evaporated, and the residue was subjected to preparative TLC, eluting with 15% methanol/$CHCl_3$ with several drops of NH_4OH added, to give 4 mg (0.013 mmol, 26%) of (±)-thebaine (**22**): mp 184–187 °C (lit.[19] mp 184–186 °C); NMR ($CDCl_3$) δ 6.66 (1, d, J = 8), 6.59 (1, d, J = 8), 5.55 (1, d, J = 7), 5.29 (1, s), 5.04 (1, d, J = 7), 3.85 (3, s), 3.60 (3, s), 2.46 (3, s).

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Registry No. **8**, 94707-55-8; **9**, 94707-56-9; **10**, 1699-38-3; **11**, 94707-57-0; **12**, 94707-61-6; **13**, 94707-58-1; **14**, 94707-59-2; **15**, 94707-60-5; **17**, 55869-76-6; **18**, 55729-21-0; **19**, 87332-78-3; **21**, 72402-41-6; **22**, 23979-19-3; 2-chloro-2-(methylthio)acetyl chloride, 79388-13-9; *O*-methyl-13-oxothalisopavine, 68890-17-5; isoboldine, 3019-51-0; reticuline, 485-19-8; thalidine, 63110-83-8.

Nucleosides from Carbohydrate Adducts of Diaminomaleonitrile. A Novel Synthesis of 5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide and 5-Amino-1-(β-D-ribopyranosyl)imidazole-4-carboxamide

James P. Ferris,* Balekadru Devadas, Chun-Hsien Huang, and Wu-Yen Ren

Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12180-3590

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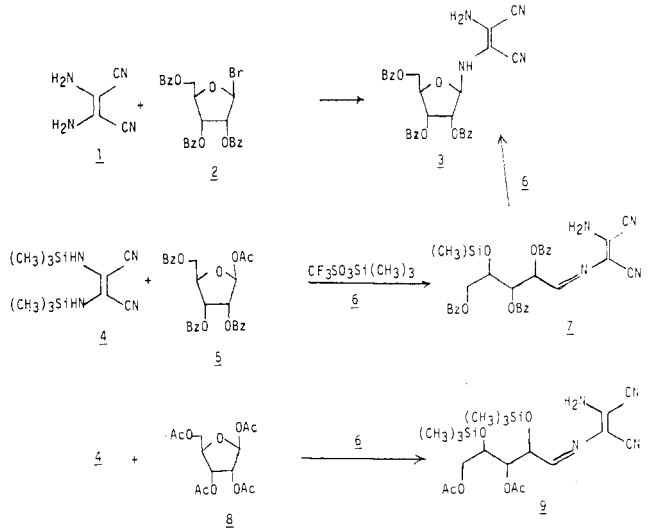
The stereospecific and regiospecific synthesis of 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (**16**) was achieved in six steps. A key intermediate in the synthesis, *N*-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)diaminomaleonitrile (**3**), was prepared by two routes: the reaction of diaminomaleonitrile (**1**) with 1-bromo-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**) and the reaction of the bis(trimethylsilyl) derivative of diaminomaleonitrile (**4**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**5**). Reaction of **3** with triethyl orthoformate yielded 4,5-dicyano-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole (**10**). Alternatively **10** was synthesized by the acid-catalyzed cyclization of the *N*-formyl derivative **12** which was prepared by the reaction of the trimethylsilyl derivative of *N*-formyldiaminomaleonitrile **11** with **5**. Deblocking **10** with 1 equiv of sodium methoxide at room temperature resulted in the regiospecific formation of the 5-imidate **14**. Reaction of **14** with alkaline hypochlorite yielded 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carbonitrile (**15**) by a Hofmann rearrangement. Alkaline hydrolysis of the nitrile function yielded the corresponding amide **16**. 5-Amino-1-(β-D-ribopyranosyl)imidazole-4-carboxamide (**28**) was prepared by a similar synthetic sequence. Reaction of diaminomaleonitrile (**1**) with ribose gave a mixture of the α- and β-anomers of D-ribopyranosyldiaminomaleonitrile (**17**). Compound **17** was converted to a mixture of the anomeric tri-*O*-acetates which on heating with triethyl orthoformate gave a separable mixture of the α- and β-anomers of 4,5-dicyano-1-(2′,3′,4′-tri-*O*-acetyl-D-ribopyranosyl)imidazole (**19** and **20**, respectively). Reaction of **19** with NH_3/CH_3OH at room temperature cleaved the three acetyl groups and regiospecifically converted the 5-cyano to the 5-imidate (**26**). The regiospecificity is due to the attack of the 2′-oxy anion on the 5-cyano group as shown by the isolation of the cyclic imidate **25** when the reaction is carried out at 0 °C. The Hofmann rearrangement of imidate **26** followed by alkaline hydrolysis gave 5-amino-1-(β-D-ribopyranosyl)imidazole-4-carbonitrile **27** and **28**, respectively. The ^1H and ^{13}C NMR spectra of imidates **14** and **26** have multiple peaks for the protons and carbons, respectively. Restricted rotation of the 5-imidate (energy of activation 18 kcal) results in isomers of **14** and **26** with different NMR spectra. The C-2, H-1′ coupling constants of 2.5–3.1 Hz of the isomeric species comprising imidates **14** and **26** are consistent with a H-2, H-1′ dihedral angle of 135° and an anti orientation of the imidazole with respect to the ribose ring; a conclusion confirmed by NOE measurements.

