11 000), min 222, 266 nm (ϵ 27 200, 6900); ^{1}H NMR (500 MHz) δ 8.30 (8.28) (s, 1H), 8.22 (s, 1H), 7.98−8.00 (m, 2H), 7.85−7.89 (m, 2H), 7.18−7.31 (m, 4H), 7.06−7.12 (m, 5H), 6.90 (br s, 1H), 6.58−6.59 (m, 1H), 5.80 (s, 1H), 4.80−4.82 (m, 1H), 4.68−4.70 (m, 2H), 3.75−3.82 (m, 1H), 3.55−3.60 (m, 1H), 3.30−3.36 (m, 1H), 2.94−2.99 (m, 2H), 2.45 (s, 3H), 2.36 (s, 3H), 1.32 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz) δ 166.1, 166.0, 154.1, 153.0, 149.4, 149.3, 147.9, 145.9, 145.8, 144.7, 144.4, 142.3, 129.9, 129.6, 129.4, 128.9, 128.0, 127.01, 126.98, 126.5, 126.3, 125.7, 122.9, 120.6, 85.1, 83.6 (83.5), 74.9, 63.9, 39.6 (39.5), 38.6, 38.5, 21.8, 21.7, 20.8; HRMS *m*/*z* 691.2439 (MH^+ [$C_{38}H_{36}ClN_6O_5$ = 691.2436]).

6-(2-Benzylimidazol-1-yl)-2-chloro-9-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl]purine (6g). UV max 240, 289 nm (ϵ 35 900, 14 600), min 231, 266 nm (ϵ 33 500, 9300); ^{1}H NMR (500 MHz) δ 8.60 (s, 1H), 8.22 (s, 1H), 7.97 (d, J = 8.3 Hz, 2H), 7.83 (d, J = 9.0 Hz, 2H), 7.11−7.33 (m, 10H), 6.55 (t, J = 6.8 Hz, 1H), 5.77−5.78 (m, 1H), 4.77−4.80 (m, 3H), 4.64−4.68 (m, 2H), 2.92−2.94 (m, 2H), 2.45 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (125 MHz) δ 166.03, 165.96, 154.0, 153.0, 149.1, 147.5, 144.7, 144.4, 142.2, 137.4, 129.9, 129.5, 129.34, 129.31, 129.2, 129.1, 128.2, 126.4, 126.3, 126.2, 122.5, 120.9, 85.1, 83.5, 74.9, 63.9, 38.6, 36.8, 21.8, 21.7; HRMS *m*/*z* 663.2108 (MH^+ [$C_{36}H_{32}ClN_6O_5$] = 663.2123).

2-Chloro-9-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl]-6-(4,5-diphenylimidazol-1-yl)purine (6h). UV max 240, 275 nm (ϵ 53 400, 19 300), min 223, 270 nm (ϵ 42 000, 19 100); ^{1}H NMR (500 MHz) δ 8.97 (s, 1H), 8.25 (s, 1H), 7.97 (d, J = 7.9 Hz, 2H), 7.86 (d, J = 7.9 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 7.19−7.40 (m, 12H), 6.56 (t, J = 7.0 Hz, 1H), 5.77−5.78 (m, 1H), 4.76−4.79 (m, 1H), 4.65−4.69 (m, 2H), 2.92−2.96 (m, 2H), 2.45 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (125 MHz) δ 166.1, 165.9, 154.0, 153.2, 147.1, 144.7, 144.5, 142.8, 140.4, 139.2, 133.5, 131.0, 129.9, 129.6, 129.4, 129.3, 128.3, 128.2, 127.5, 127.2, 126.4, 126.2, 124.0, 85.1, 83.5, 74.9, 63.8, 38.6, 21.8, 21.7; HRMS *m*/*z* 747.2100 (MNa^+ [$C_{41}H_{33}ClN_6O_5Na$] = 747.2099).

2-Chloroadenosine.[35] **General Method 3.** A stock solution of benzyl iodide in acetonitrile (∼0.3 M) was prepared in situ by stirring NaI (15 g, 94 mmol) and BnCl (3.50 mL, 3.85 g, 30.4 mmol) in CH_3CN (100 mL) at ambient temperature. A sample of 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2-chloro-6-(2-propylimidazol-1-yl)purine[20] (890 mg, 1.71 mmol) was added to a stirred solution of BnI/CH_3CN (0.3 M, 70 mL, 21 mmol), and stirring was continued at 60 °C for 1.5 h. Volatiles were evaporated, and the residue was chromatographed ($MeOH/CH_2Cl_2$, 1:90 → 1:30) to give 1-[9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2-chloropurin-6-yl]-3-benzyl-2-propylimidazolium iodide: ^{1}H NMR (500 MHz) δ 8.97 (d, J = 2.0 Hz, 1H), 8.59 (s, 1H), 7.86 (d, J = 2.5 Hz, 1H), 7.43−7.51 (m, 5H), 6.37 (d, J = 5.5 Hz, 1H), 5.84 (t, J = 5.8 Hz, 1H), 5.80 (s, 2H), 5.58−5.60 (m, 1H), 4.45−4.54 (m, 3H), 3.70 (t, J = 7.5 Hz, 2H), 2.20 (s, 3H), 2.18 (s, 3H), 2.13 (s, 3H), 1.77 (sext, J = 7.8 Hz, 2H), 1.14 (t, J = 7.5 Hz, 3H); HRMS *m*/*z* 611.2026 (M^+ [$C_{29}H_{32}ClN_6O_7$] = 611.2021). This salt was stirred in NH_3/MeOH (∼26%, 50 mL) at 60 °C for 11 h (reaction complete, TLC). Volatiles were evaporated, and the residue was chromatographed ($MeOH/CH_2Cl_2$, 1:20 → 1:15) to give a solid (quantitative). Recrystallization (EtOH) gave the title compound (92 mg). Volatiles were evaporated from the mother liquor, and the residue was recrystallized (H_2O) to give additional product (255 mg, 50% total): UV max 212, 265 nm (ϵ 21 200, 13 300), min 230 nm (ϵ 2300); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.38 (s, 1H), 7.86 (br s, 2H), 5.81 (d, J = 6.1 Hz, 1H), 5.48 (d, J = 6.1 Hz, 1H), 5.21 (d, J = 4.9 Hz, 1H), 5.07 (dd, J = 6.4, 5.2 Hz, 1H), 4.51 (dd, J = 11.0, 6.1 Hz, 1H), 4.10−4.13 (m, 1H), 3.92−3.94 (m, 1H), 3.64−3.68 (m, 1H), 3.53−3.57 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.7, 152.9, 150.2, 139.9, 118.1, 87.2, 85.6, 73.5, 70.3, 61.3; HRMS *m*/*z* 301.0576 (M^+ [$C_{10}H_{12}ClN_5O_4$] = 301.0578).

