37. A Direct Route to 3-(D-Ribofuranosyl)pyridine Nucleosides

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A route for synthesizing *C*-nucleosides with 2,6-substituted pyridines as heterocyclic aglycones is described. Condensation of appropriately substituted lithiated pyridines with ribono-1,4-lactone derivatives yields hemiacetal **4a–g** (*Table 1*), which can be reduced by Et_3SiH and $BF_3 \cdot Et_2O$ to the corresponding *C*-nucleoside (see *Scheme 1* for **4d** → β-D-**5**). Conditions are presented that optimize the amount of the 2,6-dichloropyridine-derived β-D-anomer β-D-**5** formed (*Table 3*). Aminolysis of β-D-**5** yields the diaminonucleoside **14** (*Scheme 3*).

Introduction. – During studies of nucleoside analogs with novel H-bonding patterns [1], a route for the synthesis of *C*-nucleosides bearing a substituted pyridine ring as the heterocyclic aglycone was desired. Such a route could provide access to a variety of analogs of pyrimidine nucleosides with novel H-bonding patterns. Such molecules might serve as components of an expanded genetic 'alphabet' [1] [2] or, like other *C*-nucleosides, display pharmaceutically useful biological activity [3].

As synthetic targets, *C*-glycosides have received much attention. Synthetic routes include nucleophilic additions to glycals [4], addition of allylmetal compounds to glycosyl derivatives [5], electrocyclic reactions [6], and radical addition [7]. Other routes join C-fragments to an oxonium ion at C(1) of a carbohydrate precursors. *Townsend* and coworkers [8], *Danishefsky* and *Kerwin* [9], *Kishi* and coworkers [10], and *Kozikowski* and *Sorgi* [11] exploited the nucleophilicity of allyltrimethylsilane towards electrophilic centers formed by treating glycosyl acetates with *Lewis* acids. *Stewart* and *Williams* [12] formed the 'anomeric' bond, a term used here in analogy to the anomeric bond of normal glycosides, by treating thiopyridyl glycosides with silver ion, activating them for attack by either trimethylsilyl enol ethers or electron-rich aromatic rings. *Schmidt* and *Hoffmann* [13] employed a similar strategy with glycosyl trichloroacetimidates. *Kametani et al.* [14] formed the 'anomeric' bond by reacting a carbenoid with phenyl thioglycosides.

Other approaches show that the electronic character of C(1) of ribose derivatives can be versatile. *E.g., DeShong et al.* [15] showed that pentacarbonyl (pyranosyl) and pentacarbonyl (furanosyl)manganese complexes can be prepared stereoselectively from the corresponding glycosyl bromides. These transition-metal complexes can then be transformed into *C*-glycosides. *Vasella* and *Baumberger* [16] reduced nitro sugars with tin hydride to *C*-glycosides *via* radical intermediates. These and other examples [17] [18] show the degree of interest in this area.

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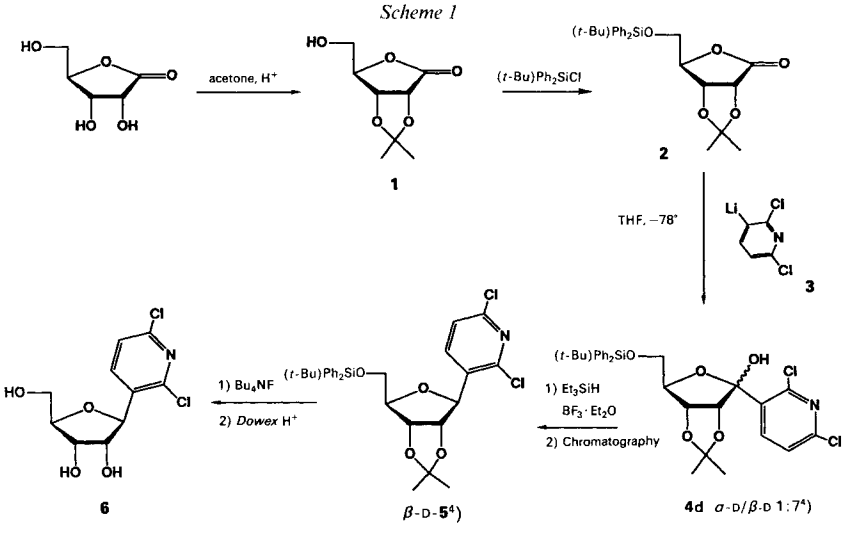
Little work, however, has been directed towards the preparation of nucleoside analogs bearing functionalized pyridine rings [19]. To this end, acid-catalysed *C*-ribofuranosylation of substituted pyridines appears, in its simplest form, to be unsatisfactory. *E.g.*, the reaction of 1,2,3,5-tetra-*O*-acetyl-ribofuranose with 2,6-dimethoxypyridine in the presence of $SnCl_4$ in dichloroethane gave very low yields of *C*-nucleoside in our hands. Thus, an alternative approach was sought.

The route described here is based on the following considerations: *a*) alkyl and aryl organometallic reagents add to carbohydrate lactones to form hemiacetals [20], *b*) reduction of the resulting hemiacetal to the corresponding cyclic ether would generate a nucleoside with a substituted pyridine as the aglycone [20], and *c*) introduction of various functionalities can be accomplished by displacement of the substituents on the pyridine ring. This route is illustrated in detail here for the synthesis of chloro- and aminopyridine analogs of nucleosides. Further, procedures for preparing the deoxynucleoside analog bearing dichloropyridine and the 5′-monophosphate of the diaminopyridine derivative are given.

Results and Discussion. – The general route for forming the C–C bond between the sugar and the base leading to pyridine ribonucleosides is shown in *Scheme 1*. The route is

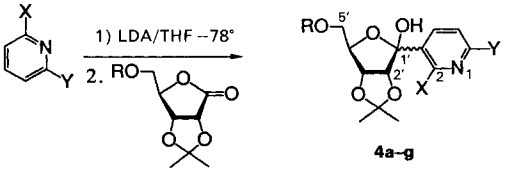
Scheme 1



exemplified by the synthesis of the 2,6-dichloropyridine 3-riboside **6**. Directed *ortho*-metallation of 2,6-dichloropyridine was achieved in a LDA solution in THF at −78° (→ **3**). Addition of 5-*O*-[(*tert*-butyl)diphenylsilyl]-2,3-*O*-isopropylidene-D-ribono-1,4-lactone (**2**; from **1**) resulted in a 1:7 α-D/β-D[4]) anomeric mixture **4d** of hemiacetals with an overall yield of 70%. The generality of this approach was demonstrated by the use of

[4]) It should be pointed out that for hemiacetals **4**, the prefix α-D refers to the position of the glycosidic OH group relative to the configuration at the reference C-atom (C(4′) in **4**; *i.e.* the pyridyl moiety is in the β-position). For *C*-glycosides (no glycosidic OH present), the prefix α-D refers to the alkyl (or pyridinyl) position relative to the reference C-atom (C(4′) in **5**).

