(4-[^{123}I]iodophenyl)-α-phenylacetate (18a) was obtained in the same manner as 1c (Brookhaven National Laboratory). A final average specific activity of 729 Ci/mmol (236–1385) and a radiochemical yield of 17% (n = 5) were obtained. The solutions of 18a used were prepared in the same way as for 18.

(*S*)-(+)-1-Azabicyclo[2.2.2]oct-3-yl (*RS*)-α-hydroxy-α-(4-[^{123}I]iodophenyl)-α-phenylacetate (19) was obtained in the same manner as 1c. The final product had a radiochemical yield of 8% (n = 1). The solutions of 19 for receptor and animal studies were prepared in the same way as for 18a.

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Synthesis of 3-Hydroxy-2- and -4-pyridone Nucleosides as Potential Antitumor Agents

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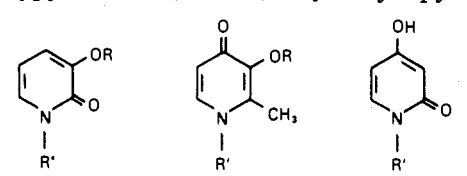
The ribo- and arabinofuranosyl nucleosides of antitumor active 2- and 4-pyridones 1a and 2a were prepared by direct condensation of the silylated bases with either 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (4a) or 2,3,5-tri-*O*-benzyl-1-*p*-nitrobenzoyl-D-arabinofuranose (7) in the presence of trimethylsilyl triflate (Me_3SiOTf). In the case of the arabinofuranosyl nucleosides, separation of the α and β anomers was accomplished at the stage of *O*-benzyl-protected compounds (8b + 9b, and 10b + 11b) after chemical functionalization of the 3-hydroxy group of the pyridone aglycons with acetyl and benzyl groups, respectively. Deblocking of the protected ribo- and arabinofuranosyl nucleosides was performed by the standard methods. In vitro activity against P-388 cells in culture indicated that the 4-pyridone riboside 6d was the most active member of the series with a twofold lower ID_{50} than the parent pyridone 2a. However, this and all the other compounds tested in this series showed no activity against the in vivo model system of murine P-388 leukemia at doses ranging from 25 to 400 mg/kg qd 1–5.

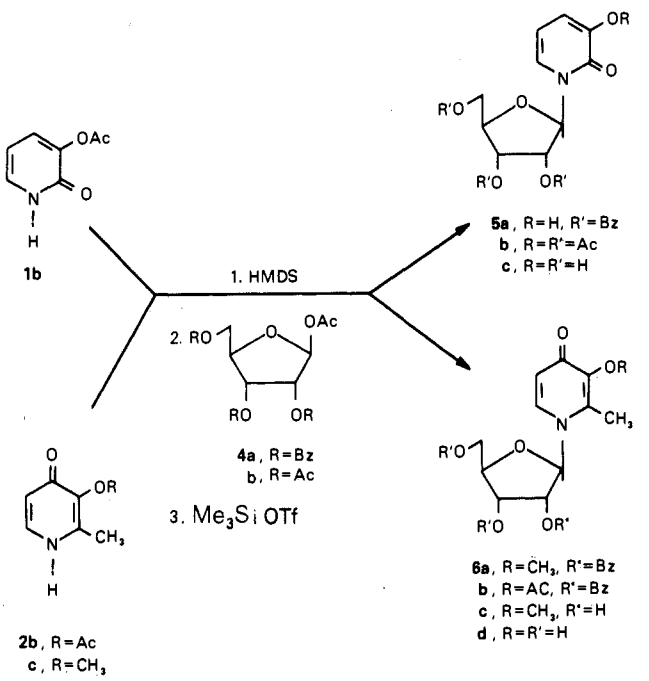
As a result of an extensive structure–activity study on hydroxypyridine derivatives, 3-hydroxy-2-pyridone (1a)



1a, R=R'=H; b, R=Ac, R'=H — 2a, R=R'=H; b, R=Ac, R'=H — 3a, R'=H; b, R'=β-D-Ribofuranosyl

and 3-hydroxy-2-methyl-4-pyridone (2a) were discovered to possess moderate reproducible activity against murine P-388 leukemia.[1,2] The corresponding acetylated derivatives 1b and 2b showed even better activity than the parent compounds, possibly as a result of improved transport properties.[1,2] Although nothing definite is known about the mechanism of action of these compounds, it has been suggested that biological oxidation to quinoid forms could be responsible for their antitumor activity.[2] Anabolic activation of these pyridones to the nucleotide level also remains as a possible but likewise unproven alternative. An interesting observation in this connection was that 4-hydroxy-2-pyridone (3a), a completely inactive compound, constitutes the aglycon of the antitumor agent 3-deazauridine (3b).[1,3] Consequently, we became interested in finding out whether or not the activity of 1a and 2a could be improved further by conversion to the corresponding nucleosides. It was hoped that these nucleosides would interfere with specific enzymes in pyrimidine metabolism in a similar manner as 3-deazauridine.[4] Alternatively, it was possible that these nucleosides could

Scheme I



constitute efficient prodrug forms for their respective active bases. The synthesis, characterization, and biological study of ribo- and arabinofuranosyl nucleosides of the antitumor-active aglycons 1a and 2a are the subject of the present work.