Enamino nitriles are versatile starting materials for the synthesis of heterocyclic compounds[1] and carbohydrate adducts of enaminonitriles have been utilized in this laboratory for the thermal[2] and photochemical[3] synthesis of novel nucleosides. Diaminomaleonitrile (DAMN) (**1**), a "double" enaminonitrile, has rich and varied chemistry, both in the areas of organic synthesis[4] and prebiotic synthesis.[5] The use of ribopyranosylDAMN as the starting material for the synthesis of the ribopyranosides of 4,5-dicyanoimidazole and 4,5-dicyanotriazole was outlined in a preliminary communication.[6]



The synthesis of a corresponding β-D-ribofuranoside and β-D-ribopyranoside adducts of DAMN is reported herein along with their conversion to the corresponding ribo-

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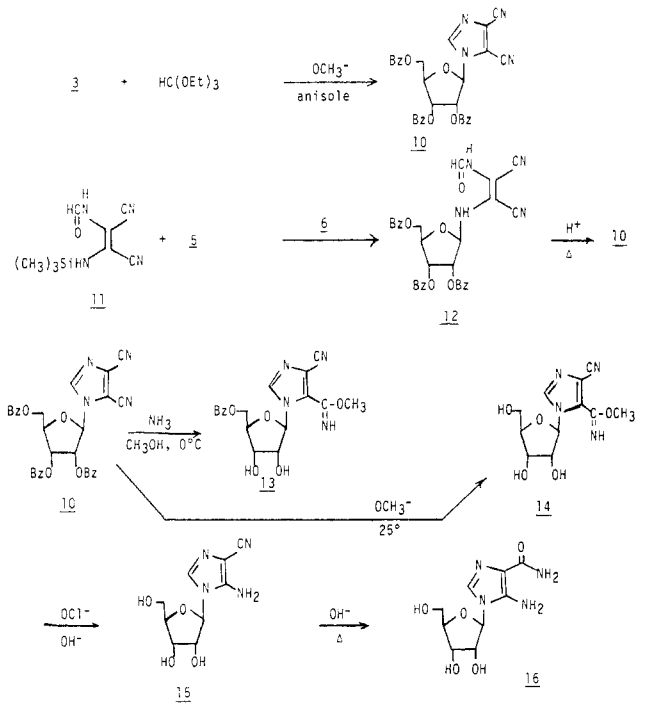
Scheme I



nucleosides of 5-aminoimidazole-4-carboxamide.