Table 1. *Addition of* ortho-*Lithiated Pyridines to Ribono-1,4-lactones*



X	Y	R	Product	Yield [%]	β-D/α-D
F	F	(*t*-Bu)Me_2Si	**4a**	72	9:1
F	F	Ph_3C	**4b**	81	6:1
Cl	Cl	(*t*-Bu)Me_2Si	**4c**	80	7:1
Cl	Cl	(*t*-Bu)Ph_2Si	**4d**	70	7:1
Br	Br	(*t*-Bu)Ph_2Si	**4e**	21	6:1
(*t*-Bu)CONH	(*t*-Bu)CONH	(*t*-Bu)Me_2Si	**4f**	23	5:1
Cl	H	(*t*-Bu)Ph_2Si	**4g**	45	10:1
F	H	Ph_3C	**4h**[a])	60	–

[a]) Data from [21].

various other *ortho*-lithiated pyridine derivatives in the reaction with **2** and similar, protected ribono-1,4-lactones (*Table 1*). In general, the best metallation conditions were obtained in THF at −78° for 1.5 h with 1.0 equiv. of lithium diisopropylamide (LDA). Pyridyl aromatic signals in the NMR spectrum of the hemiacetals **4a–g** indicated that in all cases examined, lithiation was regioselective and that addition of the nucleophile yielded the β-D-product[4]) predominantly (*Table 1*).

To assign the configuration at C(1′) of the hemiacetals **4a–g**, the chemical shifts of the 2 Me signals of the isopropylidene group were compared. As a general rule, their difference is greater for the α-D-anomer than for the β-D-anomer[4]) [22] [23], and this pattern was also observed in the case of **4a–g**: these differences ranged from 0.05 to 0.12 ppm for the β-D-anomers and from 0.24 to 0.27 ppm for the α-D-anomers (*Table 2*). The corresponding assignments are also consistent with chemical considerations (*vide infra*). However, the configurational assignment is less critical at this stage than after reduction, where the assignment was made more thoroughly (*vide infra*).

The α-D-anomer (no glycosidic OH present)[4]) appears to be the thermodynamic product in many ribofuranose derivatives where the 2,3-*O* positions of the D-ribose are protected by an isopropylidene group. *E.g.*, reaction of 2,3-*O*-isopropylidene-D-ribose with various phosphorus ylides give β-D-isomers as kinetic products which, when treated with NaOMe/MeOH, form the α-D-anomers upon equilibration [24]. This suggests that in the case reported here (**2** → **4**), attack of the anion occurs initially from the less hindered (and stereoelectronically 'allowed') β-face (→α-D-anomer[4])), followed by equilibration (*via* opening of the hemiacetal ring) and reclosure to give the more stable β-D-product[4]).

The mixture of 2,6-dichloropyridine hemiacetals (α-D/β-D 1:7) **4d** was reduced with Et_3SiH in the presence of $BF_3 \cdot Et_2O$ at −1° to an anomeric mixture **5** of protected *C*-nucleosides in 60% overall yield. An initial assignment of the configuration at C(1′) of the ribose ring of **5** was based on ^{1}H-NMR studies.

A literature survey involving more than 20 isomeric pairs of *C*-glycosyl derivatives (no glycosidic OH)[4]) including *C*-nucleosides showed that the H–C(1′) signal always appears at lower field when it is *cis* to H–C(2′) [25] [26] than when it is *trans*. Further, the spin-spin coupling constant $J(1',2')$ is usually greater for the β-D-anomer[4]) ($\Delta J = 0.2$ Hz) which supports the assignment. Both correlations product a consistent assignment for these

Table 2. *^{1}H-NMR Parameters* ($CDCl_3$) *for Hemiacetals*

	X	Y	R	H–C(2′)	H–C(3′)	H–C(4′)	2 H–C(5′)
4a	F	F	(*t*-Bu)Me_2Si	4.86 (*m*)	4.86 (*m*)	4.5 (*td*)	3.92 (*dq*), 3.85
4b	F	F	Ph_3C	–	–	4.49	
4c	Cl	Cl	(*t*-Bu)Me_2Si	5.09 (*d*)	4.87 (*dd*)	4.48 (*td*)	3.91 (*dd*), 3.84
4d	Cl	Cl	(*t*-Bu)Ph_2Si	5.15 (*d*)	4.84 (*td*)	4.42 (*td*)	3.95 (*dq*), 3.77
4e	Br	Br	(*t*-Bu)Ph_2Si	5.25 (*m*)	4.82 (*m*)	4.40	3.95, 3.75
4g	Cl	H	(*t*-Bu)Ph_2Si	5.22 (*m*)	4.85 (*m*)	4.42	3.97, 3.77
4f[c])	(*t*-Bu)CONH	(*t*-Bu)CONH	(*t*-Bu)Me_2Si	4.66 (*d*)	4.85 (*dd*)	4.54	3.92, 3.86

[a]) Values of the α-D-anomer in parentheses. [b]) H–C(6) at 8.34 ppm. [c]) (*t*-Bu) of X and Y at 1.29 and 1.30 ppm.

compounds. *E.g.*, the H–C(1′) signal of the α-D-anomer of **5** (δ 5.58) appears at lower field than that of the β-D-anomer (δ 5.26). The difference in chemical shift of the two Me signals of the isopropylidene group, as mentioned above, is also consistent with this assignment [27].

To confirm the assignment, a series of nuclear *Overhauser* enhancements (NOE) were obtained by difference spectroscopy. Irradiation at 5.58 ppm (H–C(1′) of the presumed α-D-anomer of **5**) led to an enhancement at 5.15 (H–C(2′)) and 1.10 ppm (*t*-Bu of the 5′-*O*-protecting group). In contrast, irradiation at 5.26 ppm (H–C(1′) of the presumed β-D-anomer of **5**) enhanced the signals at 1.62 (1 Me of the isopropylidene group), 4.20 (H–C(4′)), and 7.94 ppm (H–C(4) of the pyridine ring). Irradiation at 1.62 ppm (1 Me presumably '*endo*') of the isopropylidene group) enhanced the signals at 5.26 (H–C(1′)) and 4.20 ppm (H–C(4′)).