Conversion of 6b to Cladribine[11] **(10) by General Method 3.** Intermediate **6b** (615 mg, 1.0 mmol) was added to BnI/CH_3CN (0.3 M, 40 mL, 12 mmol), and the mixture was stirred at 60 °C for 1.5 h. Volatiles were evaporated to give the residual benzylimidazolium iodide **9** (830 mg): ^{1}H NMR (500 MHz) δ 8.94 (s, 1H), 8.49 (s, 1H), 8.00 (d, J = 8.5 Hz, 2H), 7.88 (d, J = 8.0 Hz, 2H), 7.81 (s, 1H), 7.46−7.50 (m, 5H), 7.32 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 6.67 (t, J = 7.3 Hz, 1H), 5.75−5.85 (m, 3H), 4.71−4.82 (m, 3H), 3.67−3.74 (m, 2H), 2.99−3.02 (m, 2H), 2.47 (s, 3H), 2.42 (s, 3H), 1.75−1.81 (m, 2H), 1.17 (t, J = 7.5 Hz, 3H); HRMS *m*/*z* 705.2606 (M^+ [$C_{39}H_{38}ClN_6O_5$ = 705.2592]). This material was transferred into a pressure flask with a small volume of MeOH, cooled at −4 °C, and cold NH_3/MeOH (∼26%, 50 mL) was added. The sealed mixture was stirred and heated at 60 °C for 11 h. Volatiles were evaporated, and the residue was dissolved in H_2O and applied to a column of Dowex 1 × 2 (OH^-) resin packed in H_2O. The product was eluted (H_2O → MeOH/H_2O, 2:3) **rapidly** (MeO^- and HO^- can displace the 2-chloro group upon extended exposure) to give **10** (quantitative). A small sample of this homogeneous (TLC and ^{1}H NMR) product was recrystallized (EtOAc) to give analytically pure **10**: mp >300 °C; UV max 212, 265 nm (ϵ 24 000, 14 600), min 229 nm (ϵ 2000); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.36 (s, 1H), 7.83 (br, 2H), 6.26 (t, J = 6.7 Hz, 1H), 5.32 (d, J = 4.3 Hz, 1H), 4.97 (t, J = 5.5 Hz, 1H), 4.38 (s, 1H), 3.85 (s, 1H), 3.57−3.61 (m, 1H), 3.48−3.53 (m, 1H), 2.62−2.67 (m, 1H), 2.25−2.29 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.5, 153.6, 150.8, 140.5, 118.8, 88.6, 84.2, 71.4, 62.3, 38.0; HRMS *m*/*z* 285.0615 (M^+ [$C_{10}H_{12}ClN_5O_3$] = 285.0629). Anal. Calcd for $C_{10}H_{12}ClN_5O_3$: C, 42.04; H, 4.23; N, 24.51. Found: C, 41.87; H, 4.50; N, 24.39.

General Method 4. Direct Conversion of 6e to Cladribine (10). A solution of **6e** (350 mg, 0.55 mmol) in NH_3/MeOH (∼14%) was stirred at 80 °C for 13 h. Volatiles were evaporated, and the oily residue was extracted with CH_2Cl_2 (10 mL) to remove lipophilic byproducts. The resulting semisolid was dissolved in acetone (with small additions of MeOH if necessary), volatiles were evaporated, and the residue was allowed to crystallize (∼1 h). This material was extracted with CH_2Cl_2 (10 mL), and the ^{1}H NMR spectrum of the resulting white powder (113 mg, 70%) was identical to that of **10** prepared by general method 3. Additional **10** (24 mg, 15%; containing traces of the α anomer) was recovered from the combined CH_2Cl_2 extracts by chromatography (EtOAc → MeOH/EtOAc, 1:10) followed by extraction (CH_2Cl_2) of byproducts.

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Supporting Information Available: General experimental items and NMR spectra of compounds **6c**−**6h** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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