Chemistry. The preparation of ribofuranosides 5a,b and 6a,b was initially performed by the general condensation method developed by Niedballa and Vorbruggen

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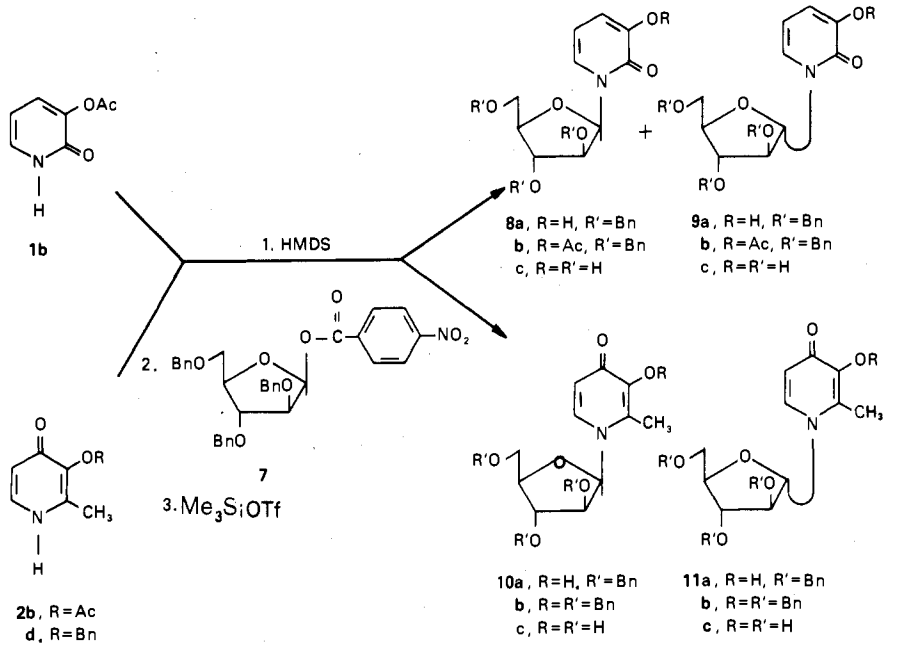
Scheme II



that employs $SnCl_4$ as catalyst.[5] As shown in Scheme I, the heterocycle bases **1b**, **2b**, and **2c** were silylated and reacted with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (**4a**) in methylene chloride. The yields of these condensations were generally low (16–37%), possibly due to the instability of the heterocycle aglycon in the presence of $SnCl_4$. This observation appears to be correct, since changing the Friedel–Craft-type catalyst to the weaker trimethylsilyl triflate (Me_3SiOTf), also developed by Vorbruggen et al.,[6,7] produced a considerable increase in the yield of products (45–88%).

Despite the existing possibility of forming *O*-ribosides in these condensation reactions,[8] the structure of products **5a,b** and **6a,b** are formulated as *N*-ribosides. During these reactions the use of Me_3SiOTf produced only a single product during a 24-h observation period. In addition, it is known that Friedel–Craft catalysts either favor a direct formation of the thermodynamically stable *N*-riboside or induce a very fast and facile O to N rearrangement.[5,7,9] The NMR data of these products also agreed with the spectra of previously reported 2-pyridone and 4-pyridone *N*-ribosides.[5]

Under the reaction and workup conditions, the acetyl group of **1b** was hydrolyzed, and, therefore, compound **5a** was isolated as the sole product. In the case of **5b**, obtained from tetra-*O*-acetyl-D-ribofuranose (**4b**), the 3-*O*-acetyl group was reintroduced with acetyl chloride after the condensation reaction. The 3-*O*-acetyl group of **2b** was somewhat more stable and permitted the isolated of **6b** as the major product. When the 3-substituent was a methoxy group, as in **2c**, the yield of nucleoside was the highest obtained by this procedure (**6a**, 88%). Deblocking of **6a,b** proceeded as expected after methanolysis with saturated methanolic ammonia. Both compounds, **6c,d**, were isolated as crystalline solids. The 2-pyridone riboside **5c**, on the contrary, proved to be somewhat unstable, and it was best obtained from the tetraacetylated compound **5b** after treatment with diisopropylamine under reflux for 1 h in methanol.