Results and Discussion

Ribofuranose Series. In our initial studies[6,7] we succeeded in preparing a mixture of the α- and β-anomers in 1-(2′,3′,5′-tri-*O*-acetyl-D-ribofuranosyl)-4,5-dicyanoimidazole by the acid-catalyzed fusion[8] of 4,5-dicyanoimidazole[9] with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose.[10] Difficulties encountered in separating the anomeric mixture led to the abandonment of this approach for the synthesis of the imidazole ribofuranose series of nucleosides. The synthesis of ribofuranosylDAMN adducts was then investigated since these are readily convertable to ribofuranosyl adducts of heterocycles.[6] Attempted isomerization of ribopyranosylDAMN to the ribofuranosyl derivative by procedures reported for other sugar–amine adducts[11,12] was unsuccessful.[7] The condensation of DAMN with 5-*O*-trityl-2,3-isopropylidene-D-ribofuranose,[13] 2,3,5-tri-*O*-acetyl-D-ribofuranose,[10] 1-chloro-2,3,5-tri-*O*-acetyl-β-D-ribofuranose,[2,14] or 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose[10] either did not proceed or else a complex product mixture was obtained.[15]

The synthesis of *N*-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)diaminomaleonitrile (**3**) was finally achieved by two routes (Scheme I). The direct reaction of DAMN (**1**) with 1-bromo-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**)[16] gave **3** in 50% yield. The condensation of the bis(silylated) adduct of DAMN (**4**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**5**)[17] in the presence of 2 equiv of trimethylsilyl trifluoromethanesulfonate (**6**)[18] gave a 50% yield of **3**. The open chain adduct **7** is also formed in 24% yield when 2 equiv of **6** are used as a catalyst but it is the main product (88%) when only 1 equiv of **6** is used. The formation of **7** by transfer of a trimethylsilyl group from DAMN is undoubtedly the first step in the reaction since it is possible to convert **7** to **3** by treatment with 1 equiv of **6**. Reaction of bis(silyl)DAMN (**4**) with 1,2,3,5-tetra-*O*-acetylribofuranose (**8**)[10] yielded the open chain bis(trimethylsilylated) adduct **9** which could not be cyclized to the corresponding ribofuranose derivative.

The structures assigned to **7** and **9** were confirmed by ^{1}H NMR studies. The protons bound to carbons bearing $-OSiMe_3$ groups are at higher field than the corresponding –OCOR derviatives and are readily identified. The assignment of the position of $-OSiMe_3$ substitution was confirmed by proton spin decoupling studies.

Cyclization of **3** with triethyl orthoformate yielded 4,5-dicyano-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-imidazole (**10**) in 57% yield. An alternative synthesis of **10** was achieved by the acid-catalyzed cyclization of the *N*-formyl derivative **12**, a compound formed by the reaction of the trimethylsilyl derivative of *N*-formylDAMN (**11**)[19] with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**5**). Comparative yields of **10** were obtained by either route but the reaction of **3** with triethyl orthoformate is the method of choice since one less synthetic step is required.

Deblocking **10** with 1 equiv of sodium methoxide at room temperature resulted in the formation of the imidate ester **14**. The 5′-benzoyl adduct **13** was the product when the reaction is performed at 0 °C. The ^{1}H and ^{13}C NMR of **14** and the ^{1}H NMR of **13** exhibited two sets of signals for the protons and carbons present suggesting that a mixture of imidates had been formed. HPLC and TLC analysis of **14** suggested that only one compound was formed, a conclusion confirmed by subsequent chemical transformations. The unusual NMR results and the remarkable regiospecificity of the reaction will be discussed below.

Our original synthetic strategy was to hydrolyze **14** to the corresponding monoamide and then convert the amide to the corresponding amino group by the Hofmann rearrangement. Regiospecific Hofmann rearrangements of the 4-carboxamide of sugar adducts of 4,5-imidazoledicarboxamide have been reported.[20] However, attempted hydrolysis of the imidate to the amide gave a mixture of reaction products. Consideration of the mechanism of the Hofmann rearrangement suggested that it may proceed with imidates and we observed that 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carbonitrile (**15**) was produced in 55% yield on reaction of **14** with 5% sodium hypochlorite. The reaction may proceed by the elimination of CH_3Cl from the initially formed *N*-chloro derivative of **14**. The corresponding Beckman rearrangement of an *N*-chloroimidate and *N*-(phenylsulfonyl)imidates has been reported.[21,22] In the latter example, ethyl benzenesulfonate, a product analogous to the elimination of CH_3Cl from **14**, is formed. The possibility that the Hofmann reaction