Several reaction parameters of the reduction of the hemiacetal **4d** to **5** were varied to optimize yields and the α-D/β-D ratio[4]) of **5** (*Table 3*). Solvents with high dielectric constants, such as nitromethane, afforded the greatest α-D/β-D ratio (2:1) in an overall yield of 57%. In less polar solvents such as toluene, a 1:1 mixture of anomers was obtained in approximately the same yield. These results suggest that in less polar solvents, a nondissociative pathway (proceeding with inversion of configuration) is effectively competing with a dissociative pathway [28]. Since the β-D-anomer[4]) is the predominant product of the first reaction (hemiacetal formation), and since, after reduction, the β-D-anomer (no glycosidic OH)[4]) is normally desired as the analog of the natural nucleoside, the non-dissociative pathway produces the product with the desired configuration. Thus, non-polar solvents should be preferred when the β-D-anomer[4]) of the *C*-glycoside is desired.

Table 3. *Stereoselectivity of Hemiacetal Reduction* **4d** → **5** (see *Scheme 1*) *under Various Conditions*

Solvent	[Et_3SiH][a])	*T* [°]	Time [h]	*Lewis* acid	Overall yield of **5** [%]	α-D/β-D[4])
CH_3NO_2	2	–5	1.5	$BF_3 \cdot Et_2O$	57	2.6:1
Toluene	2	–10	1.5	$BF_3 \cdot Et_2O$	55	1:1
CH_2Cl_2	1	0	1.5	$BF_3 \cdot Et_2O$	77	2:1
Hexane/Et_2O	1	0	1.5	$BF_3 \cdot Et_2O$	62	2:1
Toluene/Et_3SiH 2:8	–	–5	1.5	$BF_3 \cdot Et_2O$	46	1.2:1
Dichloroethane	1	0	1.5	$BF_3 \cdot Et_2O$	49	2:1
Toluene	1	–5	1.5	$SnCl_4$	30	1:5
Toluene	1	–5	1.5	$ZnBr_2$	–	–
Toluene	2	25	5	$ZnCl_2 \cdot Et_2O$	63	2:1
CH_2Cl_2	2	25	3	$ZnCl_2 \cdot Et_2O$	68	2:1

[a]) Equiv. rel. to hemiacetal **4d**.

4a–g: *β*-D-*Anomer*[4]). *δ* in ppm rel. to TMS.

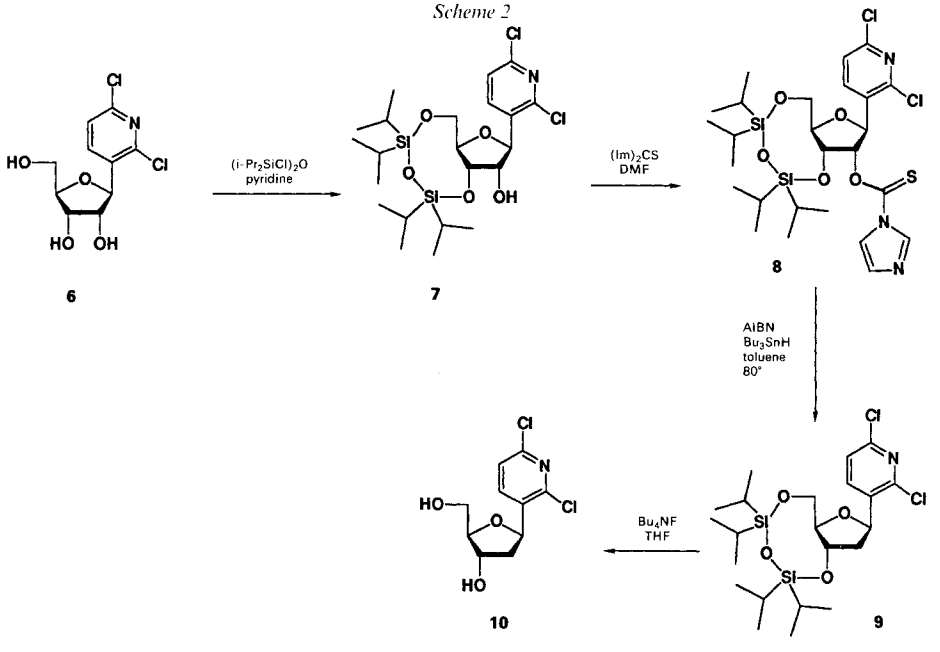
$(CH_3)_2CO_2$[a])	R			H–C(5)	H–C(4)	OH
	t-Bu	Ph	Me			
1.26, 1.21 (1.43, 1.67)	0.95		0.17, 0.18	6.76	8.18	5.5
1.27. 1.21 (1.40, 1.66)		7.45 (*m*), 7.30 (*m*)		6.77 (*m*)	8.18	
1.27, 1.17 (1.36, 1.63)	0.96		0.17, 0.19	7.24	8.09	5.43
1.25, 1.16 (1.42, 1.68)	1.12	7.70, 7.42		7.23	8.08	4.77
1.26, 1.17 (1.42, 1.67)	1.12	7.65, 7.42		7.38	7.93	
1.26, 1.14 (1.42, 1.68)	1.12	7.70, 7.42		7.22	8.12[b])	4.84
1.26, 1.20 (1.44, 1.68)	0.97		0.18, 0.20	7.88	8.00	4.84

Another way to increase the rate of the non-dissociative pathway is, in principle, to increase the concentration of the reducing agent. However, in our hands, the concentration of reducing agent had little effect on the relative yields of the two anomers.

The effect of different *Lewis* acids was next examined. The highest yields of **5** were obtained with $ZnCl_2$, but the ratio of anomers was unchanged (*α*-D/*β*-D 2:1), regardless of the solvent. No reaction occurred in the presence of $ZnBr_2$, even when the reaction mixture was heated to 90°. With $SnCl_4$, the stereospecificity was reversed, and a *α*-D/*β*-D ratio of 1:5 was obtained. However, there were many side products due to the incompatibility of the protecting groups.