The preparation of the arabinofuranosides is exemplified in Scheme II. In previous instances where arabinofuranosyl nucleosides have been synthesized by a direct condensation with silylated heterocycles, the halogeno sugar 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride, which is prepared from commercially available 2,3,5-tri-*O*-benzyl-1-(*p*-nitrobenzoyl)-D-arabinofuranose (**7**), has been commonly used.[10,11] The reactions employing this halogeno sugar are usually very long and the yields are generally low.[12] Recently, however, the use of molecular sieves has improved the yields, as well as the selectivity toward the preparation of β-isomers.[13] We found that Me_3SiOTf allowed for a very simple and efficient synthesis of anomeric mixtures of these arabinofuranosyl nucleosides by reacting the silylated pyridones with **7** in acetonitrile at room temperature. The β/α ratio was generally around 2, and separation of both isomers by chromatographic means was accomplished either directly or after simple functionalization of the 3-hydroxy group. Specifically, for **8a** and **9a**, separation was readily accomplished by preparative HPLC after reacetylation to the corresponding 3-*O*-acetoxy compounds **8b** and **9b**. The α- and β-isomers were easily distinguished by the coupling constant of the anomeric proton in the NMR spectrum. In the α-isomer (**9b**) the dihedral angle for the 1′,2′ protons approaches 90°, and thus the anomeric proton was observed as a singlet at δ 6.18. In the β-isomer (**8b**) the anomeric proton is in a cis relationship with the 2′-hydrogen, consequently, it appeared as a doublet (J = 5 Hz) at δ 6.36. In a similar fashion, separation of **10a** and **11a** was accomplished after formation of the *O*-benzyl derivatives **10b** and **11b**. The preparation of these compounds was best accomplished by the direct condensation of the corresponding 3-O-benzylated heterocycle **2d** and the sugar **7** in the presence of Me_3SiOTf. As before, the NMR spectra allowed for easy characterization of both isomers. The α-isomer gave the anomeric proton signal with the expected smaller coupling constant (d, J = 3 Hz at δ 5.70), whereas for the β-isomer

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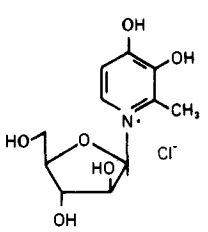
Table I. Spectral Properties of 4-Pyridone Nucleosides

compd	NMR,[a] δ H-1'	H-5	H-6	IR, cm^{-1}	UV λ_{max}, nm (log ε)
6d	5.50 (d)	6.10 (d)	7.86 (d)	1620 (m), 1550 (s), 1500 (m)	286 (4.15), 225 sh (4.17), 220 (4.20)
6c	5.60 (d)	6.20 (d)	8.00 (d)	1620 (s), 1550 (s), 1500 (m)	275 (4.27), 216 (4.06)
6c·HCl[b]	5.90 (d)	7.40 (d)	8.80 (d)	1620 (s), 1505 (m), 1470 (m)	274 (4.19), 215 (4.09)
12	6.36 (d)	7.41 (d)	8.66 (d)	1630 (s), 1530 (m), 1480 (m)	285 (3.90), 225 sh (3.98), 221 (3.99)

[a] NMR spectra were recorded in Me_2SO-d_6. [b] This hydrochloride salt was prepared by treating a methanolic solution of 6c with an excess of methanolic HCl, followed by evaporation to dryness under high vacuum.

the anomeric proton exhibited the larger coupling constant (d, J = 4.5 Hz at δ 5.80). Attempted deprotection of **8b** and **10b** to obtain the corresponding target nucleosides produced only partially deblocked materials in the presence of Pd/C at 50 psi of hydrogen. Only after using Pd black, prepared from the hydrogenation of $PdCl_2$, did the reaction work well. Therefore, as reported in other instances,[14] the presence of HCl appears to be necessary for a complete debenzylation. Furthermore, use of a freshly prepared but neutralized mixture of Pd black also failed to achieve complete deblocking. Under the acidic conditions of the hydrogenation, the deprotected arabinofuranosyl nucleosides **8c** and **10c**, each containing 1 equiv of HCl, were precipitated from the solution by the addition of acetone. From the discussion that follows it appears that with compound **10c** a true hydrochloride salt has been formed, whereas in compound **8c** the molecule simply crystallizes out with an extra equivalent of HCl. The question of O-protonation vs. N-protonation in amides and heterocycle analogues has long been in dispute. UV and IR methods do not appear reliable for discrimination between the two alternatives, and the results have often been misinterpreted.[15,16] NMR spectroscopy, on the other hand, is considered more reliable, and with the use of model compounds, O-protonation has been clearly demonstrated for the 4-pyridone case.[15,16] For the hydrochloride salt of **10c**, O-protonation seems to agree with the NMR data (Table I); therefore, the structure of this compound (as a hydrochloride salt) should be written as **12**.



12

As observed in Table I, both α- and β-protons of the pyridone ring in compounds **12** and **6c** (after the addition of HCl) showed the expected lowering effect in chemical shift with respect to the unprotonated 4-pyridone nucleosides **6c,d**. This trend, consistent with O-protonation, was similar in magnitude and δ value to the changes observed for *N*-methyl-4-pyridone before and after protonation.[15,16] The different sugar moieties (ribose vs. arabinose) may account for the small variance in chemical shift between **12** and **6c**·HCl. Attempts to prepare the free nucleoside from **12** resulted in failure and decomposition, suggesting that the proton was strongly bound. In the 2-pyridone case, however, even though elemental analysis revealed the presence of 1 equiv of HCl, the compound (**8c**) appeared to be a simple HCl adduct. In this case, the extra HCl was easily neutralized with ammonia, and both NMR spectra before and after neutralization were exactly identical and similar with the spectrum of the unprotonated 2-pyridone ribonucleoside **5c**.