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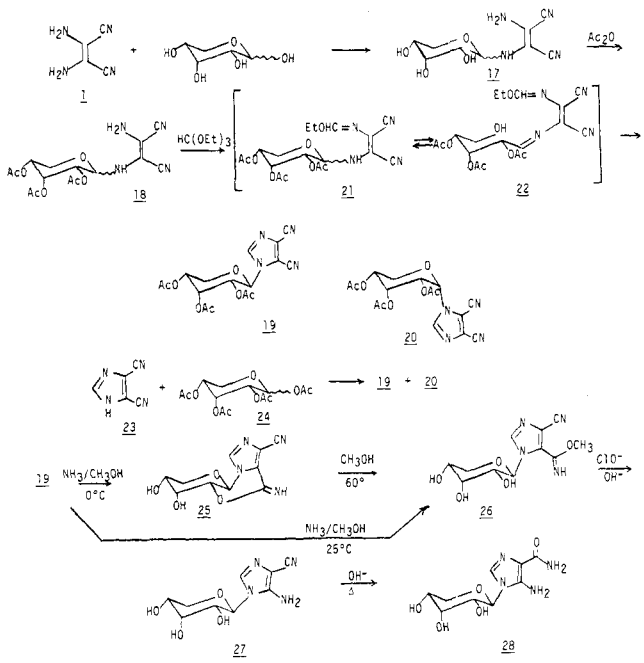
Scheme II



proceeded after the hydrolysis of the imidate to the amide cannot be excluded at the present time. Hydrolysis of **15** with aqueous NaOH gave 5-amino-1-(β-D-ribofuranosyl)-imidazole-4-carboxamide (**16**) in 72% yield.

The carbonitrile **15** has the same melting point reported previously[23] while the carboxamide **16** exhibited IR, UV and ^{1}H NMR spectra identical with those of an authentic sample.[24] The conversion of **14** to **15** and **16** provides the basis for the structure assigned to imidate **14**.

Ribopyranose Series. The reaction of DAMN (1) with ribose was investigated because the condensation of arylamines with sugars is a well-known reaction to give *N*-glycosides[25,26] and because DAMN reacts with aldehydes to give Schiff base adducts.[27,28] Reaction of DAMN and ribose in methanol containing acetic acid gave a 51% yield of the α- and β-anomers of **17** (Scheme II).[29] The presence of anomers was established by the ^{1}H NMR which had signals at δ 5.80 (J = 1 Hz) and 5.55 (J = 10 Hz) for H-1′ of the α- and β-isomers, respectively.[30] The pure β-anomer was obtained by crystallization from CH_3OH–CH_3CN but the anomeric mixture was used in subsequent synthetic steps.

The condensation of DAMN and ribose in aqueous solution was investigated briefly because of the central role of both compounds in pathways proposed for the formation of biomolecules on the primitive Earth.[5] A 10–20% yield of **17** was obtained after reaction for 48 h at room temperature at pH 6.0 in phosphate buffer. Only trace amounts of adduct **17** were detected when the reaction was performed at pH 7 and 8 for 64 h.

An amorphous mixture of tri-*O*-acetates (**18**) was obtained by reaction of **17** with acetic anhydride. Attempted fractional crystallization of this mixture was unsuccessful so it was used directly in the next synthetic step. Reaction of **18** with triethyl orthoformate gave an anomeric mixture of 4,5-dicyanoimidazole derivatives which were separable by silica gel column chromatography. The β-anomer was identified by a ^{1}H NMR signal for H-1′ at δ 5.65 (J = 8.4 Hz) and the α-anomer by the H-1′ resonance at δ 5.77 (J = 2.4 Hz). The H-1′, H-2′ coupling constant of 9.5 Hz in **19** is consistent with the C1 conformation shown for the pyranose ring with the antiperiplanar relationship between H-1′ and H-2′.[30,31a] A coupling constant of 9 Hz was observed for a structurally related ribopyranoside.[32] The coupling constant of 2.4 Hz for H-1′ of **20** is consistent with either the C1 or 1C conformation as the H_1'–H_2' dihedral angle is 60° in both conformers.