As shown in *Table 3*, the highest overall yield of the anomer *β*-D-**5** was obtained using toluene in the presence of 2 equiv. of reducing agent with $BF_3 \cdot Et_2O$ as the *Lewis* acid. The anomers could be separated by flash chromatography. Removal of the silyl and acetal

Scheme 2



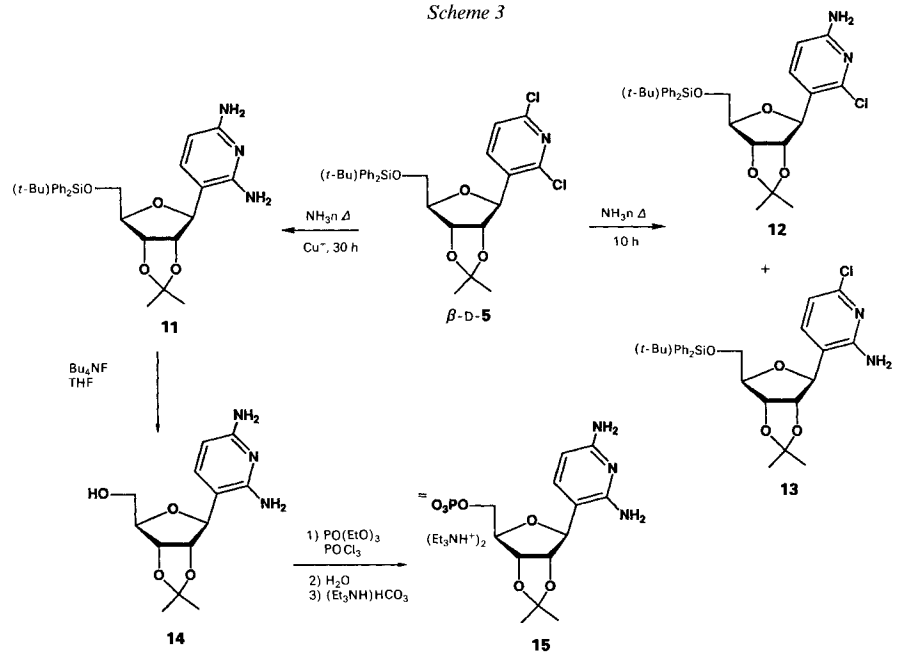
protecting groups proceeded smoothly to yield the dichloropyridine nucleoside **6** (*Scheme 1*). Therefore, these conditions were used in large-scale preparations of the β-D-anomer **6** of dichloropyridine nucleoside.

An attempt was made to extend this procedure to 2-deoxyribono-1,4-lactone to obtain the deoxynucleoside directly. However, when 3,5-bis[(*tert*-butyl)diphenylsilyl]-2-deoxyribono-1,4-lactone was added to 2,6-dichloro-3-lithiopyridine **3**, only a very poor yield of hemiacetal was obtained, perhaps due to enolization at C(2). Fortunately, the OH group at C(2′) of 2,6-dichloropyridine *C*-nucleoside **6** could be removed by a four step reaction sequence [29] (*Scheme 2*). Selective protection of the ribonucleoside as its 3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl) derivative **7**, conversion to its 2′-*O*-[(1*H*-imidazol-1-yl)thiocarbonyl] derivative **8**, homolytic deoxygenation initiated by azo-bis[isobutyronitrile] (AIBN) with Bu_3SnH (→ **9**), and deprotection with Bu_4NF provide the 2′-deoxynucleoside **10** in an overall yield of 58%.

The versatility of **5** as an intermediate in *C*-nucleoside synthesis was demonstrated by displacement of the halogen atoms with NH_3 (*Scheme 3*). Heating β-D-**5** at 115° in a steel bomb with NH_3 for 22 h afforded a mixture of regioisomers **12** and **13** containing a single NH_2 group in yields > 65%. By adding Cu^+ as a catalyst to these reactions, the diamino derivative **11** could be obtained in yields > 50%. These substances served as precursors of several biologically interesting nucleoside analogs, including the 5′-phosphate. The procedure for preparing 5′-phosphate **15** from **11** *via* **14** is given in the *Exper. Part.*

Conclusions. – *C*-Nucleosides containing a pyridine-3-yl substituent at C(1′) of the ribose moiety are novel analogs of pyrimidine nucleosides. Synthetic entry into this class of analogs can be obtained by treatment of a suitably protected ribono-1,4-lactone with

Scheme 3



(2,6-dichloropyridin-3-yl)lithium in THF to give the corresponding hemiacetal followed by reduction with Et_3SiH in the presence of a *Lewis* acid. This approach is synthetically flexible, and a variety of pyridine nucleosides can be prepared by parallel routes or by transformation of an appropriately substituted pyridine ring. Additionally, the ease of large-scale preparation, storage, and handling of products such as β-D-**5**, containing readily manipulatable functional groups, make them valuable precursors to a variety of nucleoside derivatives.

Experimental Part

General. D-Ribono-1,4-lactone was purchased from *Aldrich*. THF was distilled over sodium benzophenone, toluene from CaH_2, and DMF from $MgSO_4$. Solvents used for chromatography (FC = flash chromatography) were purchased in bulk and distilled from $CaCl_2$. M.p. uncorrected. ^{1}H-NMR spectra: *Bruker WM 300* (300 MHz); chemical shifts δ in ppm rel. to TMS, *J* in Hz; in $CDCl_3$ if not stated otherweise. FAB-MS: *Kratos AEI MS-5*. MS: *Hitachi-Elmer-RMU-6M; m/z* (rel. intensity).

*2,3-Isopropylidene-*D*-ribono-1,4-lactone* (**1**). A mixture of D-ribono-1,4-lactone (50.0 g, 338 mmol), acetone (1 l), and conc. H_2SO_4 (20 ml) in a dry flask was stirred at r.t. for 6 h (slightly yellow→yellow orange). Solid $NaHCO_3$ was then added until the pH reached *ca.* 6 (absence of further foaming). The mixture was filtered to remove insoluble salts and the solvent evaporated. The residue was recrystallized from acetone/hexane: 60 g (94%) of **1**. M.p. 132–135° ([19]: 130°). ^{1}H-NMR (300 MHz): 4.85 (*d*, H–C(2)); 4.79 (*d*, H–C(3)); 4.64 (*m*, H–C(4)); 3.89 (*dd*, 2 H–C(5)); 3.2 (*m*, OH); 1.47, 1.39 (2*s*, 3 H each, Me_2C).

*5-[(*tert*-Butyl)diphenylsilyl]-2,3-isopropylidene-*D*-ribono-1,4-lactone* (**2**). To a soln. of **1** (6.7 g, 35.6 mmol) and 4-(dimethylamino)pyridine (220 mg) in CH_2Cl_2 (60 ml) was added (*t*-Bu)Ph_2SiCl (10.0 ml, 39.2 mmol, 1.1 equiv.) and Et_3N (6.5 ml, 44 mmol). The mixture was stirred at r.t. for 42 h. The resulting suspension was partitioned between H_2O/CH_2Cl_2 1:1 (100 ml). The org. layer was washed with H_2O (50 ml), dried ($MgSO_4$), and evaporated and the residue chromatographed (silica gel, 15% AcOEt/hexane): 13.2 g (87%) of **2** as a clear colorless oil which was crystallized from AcOEt/pentane. M.p. 68°. ^{1}H-NMR: 7.62 (*m*, 4 H, Ph); 7.44 (*m*, 6 H, Ph); 4.90 (*d*, *J*(2,3) = 5.6, H–C(2)); 4.73 (*d*, *J*(3,4) = 0, H–C(3)); 4.58 (*m*, H–C(4)); 3.92 (*dd*, *J*(4,5) = 2.3, *J*(5,5) = 11.5, H–C(5)); 3.76 (*dd*, *J*(4,5) = 1.5, H′–C(5)); 1.49 (*s*, Me (*'endo'*)); 1.40 (*s*, Me); 1.04 (*s*, *t*-Bu). MS: 411 (2, $[M - Me]^+$), 241 (67, *t*-BuPh_2Si^+). Anal. calc. for $C_{24}H_{30}O_5Si$: C 67.57, H 7.09; found: C 67.43, H 6.83.