Biological Activity. Initially, the activity of the final target compounds was measured in vitro against P-388 cells in culture. The objective of this preliminary single determination was to obtain a rough comparison between the active aglycons and their nucleosides. The lowest ID_{50} obtained was that for the 4-pyridone riboside **6d** (60 μM), which was approximately 2-fold lower than that of the free pyridone **2a** (110 μM). On the contrary, the 2-pyridone riboside **5c** appeared to be less cytotoxic (450 μM) than the parent 2-pyridone **1a** (300 μM). This trend agrees with previous in vivo results, which showed that 4-pyridone derivatives are, in general, superior to their 2-pyridone counterparts.[1,2] The activities of the arabinofuranosyl analogues were disappointingly low, and cytotoxicity vanished completely in the case of the 2-pyridone analogue even at 10^{-4} M. After the separation methods were refined and the yields of the reactions improved, complete in vivo evaluations were performed with the β-isomers of compounds **5b,c**, **6c,d**, **8c**, and **12** against murine P-388 leukemia with doses ranging from 25 to 400 mg/kg qd 1–5. None of the compounds showed minimally active T/C values of 125 in this tumor system.

In conclusion, it appears that the mechanism of action of the parent pyridones **1a** and **2a** may not be mediated through in vivo anabolism to the corresponding nucleosides or nucleotides. The fact that the 4-pyridone riboside **6d** showed superior in vitro activity with respect to the base **2a** appears to suggest that this nucleoside (or its corresponding nucleotide) may indeed interfere with some critical enzyme(s) in pyrimidine metabolism. It is possible that under in vivo conditions this nucleoside is cleaved back to its components, producing inadequate levels of **2a**.

Experimental Section

All chemical reagents are commercially available and were purchased from Aldrich Chemical Co. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were measured with a Perkin-Elmer 727B spectrometer as KBr pellets unless otherwise specified. Proton NMR spectra were determined on Varian T-60 and HR220 instruments. Chemical shifts are given as δ values with reference to Me_4Si or deuterated sodium 3-(trimethylsilyl)propionate (TSP). UV spectra were recorded on a Beckman Model 34 spectrophotometer using 1-cm path-length cells. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, TN. Preparative HPLC chromatography was performed on a Waters Instrument Prep LC/system 500A. Columns for flash chromatography were packed with silica gel (Bio-Sil A, 200–400 mesh, Bio-Rad Laboratories) and eluted with the solvents indicated in the individual experiments. Electron-impact mass spectra were obtained on either a DuPont 21-492B gas chromatograph–mass spectrometer (GC/MS) system or a VG Micromass 7070E GC/MS system. Both instruments were interfaced to a VG 2040 data system for on-line data collection and reduction. Samples were introduced either by direct probe or via a GC (trimethylsilyl

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derivatives) coupled to the mass spectrometer by a single-stage glass jet separator. Microscale silylation was effected by reacting approximately 1 mg of sample with 0.15 mL of bis(trimethylsilyl)trifluoroacetamide and 0.30 mL of CH_3CN at room temperature for 1 h. For these silylated mixtures, the components were separated on a 1.83 m × 2 mm i.d. glass column packed with 3% OV-17 on 100-120 mesh Gas Chrom Q and operated by temperature programming at 4 °C/min in the range 180–250 °C. Nucleosides **5c**, **6c,d** and **8c** all gave a single major peak on GC after trimethylsilylation, indicating a purity greater than 95%. Standard GC operating conditions employed an injector and detector temperature of 250 °C, a 30 mL/min flow rate for both helium carrier gas and hydrogen, and a 300 mL/min flow rate for air. Typical mass spectrometer operating conditions were as follows: transfer line and jet separator, 240 °C; ion source, 250 °C; electron energy, 70 or 75 eV; accelerating voltage, 1.6 kV (Dupont 21-492B) or 6 kV (VG 7070E); ionizing current, 200–250 μA; scan speed, 2 s/decade. Positive ion fast atom bombardment (FAB) mass spectra were obtained on the VG7070E mass spectrometer, which was equipped with a FAB ion source. The underivatized pyridinium salt **12** was dissolved in a glycerol sample matrix, and ionization was effected by a beam of xenon atoms derived by neutralizing xenon ions accelerated through 8.6 kV. Accurate masses for the peak corresponding to the protonated molecular ion (MH^+) were obtained by data system peak matching using a VG digital scan controller. The peak at m/z 185.1025 corresponding to a protonated glycerol dimer was used as the reference peak.