The **19**:**20** ratio is dependent on the extent to which the reaction mixture is heated. In a typical experiment, when a 2:1 ratio of **19** to **20** is obtained, **18** is heated at 90–100 °C for 30 min and then a small amount of sodium methoxide is added and the temperature is rapidly increased to 150 °C and maintained at that temperature for 20 min. A 1:3 ratio of **19** to **20** was observed when the initial heating at 90–100 °C is allowed to proceed for 1–4 h and then the temperature is increased to 155 °C over a 40-min period after adding the sodium methoxide. These findings indicate that the β-anomer **19** is the product of kinetic control and the α-anomer **20** is the product of thermodynamic control. A comparable variation in the anomeric ratios was observed with intermediates used for the preparation of C-nucleosides.[33] Since the dicyanoimidazole ribopyranosides **19** and **20** are not interconvertable under the reaction conditions, the product distribution must be determined prior to the cyclication of the imidazole ring. It is postulated that the anomerization observed on heating prodeeds via the equilibration of **21** and **22**, although it was not possible to isolate these intermediates. The greater thermodynamic stability of the α-anomer **20** is probably a consequence of the anomeric effect.[31b]

The presence of ribopyranosyl and 4,5-dicyanoimidazole structural units in **19** and **20** and the stereochemistry assigned at C-1′ were established by their independent syntheses. The acid-catalyzed fusion of 4,5-dicyanoimidazole (**23**)[9] with 1,2,3,4-tetra-*O*-acetyl-β-D-ribopyranose (**24**)[34] gave **19** (26%) as the major product and **20** (2%) as a minor product. Neighboring group participation by the 2′-acetoxy group directs the nucleophile to the β-side so the β-pyranoside (**19**) is the major reaction product.[35]

Reaction of **19** with methanolic ammonia at room temperature not only resulted in the cleavage of the *O*-acetyl groups but also converted the 5-cyano to the corresponding 5-imidate **26**. If the reaction and workup are performed at 0–5 °C, the cyclic imidate **25** can be isolated. When **25** is warmed in methanol it is converted to **26**.

Treatment of **26** with a solution of KF and 18-crown-6 in acetonitrile yielded the dinitrile **29**. This transformation is comparable to the base-catalyzed elimination of CH_3OH from an imidate[36] with F^- serving as the base. The for-

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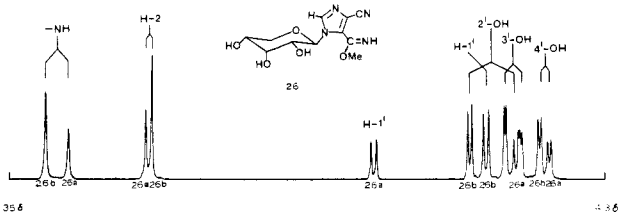
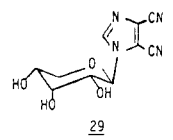


Figure 1. ^1H NMR spectrum of imidate **26** with the signals of the two rotameric forms of the imidate grouping, **26a** and **26b**, identified.

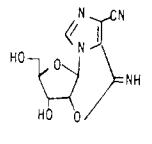
mation of one product in this and other reactions of **26** confirmed our previous conclusion that **26** is not a mixture of isomers.

The Hofmann rearrangement of imidate **26** proceeded in 48% yield to give the amino nitrile **27** as the product. The UV spectral maxima of **27** in acidic and neutral solution are identical with those of the corresponding ribofuranosyl isomer and differ from the spectra of the corresponding 1-substituted 4-aminoimidazole-5-carbonitriles.[37] Hydrolysis of **27** in 1.5 N NaOH at 100 °C gave the β-D-ribopyranose adduct of 5-aminoimidazole-4-carboxamide (**28**) which had UV spectra in acidic and neutral solution identical with other derivatives and different from that of the isomeric 1-substituted 4-aminoimidazole-5-carboxamides.[38,39]