General Procedure for the Synthesis of Hemiacetals **4a–g**. To a soln. of $(i\text{-}Pr)_2NH$ (4.47 ml, 3.5 mmol) in THF (80 ml) in a dry, N_2-flushed flask, BuLi (1.6M in hexane; 20.0 ml, 32 mmol) was added at 0°. The mixture was stirred at r.t. for 30 min and then cooled to −78°. Additional THF (100 ml) was added, followed by a soln. of the pyridine derivative (32 mmol, 1 equiv.) in THF (40 ml). The mixture was stirred for 1 h at −78°, and then **2** (13.0 g, 0.95 equiv.) in THF (40 ml) was added. The mixture was allowed to warm to −40° over 90 min and then quenched with H_2O. Partitioning between H_2O/Et_2O, extraction of the aq. layers with Et_2O, washing of the combined extract with sat. NaCl soln., drying ($MgSO_4$), and evaporation gave a mixture which was resolved by FC (silica gel, 10% AcOEt/hexane): hemiacetal **4** (α-D- and β-D-anomers) as an oil. Yields and β-D/α-D ratios: *Table 1*. Data for **4d**, see below. Summary of NMR data for **4a–g**: see *Table 2*.

*3-{5′-O-[(*tert*-Butyl)diphenylsilyl]-1′-hydroxy-2′,3′-*O*-isopropylidene-*D*-ribofuranosyl}-2,6-dichloropyridine* (= *5-O-[(*tert*-Butyl)diphenylsilyl]-1-C-(2,6-dichloropyridin-3-yl)-2′,3′-O-isopropylidene-*D*-ribofuranose*; **4d**). ^{1}H-NMR (300 MHz): α-D/β-D[4]) 1:7; α-D-anomer[4]): 8.16 (*d*, *J*(4,5) = 8.2, H–C(4)); 7.15 (*d*, H–C(5)); 4.33 (*dd*, *J*(3′,4′) = 3.5, H–C(4′)); 3.86 (*dd*, partially masked, *J*(5′,5′) = 11.5, *J*(4′,5′) = 4.5, H′–C(5′)); 1.68 (*s*, Me); 1.42 (*s*, Me); 1.00 (*s*, *t*-Bu); H–C(5′), H–C(3′), and H–C(2′) masked by β-D-anomer; β-D-anomer[4]): 8.08 (*d*, H–C(4)); 7.70 (*m*, 4 H, Ph); 7.42 (*m*, 6 H, Ph); 7.23 (*d*, H–C(5)); 5.15 (*d*, H–C(2′)); 4.7–4.9 (*m*, H–C(3′)); 4.40 (*m*, H–C(4′)); 3.85 (*dd*, 2 H–C(5′)); 1.25 (*s*, Me(*'endo'*)); 1.16 (*s*, Me(*'exo'*)); 1.12 (*s*, *t*-Bu). MS: 411 (< 1, $[M - Me - base]^+$), 241 (4, (*t*-Bu)Ph_2Si^+), 199 (14, Ph_2SiOH^+), 147, 149, 151 (16.4, 10.7, and 1.6 resp., $C_5H_3Cl_2N^+$). Anal. calc. for $C_{29}H_{33}Cl_2NO_5Si$: C 60.62, H 5.79, N 2.44; found: C 60.58, H 5.85, N 2.31.

Reduction of **4d** *to* **5**. For various conditions, see *Table 3*. The following procedure is most satisfactory on a 1-g scale, but can be performed on a large scale. It gave the best yields of the β-D-anomer[4]): To a soln. of **4d** (α-D/β-D[4]) 1:7; 1.06 g, 1.8 mmol) in toluene (1 ml) in a dry, N_2-flushed flask at 0–5° (ice/salt bath), Et_3SiH (580 μl, 2 equiv.) was added, followed (dropwise) by $BF_3 \cdot Et_2O$ (228 μl) in toluene (1 ml). The mixture was stirred for 1.5 to 2 h, whilst it reached r.t. The reaction was generally complete after 2 h. TLC (silica gel, AcOEt/hexane 1:4): 2 major products,

R_f 0.41 and 0.35. Sat. $NaHCO_3$ soln. was then added to quench the reaction, and the resulting suspension was partitioned between H_2O/Et_2O. The org. layer was washed with sat. NaCl soln., dried ($MgSO_4$), and concentrated *in vacuo* to a syrup. Chromatography (silica gel, hexane/AcOEt 19:1) gave first β-D-**5**[4] (231 mg, 23%) as a clear oil (TLC: R_f 0.41). After some mixed fractions (4%), the more polar α-D-**5**[4] (221 mg, 22%) was obtained as a syrup (TLC: R_f 0.35). The mixed fractions from separate reduction reactions were combined and rechromatographed.

*3-{5'-O-[(*tert*-Butyl)diphenylsilyl]-2',3'-O-isopropylidene-α-*D*-ribofuranosyl}-2,6-dichloropyridine* (α-D-**5**). ^{1}H-NMR: 7.89 (*dd*, *J*(1',4) = 0.7, *J*(4,5) = 8.1, H–C(4)); 7.28 (*d*, H–C(5)); 5.55 (*d*, *J*(1',2') = 4.2, H–C(1')); 5.13 (*dd*, *J*(2',3') = 6.0, H–C(2')); 4.93 (*dd*, *J*(4',5') = 3.0, *J*(5',5') = 11.3, H–C(3')); 4.31 (*m*, H–C(4')); 3.93 (*dd*, H–C(5')); 3.77 (*dd*, *J*(4',5') = 3.2, H'–C(5')); 1.28 (*s*, Me); 1.27 (*s*, Me); 1.11 (*s*, *t*-Bu). NOE: irradiation at (5.58, H–C(1'))→enhancement at 7.90 (H–C(4)); 7.70 and 7.40 (Ph), 5.15 (H–C(2')); 3.86 (H–C(5')); 1.10 (*t*-Bu). Anal. calc. for $C_{29}H_{33}Cl_2NO_4Si$: C 62.34, H 5.95, N 2.51; found: C 62.17, H 6.02, N 2.55.