Biological Methods. In vitro activity was measured with P-388 cells in log phase growth (1–5 × 10^5 cells/mL) in 5 mL of culture medium (RPMI 1640 medium with 10% serum and 5 μM 2-mercaptoethanol) incubated with various concentrations of the compounds (1.56–100 μM) for 24 h. Cells were counted, and percent inhibition was calculated in comparison with the control cells incubated with saline. In vivo activity was performed by the NCI according to the standard protocols.[17]

General Condensation Procedure for the Preparation of Protected Ribo- and Arabinofuranosyl Nucleosides. Method A. The starting pyridone (**1b** or **2b**) was dissolved or suspended in hexamethyldisilazane (HMDS, 10 mL/g of pyridone) and refluxed for 2 h in the presence of catalytic amounts of ammonium sulfate. Excess reagent was removed under vaccuum, and the residue was dissolved in anhydrous methylene chloride (50 mL/g of pyridone) for the ribofuranosyl series or acetonitrile (50 mL/g of pyridone) for the arabinofuranosyl series. To this solution, maintained under nitrogen, were added the protected starting sugar **4a,b** or **7** (molar ratio of sugar/pyridone = 0.91) and the catalyst trimethylsilyl trifluoromethanesulfonate (TMSOTf, molar ratio of catalyst/pyridone = 1.2). The resulting bright-yellow solution was stirred at ambient temperature for 24 h. The reaction mixture was then diluted with methylene chloride and washed twice with 30-mL portions of ice-cold saturated $NaHCO_3$ solution and once with brine. The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The resulting crude material was purified by either HPLC or by recrystallization from suitable solvents.

Method B. This method was exactly as the one described under method A above, with the exception that $SnCl_4$ was used as the condensation catalyst.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-3-hydroxy-2-pyridone (5a). Method A. The crude material obtained from 1.68 g of **1b** (11 mmol) and 5 g of **4a** (10 mmol) was purified by recrystallization from acetone–hexane to give 4.5 g (81%) of **5a** as fine needles: mp 145–146 °C; NMR ($CDCl_3$) δ 4.90 (m, 3 H), 5.90 (m, 2 H), 6.10 (t, J = 8 Hz, 1 H), 6.60 (d, J = 4 Hz, 1 H), 6.70 (s, 1 H), 6.80 (d, J = 8 Hz, 1 H), 7.20 (d, J = 8 Hz, 1 H), 7.30–7.70 (m, 10 H), 8.00 (m, 5 H). Anal. ($C_{31}H_{25}NO_9$) C, H, N.

The yield obtained by employing method B was only 16%. After purification by HPLC, the isolated compound **5a** was identical in all respects with that obtained under method A.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-3-methoxy-2-methyl-4-pyridone (6a). Method A. The crude material obtained from 2.75 g of **2c** (20 mmol) and 11 g of **4a** (20 mmol) gave 10.3 g (88%) of pure **6a** as a white foam after purification by preparative HPLC over silica gel (5% MeOH in CH_2Cl_2): mp 59–61 °C; NMR ($CDCl_3$) δ 2.40 (s, 3 H), 3.70 (s, 3 H), 4.70 (m, 3 H), 5.60 (m, 1 H), 5.70 (m, 1 H), 6.00 (d, J = 4 Hz, 1 H), 6.10 (d, J = 6 Hz, 1 H), 7.00–8.00 (m, 16 H). This compound was used directly without further purification for the preparation of **6c**.

The yield obtained by employing method B was 37%. The compound was identical in all respects with that obtained by using method A.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-3-acetoxy-2-methyl-4-pyridone (6b). Method A. The crude product obtained from 1.84 g of **2b** (11 mmol) and 5g of **4a** (10 mmol) gave 2.7 g (45%) of **6b** as white foam after flash chromatography over silica gel (acetone–methylene chloride, 2:3): NMR ($CDCl_3$) δ 2.20 (s, 3 H), 2.30 (s, 3 H), 4.70 (m, 3 H), 5.60 (m, 1 H), 5.70 (m, 1 H), 6.00 (d, J = 4 Hz, 1 H), 6.20 (d, J = 6 Hz, 1 H), 7.20–7.50 (m, 10 H), 7.60 (d, J = 6 Hz, 1 H), 7.90 (m, 5 H). This compound was used directly without further purification for the preparation of **6d**.

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-3-acetoxy-2-pyridone (5b). Method A. The crude product obtained from 3 g of **1b** (19 mmol) and 6.36 g of **4b** (20 mmol) was immediately treated with 1.8 mL of acetyl chloride and 4.4 mL of triethylamine in 200 mL of methylene chloride at 0 °C. After 2 h, the volatile materials were removed under vacuum, and the residue was treated with 50 mL of ethyl acetate. The insoluble was removed, and the filtrate was reduced to dryness. The remaining solid was recrystallized from chloroform–hexane to give 5.1 g (63%) of **5b** as colorless crystals: mp 133–134 °C; IR (KBr) 1740, 1660, 1600 cm^{-1}; NMR ($CDCl_3$) δ 2.02 (s, 3 H), 2.05 (s, 3 H), 2.09 (s, 3 H), 2.23 (s, 3 H), 4.25 (m, 3 H), 5.20 (m, 2 H), 6.05 (t, J = 7 Hz, 1 H), 6.09 (d, J = 3.5 Hz, 1 H), 7.00 (dd, J = 7 Hz, J' = 2 Hz, 1 H), 7.30 (dd, J = 7 Hz, J' = 2 Hz, 1 H); UV (CH_3OH) λ_{max} 302 nm (log ε 3.80), 227 nm (log ε 3.60); mass spectrum, m/z (relative intensity) 369 (M – CH_2CO, 1.0), 259 (sugar, 9.6), 198 (4.4), 156 (19), 139 (14), 114 (20), 111 (21), 97 (23), 43 (100). Anal. ($C_{18}H_{21}NO_{10}$) C, H, N.