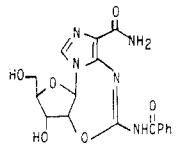
Regiospecificity of Imidate Formation. The isolation of cyclic imidate **25** established that the high regioselectivity for the conversion of the 5-cyano to the corresponding imidate is due to intramolecular catalysis by the 2′-oxy anion. Attempted isolation of the corresponding cyclic imidate in the ribofuranose series (**30**) so far has not been successful. This may reflect the greater reactivity of **30** so that it is converted to **14** even at 0 °C. The possibility that **14** is formed by general base catalysis and not via the cyclic imidate **30** cannot be eliminated at the present time. A stable seven-membered cyclic compounds (**31**) has been reported to be formed by attack of the 2′-oxy anion on a benzoylthiocarbonyl adduct[40] but, to our knowledge, **25** is the first six-membered ring to be detected between the 2′- and 5-positions in either a pyranose or furanose series of nucleosides.



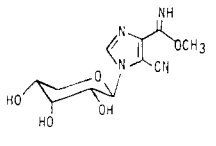
29



30

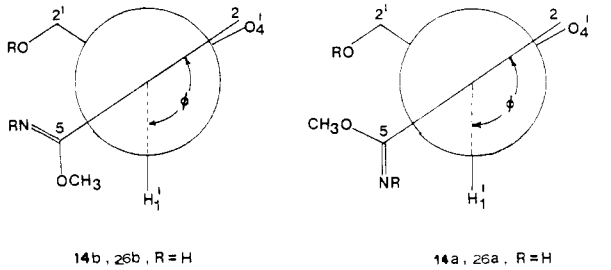


31



32

Imidate Restricted Rotation. The ^1H and ^{13}C NMR spectra of **26** are unusual in that there are multiple signals



14b, 26b, R = H **14a, 26a, R = H**

Figure 2. Newman projection of the imidate rotamers of **14** and **26** viewed along the N(1)–C(1′) bond. Φ is the dihedral angle between C(2)–N(1) and C(1′)–H(1′).

present for almost every proton and carbon, respectively (Figure 1). Similar NMR spectra were observed for (**14**). Addition of D_2O to the sample did not alter the ^1H NMR spectral pattern observed for the nonexchangeable protons of **14** and **26**.

Initially it was concluded from the NMR spectra that mixtures of the 4- and 5- imidates were obtained even though the chromatographic properties of **14** and **26** indicated they were pure compounds. The subsequent conversions to **15** and **27**, respectively, and the isolation of the 4-imidate **32** as a minor hydrolysis product when **19** is deblocked with NH_3–CH_3OH established that one regioisomer of **26** is the principal reaction product. Imidates **26** and **32** are readily separable by fractional crystallization and HPLC.

The chemical studies outlined above establish that the multiple NMR signals are due to interconverting isomers of **14** and **26**. It was apparent that two forms of each were present from the ^1H NMR spectrum. Signals due to H-1′, 2′-OH, and NH, which differ by more than 0.2 ppm in the two isomers, are readily discernable. The 2:1 intensity difference in the two groups of signals and decoupling studies facilitated the assignment of signals to the two isomers which were designated **26a** and **26b** (Figure 1). The isomeric forms of **14** are present in almost equal amounts but it was possible to assign many of the NMR signals on the basis of decoupling studies and by comparison with the NMR spectrum of **26**. Since the principal chemical shift differences were noted in the groups proximate to the imidazole ring and very small shifts (<0.05 ppm) were noted in the C–H proton signals other than H-1′ it was concluded that the observed isomerism was associated with the imidazole ring. The alternative possibility that two conformers of the pyranose ring were present was eliminated by the observation that $J_{H1',H2'}$ was the same (9.6 Hz) in both the isomeric forms of **26**.