*3-{5-O-[(*tert*-Butyl)diphenylsilyl-2',3'-O-isopropylidene-β-*D*-ribofuranosyl)-2,6-dichloropyridine* (β-D-**5**). ^{1}H-NMR: 7.94 (*dd*, *J*(4,5) = 8.0, *J*(1',4) = 0.5, H–C(4)); 7.68 (*m*, 4 H, Ph); 7.42 (*m*, 6 H, Ph); 7.06 (*d*, H–C(5)); 5.26 (*d*, *J*(1',2') = 4.0, H–C(1')); 4.76 (*dd*, *J*(2',3') = 6.3, *J*(3',4') = 4.6, H–C(2')); 4.52 (*dd*, H–C(3')); 4.20 (*m*, H–C(4')); 4.03 (*dd*, *J*(5',5') = 11.5, *J*(4',5') = 2.7, H–C(5')); 3.87 (*d*, *J*(4',5') = 3.5, H'–C(5')); 1.62 (*s*, Me); 1.36 (*s*, Me); 1.07 (*s*, *t*-Bu). NOE: irradiation at 5.26 (H–C(1'))→enhancement at 7.94 (H–C(4)); 4.20 (H–C(4')); 1.62 (Me('*endo*') of Me_2CO_2); irradiation at 1.62 (Me('*endo*'))→enhancement at 5.26 (H–C(1')); 4.20 (H–C(4')). MS: 558 (< 1, M^+), 500 (5.6, $[M - t\text{-Bu}]^+$), 502 (3.8, $[M + 2 - t\text{-Bu}]^+$), 442 (9.4, $[M - t\text{-Bu} - \text{acetone}]^+$), 444 (6.3, $[M + 2 - t\text{-Bu} - \text{acetone}]^+$). Anal. calc. for $C_{29}H_{33}Cl_2NO_4Si$: C 62.34, H 5.95, N 2.51; found: C 62.36, H 5.95, N 2.50.

*2,6-Dichloro-3-(2',3'-O-isopropylidene-β-*D*-ribofuranosyl)pyridine*. To a soln. of β-D-**5**[4] (2.17 g, 3.9 mmol) in THF (30 ml) was added (dropwise) a soln. of Bu_4NF (1M; 3.9 ml, 1.1 equiv.; →dark green→yellow). TLC ($CHCl_3$/MeOH 9:1): no β-D-**5** left after 30 min. The mixture was evaporated and the brown residue chromatographed (silica gel, 1.5% MeOH/$CHCl_3$): 1.1 g (86%) of white solid. 321 (0.8, $[M + 2]^+$), 319 (1.1, M^+), 308 (9.2, $[M^+ + 4 - \text{Me}]^+$), 306 (54.0, $[M + 2 - \text{Me}]^+$), 304 (85.6, $[M^+ - \text{Me}]^+$), 176 (58.2), 178 (335), 180 (6.2, [base + 30]$^+$). Anal. calc. for $C_{13}H_{15}Cl_2NO_4$: C 48.77, H 4.72, N 4.37; found: C 48.71, H 4.79, N 4.27.

*2,6-Dichloro-3-(β-*D*-ribofuranosyl)pyridine* (**6**). The isopropylidene-protected nucleoside from the previous step (1.03 g, 3.2 mmol) was suspended in H_2O (25 ml). *Dowex 50 W × 8* (H^+ form; 6.3 g (dry weight), 10 equiv.), which was previously washed with H_2O, was added to the suspension, and the mixture was stirred at 70°. After 30 min, all white powder had dissolved. TLC (silica gel, $CHCl_3$/MeOH 9:1) showed quantitative conversion to a more polar compound (R_f 0.15). The entire mixture was then applied to a column (silica gel), which was eluted with H_2O. The UV-active fractions were collected and lyophilized to give 7 as a white amorphous powder (845 mg, 100%). The product was of sufficient purity to be used directly in subsequent reactions. A fraction of the material was recrystallized from AcOEt/pentane to yield **6** as white needles. M.p. 152–153°. UV (MeOH): 222 (9000), 273 (4800). IR (KBr): 3406 (br.), 3280 (br.), 2920, 1575, 1555, 1420, 1335, 1100, 1042, 1020, 870, 840. ^{1}H-NMR (CD_3OD): 8.21 (*d*, *J*(4,5) = 8.1, H–C(4)); 7.43 (*d*, H–C(5)); 5.11 (*d*, *J*(1',2') = 3.8, H–C(1')); 3.99 (*m*, H–C(2'), H–C(3'), H–C(4')); 3.90 (*dd*, *J*(5',5') = 12.1, H–C(5')); 3.75 (*m*, H'–C(5')). ^{1}H-NMR ((D$_6$)DMSO): 8.23 (*d*, *J*(4,5) = 8.0, H–C(4)); 7.60 (*d*, H–C(5)); 5.25 (*d*, *J*(1',2') = 4.9, H–C(1')); 4.96 (*m*, 3 OH); 3.86 (*m*, H–C(2'), H–C(3'), H–C(4')); 3.7 (*m*, H–C(5')); 3.58 (*m*, H'–C(5)). MS: 279, 281 (< 1, M^+, $[M + 2]^+$); 176, 178, 180 (100, 64.4, and 10.5, resp., [base + 30]$^+$). Anal. calc. for $C_{10}H_{11}Cl_2NO_4$: C 42.88, H 3.96, N 5.00; found: C 42.75, H 3.87, N 4.97.

*2,6-Dichloro-3-[3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-*D*-ribofuranosyl]pyridine* (**7**). A soln. of **6** (798 mg, 3.02 mmol) in pyridine was evaporated to remove residual H_2O. This procedure was repeated twice more, the resulting oil was dried under high vacuum overnight, again dissolved in anh. pyridine (9 ml), and treated with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (1.04 ml, 3.3 mmol, 1.1 equiv.). Stirring the mixture at r.t. under Ar for 4 h resulted in complete conversion of the starting material to a less polar compound (TLC (15% AcOEt/hexane); R_f 0.72). Pyridine was evaporated and the residue partitioned between $CHCl_3/H_2O$. The org. layer was washed with H_2O (2 × 50 ml), dried (Na_2SO_4), filtered, and evaporated and the residue chromatographed (silica gel, hexane/AcOEt 9:1): white foam (1.4 g, 89%). ^{1}H-NMR: 8.08 (*d*, H–C(4)); 7.26 (*d*, H–C(5)); 5.18 (*s*, H–C(1')); 4.22 (*m*, 2 H, ribose); 4.04 (*m*, 3 H, ribose); 2.82 (*s*, OH–C(2')); 1.08 (*m*, 4 i-Pr). Anal. calc. for $C_{22}H_{37}ClNO_5$: C 56.69, H 7.34, N 2.82; found: C 56.65, H 27.9, N 2.82.