General Procedure for the Removal of Benzoyl Protective Groups. The protected nucleoside was added to a saturated solution of ammonia in anhydrous methanol (50 mL/0.5 g of nucleoside) and maintained with occasional stirring at 4 °C in a pressure bottle for 24 h. The resulting solution was then concentrated to dryness and treated with water. The aqueous solution was washed twice with chloroform and lyophilized to afford the corresponding deblocked nucleoside, which could be further purified by either crystallization or HPLC.

1-β-D-Ribofuranosyl-3-methoxy-2-methyl-4-pyridone (6c). After the general deblocking procedure was performed on 1.40 g (2.4 mmol) of **6a**, the crude material obtained was recrystallized from methanol–acetone–hexane to give 0.6 g (92%) of pure **6c** as white flakes: mp 170 °C dec; IR (KBr) 1620, 1550, 1500 cm^{-1}; NMR (D_2O) δ 2.55 (s, 3 H), 3.70 (s, 3 H), 3.80 (m, 2 H), 4.20 (m, 3 H), 5.80 (d, J = 4 Hz, 1 H), 6.50 (d, J = 7.5 Hz, 1 H), 7.90 (d, J = 7.5 Hz, 1 H), UV (CH_3OH) λ_{max} 275 nm (log ε 4.27); mass spectrum of the tris(trimethylsilyl) derivative, m/z (relative intensity) 487 ($M^{+\cdot}$, 0.3), 348 (sugar – H, 3.3), 269 (0.5), 245 (39), 243 (24), 217 (12), 147 (30), 139 (20), 103 (8.3), 73 (100). Anal. ($C_{12}H_{17}NO_6$) C, H, N.

1-β-D-Ribofuranosyl-3-hydroxy-2-methyl-4-pyridone (6d). Protected nucleoside **6b** (1.90 g) was dissolved in 400 mL of a solution of saturated ammonia in methanol and kept in a sealed container at 4 °C for 1 week. Colorless crystals precipitated slowly during this time and were collected to give 0.30 g (38%) of pure **6d**: mp 125–127 °C; IR (KBr) 3300, 1620, 1550, 1500 cm^{-1}; NMR (D_2O) δ 2.40 (s, 3 H), 3.90 (m, 2 H), 4.10 (m, 3 H), 5.80 (d, J = 4 Hz, 1 H), 6.40 (d, J = 7.5 Hz, 1 H), 7.80 (d, J = 7.5 Hz, 1 H); UV (CH_3OH) λ_{max} 286 nm (log ε 4.15); mass spectrum of the tetrakis(trimethylsilyl) derivative, m/z (relative intensity) 545 ($M^{+\cdot}$, 0.1), 530 (M – CH_3, 2.1), 348 (sugar – H, 2.6), 245 (29), 243 (18), 217 (11), 181 (14), 147 (25), 103 (18), 73 (100). Anal. ($C_{11}H_{15}NO_6$) C, H, N.

1-β-D-Ribofuranosyl-3-hydroxy-2-pyridone (5c). A mixture of 3.0 g (7.3 mmol) of **5b** and 10 mL of diisopropylamine in 150 mL of anhydrous methanol was heated gently under reflux for 1 h. The volatile materials were removed under reduced pressure,

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and the residue was chromatographed by flash chromatography over silica gel (20% MeOH in CH_2Cl_2). After the product-containing fractions were combined and the solvent was evaporated, 1.37 g (77%) of **5c** was isolated as a light pink hygroscopic and foamy powder. The solid was stable at 0 °C under nitrogen: IR (KBr) 3300, 1650, 1590, 1540, 1410, 1240, 1100, 1050, 860, 750 cm^{-1}; NMR (D_2O) δ 3.90 (m, 2 H), 4.20 (m, 3 H), 6.00 (d, J = 3 Hz, 1 H), 6.20 (t, J = 7.5 Hz, 1 H), 6.70 (d, J = 7.5 Hz, 1 H), 7.20 (d, J = 7.5 Hz, 1 H); UV (CH_3OH) λ_{max} 302 nm (log ϵ 3.77), 238 (3.48); mass spectrum of the tetrakis(trimethylsilyl) derivative, m/z (relative intensity) 531 ($M^{+\cdot}$, 3.2), 516 (M − CH_3, 3.1), 348 sugar − H, 4.9), 259 (37), 245 (27), 240 (27), 217 (18), 147 (26), 103 (35), 73 (100). Anal. ($C_{10}H_{13}NO_6$) C, H, N.