*2,6-Dichloro-3-{3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2'-O-[(1''H-imidazol-1''-yl)thiocarbonyl]-β-*D*-ribofuranosyl}pyridine* (**8**). The protected nucleoside from above (1.5 g, 2.6 mmol) was dissolved in dry DMF (6 ml) and treated with *N,N'*-thiocarbonylbis[imidazole] (1.3 g, 6.7 mmol). After stirring for 4 h at r.t. under Ar, the mixture was partitioned between AcOEt/H_2O 4:1 (125 ml). The org. phase was washed with H_2O (5 × 25 ml), dried (Na_2SO_4), and evaporated to yield a yellow oil which was purified by chromatography (silica gel, hexane/AcOEt 9:1): **7** as a white amorphous solid (1.3 g, 82%). Recrystallization from EtOH afforded white

needles. M.p. 156–157°. IR (KBr): 3440 (br.), 2940, 2860, 1575, 1505, 1460, 1420, 1380, 1350, 1320, 1280, 1230, 1040, 990, 880, 700. ^{1}H-NMR: 8.4 (*dd*, J = 1.2, $J(2'',4'')$ = 0.9, H–C(2'')); 8.13 (*d*, $J(4,5)$ = 8.1, H–C(4)); 7.70 (*dd*, $J(4'',5'')$ = 1.7, H–C(5'')); 7.32 (*d*, H–C(5)); 7.08 (*dd*, H–C(4'')); 6.16 (*d*, $J(2',3')$ = 4.8, H–C(2')); 5.37 (*s*, $J(1',2')$ = 0, H–C(1')); 4.45 (*dd*, $J(3',4')$ = 9.3, H–C(3')); 4.30 (*d*, $J(5',5')$ = 13.2, $J(4',5')$ = 0, H–C(5')); 4.06 (*m*, H–C(4'), H'–C(5')); 0.95 (*m*, 4 i-Pr). ^{1}H-NMR ((D$_6$DMSO): 8.62 (*s*, H–C(2'')); 8.06 (*d*, $J(4,5)$ = 8.1, H–C(4)); 7.93 (*t*, J = 1.5, H–C(5'')); 7.66 (*d*, H–C(5)); 7.13 (*m*, H–C(4'')); 6.19 (*dd*, $J(1',2')$ = 1.3, $J(2',3')$ = 5.0, H–C(2')); 4.66 (*dd*, $J(2',3')$ = 5.0, $J(3',4')$ = 8,7, H–C(3')); 4.24 (*m*, H–C(5'), H–C(4')); 4.02 (*dd*, $J(5',5')$ = 14.0, $J(4',5')$ = 3.0, H'–C(5')); 1.04 (*m*, 4 i-Pr). MS 631 (1, M^+), 588 (14.2, $[M - \text{i-Pr}]^+$), 503 (70, $[M - C_3H_3N_2CSOH]^+$), 460 (27, $[M - \text{i-Pr} - C_3H_3N_2CSOH]^+$). Anal. calc. for $C_{26}H_{39}Cl_2N_3O_5Si_2S$: C 49.35, H 6.21, N 6.64; found: C 49.07, H 6.32, N 6.59.

*2,6-Dichloro-3-[3',5'-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-2'-deoxy-β-*D*-ribofuranosyl]pyridine* (**9**). A soln. of **8** (1.2 g, 1.9 mmol) in toluene (19 ml) was treated with a mixture of 2,2'-dimethyl-2,2'-azobis[propiononitrile] (210 mg, 1.28 mmol) and Bu_3SnH (2.0 ml, 7.68 mmol) in toluene (19 ml). The mixture was degassed by purging with O_2-free Ar for 40 min and heated at 80° for 3 h. After evaporation, the clear oily mixture was chromatographed (silica gel). Elution with hexane/removed tin derivatives and hexane/AcOEt 19:1 afforded **9** as clear, colorless oil (808 mg, 85%). ^{1}H-NMR: 8.00 (*d*, $J(4,5)$ = 8.0, H–C(4)); 7.25 (*d*, H–C(5)); 5.27 (*dd*, $J(1',2')$ = 5.0, $J(1',2')$ = 8.3, H–C(1')); 4.38 (*q*, $J(3',4')$ = 7.2, $J(2',3')$ = $J(2',3')$ = 7.5, H–C(3')); 4.09 (*dd*, $J(4',5')$ = 3.3, $J(5',5')$ = 12.5, H–C(5')); 4.03 (*dd*, $J(4',5')$ = 4.2, H'–C(5')); 3.82 (*m*, H–C(4')); 2.60 (*m*, $J(2',2')$ = 12.5, $J(2',3')$ = $J(2',3')$ = 7.5, H–C(2')); 2.00 (*m*, H'–C(2')); 1.05 (*m*, 4 i-Pr). MS: 505, 462, (93.8, $[M - \text{i-Pr}]^+$), 464 (71.2, $[M + 2 - \text{i-Pr}]^+$), 466 (17.0, $[M + 4 - \text{i-Pr}]^+$). Anal. calc. for $C_{22}H_{37}Cl_2NO_4Si_2$: C 52.16, H 7.36, N 2.76; found: C 52.00, H 7.27, N 2.65.

*2,6-Dichloro-3-(2'-deoxy-β-*D*-ribofuranosyl)pyridine* (**10**). To a soln. of **9** (646 mg, 1.28 mmol) in THF (5 ml) was added dropwise 1M Bu_4NF in THF (2.6 ml, 2 equiv.; prepared from $Bu_4NF \cdot 3H_2O$ just prior to use). The mixture became yellow immediately. After 30 min stirring at r.t. (TLC (silica gel; $CHCl_3$/MeOH): no **9** left, only 1 more polar compound (R_f 0.38)), the mixture was evaporated and the oil applied to a *Dowex 50W-X8* cation-exchange resin (pyridinium form; 15 ml). Elution with pyridine/MeOH/H_2O 3:1:1 gave an oil which was purified by chromatography (silica gel, $CHCl_3$/MeOH 19:1): off-white solid (252 mg, 75%). Recrystallization from MeOH gave **8** as translucent plates. M.p. 160°. UV (MeOH): 274 (2201), 220 (4030), 195 (5448). IR (KBr): 3300 (br.), 2900, 1550, 1425, 1325, 1050. ^{1}H-NMR ((D$_6$)DMSO): 8.13 (*d*, $J(4,5)$ = 7.2, H–C(4)); 7.59 (*d*, H–C(5)); 5.21 (*m*, H–C(1'), OH–C(3')); 4.88 (*t*, OH–C(5')); 4.21 (*m*, H–C(4')); 3.85 (*m*, H–C(3')); 3.50 (*m*, H–C(5')); 2.30 (*m*, 1 H–C(2')); 1.70 (*m*, 1 H–C(2')). Anal. calc. for $C_{10}H_{11}Cl_2NO_3$: C 45.48, H 4.20, N 5.30; found: C 45.39, H 4.31, N 5.25.

*2,6-Diamino-3-{5'-*O*-[(*tert*-butyl)diphenylsilyl]-2',3'-*O*-isopropylidene-β-*D*-ribofuranosyl}pyridine* (**11**). A soln. of β-D-**5** (1.2 g, 2.0 mmol) in CH_2Cl_2 in test tube containing a stirring bar was evaporated under high vacuum. The tube was then placed in a steel autoclave and purged with a continuous stream of Ar. CuI (720 mg, *ca.* 2 equiv.) was added and the entire autoclave cooled in a *Dewar* vessel containing liq. N_2. Purging over the apparatus with Ar was continued to prevent the condensation of H_2O vapor. NH_3 (*ca.* 15 ml, dried over BaO) was condensed into the tube. The autoclave was then quickly closed, the mixture allowed to warm to r.t., placed in a heated oil bath at 115°, and stirred for *ca.* 36 h. The autoclave was then cooled as before and opened. Ar was flushed over the mixture as it warmed to r.t. and NH_3 evaporated. Then, the dark mixture was dissolved in MeOH, filtered, and evaporated. TLC (silica gel, MeOH/$CHCl_3$ 1:19): fluorescent product (366 nm) at R_f 0.37. The mixture was purified by chromatography (silica gel, MeOH/$CHCl_3$): **11** (596 mg, 53%). ^{1}H-NMR: 7.68 (*m*, 4 H, Ph); 7.40 (*m*, 7 H, Ph, H–C(4)); 5.85 (*d*, $J(4,5)$ = 5.7, H–C(5)); 5.04 (br. *s*, NH_2); 4.88 (*dd*, $J(2',3')$ = 6.4, $J(3',4')$ = 4.2, H–C(3')); 4.71 (*t*, H–C(2')); 4.63 (*d*, $J(1',2')$ = 5.8, H–C(1')); 4.35 (br. *s*, NH_2); 4.08 (*m*, H–C(4')); 3.99 (*dd*, $J(4',5')$ = 2.8, $J(5',5')$ = 11.3, H–C(5')); 3.86 (*dd*, $J(4',5')$ = 2.8, H'–C(5')); 1.58 (*s*, Me); 1.35 (*s*, Me); 1.07 (*s*, *t*-Bu). MS: 519 (29.9, M^+), 138 (13.3, [base + 30]$^+$), 122 (36.5, [base + CH_2]$^+$), 109 (18, base$^+$).

*6-Amino-3-{5'-*O*-[(*tert*-butyl)diphenylsilyl]-2',3'-*O*-isopropylidene-β-*D*-ribofuranosyl}-2-chloropyridine* (**12**) *and 2-Amino-3-{5'-*O*-[(*tert*-butyl)diphenylsilyl]-2',3'-*O*-isopropylidene-β-*D*-ribofuranosyl}-6-chloropyridine* (**13**). Compound β-D-**5** (716 mg, 1.28 mmol) was treated as above except that CuI was excluded. After 22 h at 115°, NH_3 was removed and the residue dissolved in MeOH. TLC (silica gel, AcOEt/hexane 2:3): 3 major components, R_f 0.65 (β-D-**5**), 0.59, and 0.39. Separation by chromatography (silica gel, AcOEt/hexane 1:4) gave β-D-**5** (461 mg), then **12** (108 mg), followed by **13** (76 mg). Yield of **12**/**13**, 78% after accounting for recovered starting material.

*2,6-Diamino-3-(2',3'-*O*-isopropylidene-β-*D*-ribofuranosyl)pyridine* (**14**). To a soln. of **11** (236 mg, 0.43 mmol) in THF (5 ml) was added 1M Bu_4NF in THF (0.43 ml). After 1 h stirring in the dark at r.t., more Bu_4NF (0.3 ml) was added. After 2 h, the solvent was evaporated and the residue purified by chromatography (silica gel, 2% MeOH/$CHCl_3$): **14** (119 mg, 86%). TLC (10% MeOH/$CHCl_3$): R_f 0.5. ^{1}H-NMR (300 MHz): 7.24 (*d*, H–C(4));

5.83 (*d*, H–C(5)); 4.81–4.63 (*m*, H–C(1'), H–C(2'), H–C(3')); 4.12 (*m*, H–C(4')); 3.87 (*dd*, 2 H–C(5')); 1.59 (*s*, CH_3); 1.35 (*s*, CH_3). MS: 281 (65, $[M + H]^+$), 137 (100, [base–CO + H]$^+$), 122 (24, $[137-NH_2]^+$), 109 (59, base$^+$).

*2,6-Diamino-3-(2',3'-O-isopropylidene-*D*-β-ribofuranosyl)pyridine Bis(triethylammonium) 5'-Phosphate* (**15**). To a soln. of **14** (67 mg, 0.36 mmol) dissolved at 0° in $PO(EtO)_3$ (3.4 ml) was slowly added $POCl_3$ (0.21 ml, 2.3 mmol). The mixture was stirred for 2 h on an ice-bath, and then allowed to stand for a further 18 h at –18°. The mixture was then added dropwise to Et_2O, and the resulting precipitate isolated by centrifugation. The supernatant was decanted and the precipitate washed 3 times with Et_2O. The residue was dissolved in ice-cold H_2O, the pH adjusted to 10, and the mixture stirred on ice for 12 h. The pH was then adjusted to 7 with conc. HCl and the mixture adsorbed onto a DEAE-cellulose column. The product was eluted with a linear gradient of (Et_3NH) HCO_3 (0–0.3M). Evaporation yielded **15** (29 mg, 22%). ^{1}H-NMR (300 MHz, D_2O): 7.59 (*d*, H–C(4)); 6.07 (*d*, H–C(5)); 5.25 (*d*, H–C(1')); 5.08–5.04 (*m*, H–C(2'), H–C(3')); 4.43 (*m*, H–C(4')); 3.98 (*m*, 2 H–C(5')); 3.16 (*q*, 2 CH_3CH_2); 1.41 (*s*, Me); 1.32 (*s*, Me); 1.24 (*t*, 2 CH_3CH_2). ^{31}P-NMR (300 MHz, D_2O, H_3PO_4 as external ref.): 1.70 (*s*). FAB-MS (neg. mode, glycerine matrix): 360 ($[M^{2-} + H^+]^-$).

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