1-(2,3,5-Tri-*O*-benzyl-D-arabinofuranosyl)-3-acetoxy-2-pyridone (8b and 9b). Method A. Starting with 1.68 g of 1b (11 mmol) and 5.2 g of **7** (10.3 mmol), an unseparable mixture of α- and β-isomers were obtained (3.5 g, 68%). To a solution of 3 g of the mixture in 50 mL of dry methylene chloride at 0 °C were added 3 mL of triethylamine and 0.7 mL of freshly distilled acetyl chloride. After the solution was stirred for 1.5 h, the volatile materials were removed under vacuum, and the remaining residue was treated and stirred vigorously with 50 mL of dry ether. The precipitated salt was removed, and the filtrate was concentrated and chromatographed by HPLC over silica gel (hexane–ethyl acetate, 3:2) to afford 0.88 g of the α-isomer **9b** (27%) and 1.64 g of the β-isomer **8b** (51%). Both compounds were obtained as yellowish syrups.

α-Isomer (9b): NMR ($CDCl_3$) δ 2.27 (s, 3 H), 3.54 (m, 2 H), 3.84 (s, 1 H), 4.18 (m, 3 H), 4.43 (m, 2 H), 4.57 (m, 2 H), 4.86 (d, J = 8 Hz, 1 H), 5.93 (t, J = 7 Hz, 1 H), 6.18 (s, 1 H), 6.84 (m, 2 H), 6.98 (dd, J = 7 Hz, J' = 2 Hz, 1 H), 7.10 (m, 13 H), 7.27 (dd, J = 7 Hz, J' = 2 Hz, 1 H); mass spectrum, m/z (relative intensity) 555 ($M^{+\cdot}$, 0, 2), 513 (M − CH_2CO, 1.9), 422 (0.3), 402 (0.9), 311 (1.2) 181 (27), 154 (13), 111 (12), 91 (100). Anal. ($C_{33}H_{33}O_7N$) C, H, N.

β-Isomer (8b): NMR ($CDCl_3$) δ 2.30 (s, 3 H), 3.60 (d, J = 5 Hz, 2 H), 3.80–4.30 (m, 9 H), 5.90 (t, J = 7 Hz, 1 H), 6.36 (d, J = 5 Hz, 1 H), 6.75–7.25 (m, 16 H), 7.4 (dd, J = 7 Hz, J' = 2 Hz, 1 H); mass spectrum, m/z (relative intensity) 555 ($M^{+\cdot}$, 0.4), 513 (M − CH_2CO, 1.5), 422 (0.4), 405 (0.6), 311 (0.8), 181 (20), 154 (13), 111 (10), 91 (100). Anal. ($C_{33}H_{33}O_7N$) C, H, N.

1-(2,3,5-Tri-*O*-benzyl-D-arabinofuranosyl)-3-hydroxy-2-methyl-4-pyridone (10a and 11a). Method A. Starting with 1.0 g of **2b** (6 mmol) and 3.4 g of **7** (5.9 mmol), an unseparable mixture of α- and β-isomers (2.7 g, 86%) was obtained after HPLC purification over silica gel (5% MeOH in ethyl acetate). From the integration of the anomeric signals in the NMR, the β/α ratio was 2. The anomeric proton for the β-isomer was observed as a doublet (J = 5 Hz) at δ 5.68, and the anomeric proton for the α-isomer appeared as a doublet (J = 3 Hz) at δ 5.64.

3-(Benzyloxy)-2-methyl-4-pyridone (2d). A mixture of maltol (10 g, 79 mmol), benzyl bromide (9.6 mL, 81 mmol), and K_2CO_3 (50 g) in 500 mL of dry acetone (over 4Å molecular sieves) was mechanically stirred for 3 days at room temperature. The precipitated inorganic solid was collected and washed with 100 mL of acetone. The combined washings and solution were concentrated to dryness under vacuum to afford 18 g of crude 3-(benzyloxy)-2-methyl-4-pyrone, which was used in the next reaction without further purification. In a 1-L flask, 4.0 g of 3-(benzyloxy)-2-methyl-4-pyrone was dissolved in 350 mL of ethanol and heated to reflux. Concentrated NH_4OH (50 mL) was added every 2 h until all of the starting material was consumed (~10 h). The solution was then concentrated in vacuo, and the residue was crystallized from chloroform–hexane to give 2.77 g (73%) of **2d** as yellow crystals: mp 165–167 °C; IR (KBr) 1615, 1500, 1460 cm^{-1}; NMR ($CDCl_3$) δ 2.20 (s, 3 H), 5.00 (s, 2 H), 6.40 (d, J = 7 Hz, 1 H), 7.30 (m, 6 H), 7.40 (d, J = 7 Hz, 1 H). This compound was used directly without further purification for the preparation of **10b** and **11b**.

1-(2,3,5-Tri-*O*-benzyl-D-arabinofuranosyl)-3-(benzyloxy)-2-methyl-4-pyridone (10b and 11b). Method A. Starting with 5.10 g of **2d** (24 mmol) and 13 g of **7** (23 mmol), a crude mixture of α/β-isomers was obtained (β/α = 1.5). This mixture was separated by HPLC over silica gel (10% MeOH in ethyl acetate) to afford 2.4 g of the α-isomer **11b** (17%) and 3.5 g of of β-isomer **10b** (32%). Both compounds were isolated as yellowish syrups.

α-Isomer (11b): NMR ($CDCl_3$) δ 2.05 (s, 3 H), 3.56 (d, J = 5 Hz, 2 H), 4.00–4.60 (m, 9 H), 5.16 (dd, J = 24 Hz, J' = 12 Hz, 2 H), 5.70 (d, J = 3 Hz, 1 H), 6.45 (d, J = 8 Hz, 1 H), 7.1–7.3 (m, 20 H), 7.60 (d, J = 8 Hz, 1 H). Anal. ($C_{39}H_{39}NO_6$) C, H, N.

β-Isomer (10b): NMR ($CDCl_3$) δ 2.00 (s, 3 H), 3.65 (d, J = 4 Hz, 2 H), 4.10 (m, 5 H), 4.60 (m, 4 H), 5.20 (dd, J = 24 Hz, J' = 12 Hz, 2 H), 5.80 (d, J = 4.5 Hz, 1 H), 6.40 (d, J = 8 Hz, 1 H), 7.00–7.30 (m, 20 H), 7.70 (d, J = 8 Hz, 1 H). Anal. ($C_{39}H_{39}NO_6$) C, H, N.

General Procedure for the Removal of the Benzyl Protective Groups in the Arabinofuranosyl Series. $PdCl_2$ (half the weight of the protected nucleoside) was suspended in methanol (40 mL/g of $PdCl_2$) and hydrogenated for 1 h under 1 atm of pressure. To the suspension of Pd black in methanol was added a methanolic solution of the protected nucleoside. The mixture was stirred vigorously under 1 atm of H_2 until uptake ceased. Under a nitrogen atmosphere, the catalyst was filtered off, and the filtrate was concentrated and subjected to further purification when necessary.

1-β-D-Arabinofuranosyl-3-hydroxy-2-pyridone Hydrochloride (8c·HCl). After the general deblocking procedure was used with 3.24 g of **8b** (5.8 mmol), the pale yellow methanolic solution was concentrated to ~30 mL, and dry acetone was added until cloudiness appeared. The solution was kept at 4 °C for several days, after which crystals formed. The crystals were collected and dried in vacuo for 24 h to give 1.20 g (74%) of **8c·HCl** as tan-colored crystals: mp 110 °C dec; IR (KBr) 3300, 2900, 1640, 1580, 1540, 1460 cm^{-1}; NMR (Me_2SO-d_6) δ 3.64 (br d, 2 H), 3.80 (m, 1 H), 4.00 (m, 1 H), 4.15 (m, 1 H), 6.10 (t, J = 7 Hz, 1 H), 6.30 (d, J = 4 Hz, 1 H), 6.70 (d, J = 7 Hz, 1 H), 6.90 (br s, 5 H), 7.30 (d, J = 7 Hz, 1 H); UV (CH_3OH) λ_{max} 301 nm (log ϵ 3.80), 240 (3.50); mass spectrum of the tetrakis(trimethylsilyl) derivative, m/z (relative intensity) 531 ($M^{+\cdot}$, 7.6), 516 (M − CH_3, 5.1), 348 (sugar − H, 5.7), 259 (38), 245 (20), 240 (19), 217 (22), 147 (17), 103 (26), 73 (100). Anal. ($C_{10}H_{14}NO_6Cl$) C, H, N, Cl. **8c·HCl** (0.1 g) was neutralized with methanolic ammonia and then evaporated to dryness. The residue was purified by flash column chromatography, giving 0.08 g of white powder. The NMR spectrum was identical with that of **8c·HCl**. Anal. ($C_{10}H_{13}NO_6$) C, H, N.

1-β-D-Arabinofuranosyl-3-hydroxy-2-methyl-4-hydroxypyridinium Chloride (12). After the general deblocking procedure was performed with 2.1 g of **10b** (3.4 mmol), the methanolic solution was reduced to dryness, dissolved in water, and lyophilized to give 0.98 g of **12** as a white hygroscopic powder: mp 90 °C dec; IR (KBr) 1630, 1530, 1480 cm^{-1}, NMR (Me_2SO-d_6) δ 2.55 (s, 3 H), 3.80–4.50 (m, 5 H), 6.36 (d, J = 5 Hz, 1 H), 7.41 (d, J = 7 Hz, 1 H), 8.66 (d, J = 7 Hz, 1 H); UV (CH_3OH) λ_{max} 285 nm (log ϵ 3.90); mass spectrum of the tetrakis(trimethylsilyl) derivative, m/z (relative intensity) 530 (M − CH_3, 11), 349 (sugar, 3.4), 312 (2.7), 259 (51), 217 (29), 181 (8.0), 147 (34), 115 (32), 103 (57), 73 (100); positive FAB MS, m/z 258.1014 (MH^+, calcd 258.0977).

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