Interconverting syn and anti isomers, resulting from restricted rotation about the C–N nucleoside bond, were initially considered to be the source of the unusual NMR spectra. The C-2, H-1′ coupling constants of 2.5–3 Hz for the isomers of both **14** and **26** established that the dihedral angle (ϕ) between H-2 and H-1′ was either ±35° (±10°) or ±125° (±10°).[41] Inspection of CPK Ealing atomic models revealed that in the syn isomers (ϕ ±35°), where C-5 of the imidazole is situated over the ribose ring, there are severe steric interactions between the 5-imidate and the ribose ring. Similar steric repulsions between the ribose moiety and the 5-substituent on an imidazole or the 6-substituent on a pyrimidine have been noted in the syn rotamer of other nucleosides.[42-44] These findings estab-

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lished the absence of syn–anti isomerism. The dihedral angle of 135° (X_{new} = 185°)[45] shown in Figure 2 was selected as the one best representing the anti isomers present in **14** and **26**. The steric interactions between H-2 and H-2′ eliminated the other anti conformer, with ϕ = 135°, from further consideration.[42]

Nuclear Overhauser enhancement (NOE) studies are in agreement with the conclusion that the multiple NMR signals of **14** and **26** are not due to the presence of syn and anti rotomers. A comparable transfer of magnetism from H-1′ to H-2 was observed for the isomers present in both **14** and **26**. This establishes that H-1′ and H-2 are the same distance apart in all the isomers. For example, a 5-fold greater transfer of magnetism from H-1′ to H-5 was observed in the syn conformation of ribavirin than was observed in the anti conformation of the 5′-phosphate of ribavirin.[46]

Elimination of syn–anti isomerism left restricted rotation about the 5′-imidate as the only source of the multiple NMR peaks in **14** and **26**. The methoxyl group of the imidate possesses considerable steric bulk and the rotation of the imidate group is restricted by two ortho substituents. The absence of restricted rotation of the 4-imidate in **32**, a compound with only one ortho substituent, was demonstrated by the absence of multiple peaks in its NMR spectrum. The energy of activation for rotation, 18 kcal, determined from the coalescence temperatures of the imidate NH and H-2 in **14** and **26**, is comparable to that measured for other molecules with restricted rotation.[47]

The interconversion of **12a** with **12b** and **13a** with **13b** at room temperature was also apparent in the NOE experiments. Saturation of H-1′ in **26a** resulted in a decrease in the H-1′ signal of **26b**. This reflects the interconversion of **26a** to **26b** at a rate that is slow on the NMR time scale.[48] Similar observations were made for the isomers of **13**. This interconversion explains why it has not been possible to separate the isomeric forms of **14** and **26** detected by ^{1}H and ^{13}C NMR.

The marked differences in the chemical shifts of H-1′, 2′-OH, and NH in the isomers of **14** and **26** can be understood on the basis of the different orientations of the imidate. In the isomers shown in the Newman projection in Figure 2 (**14a**, **26a**), where the methoxyl group of the imidate is next to the 2′-OH, the H-1′ is in the plane of the imino function and its signals is shifted to lower field by the anisotropy of the imino group (6.52 ppm in **14a** and 6.4 ppm in **26a**). The proton of the 2′-OH is positioned in the shielding region above the plane of the imino function and is shifted to higher field (5.5 ppm in **14a** and 5.2 ppm in **26a**). In the other conformation of the imidate shown in Figure 2 (**14b** and **26b**), H-1′ is in the region of shielding below the imidate while the 2′-OH is in the deshielding region in the plane of the imidate. The signal for H-1′ is shifted to higher field (5.78 ppm in **14b** and 5.46 ppm to **26b**) and the 2′-OH to lower field (5.74 ppm in **14b** and 5.6 ppm in **26b**).

The trimethylsilyl (Me_3Si) derivatives of **12** and **26**, where the three hydroxyl groups and the imino function are silylated , exhibit only one set of ^{1}H NMR signals characteristic of a single chemical species. Inspection of CPK atomic models indicates the imidate is locked into the conformation depicted in Figure 2 (**14a**, **26a**, R = $SiMe_3$) with the imidate methoxyl group next to the 2′-$OSiMe_3$ grouping. The other orientation of the imidate (**14b**, **26b**, R = $SiMe_3$) is not feasible because of severe steric interactions between the 2′-$OSiMe_3$ and the N-$SiMe_3$ grouping.

The efficient synthesis of the aminoimidazolecarboxamide nucleosides **16** and **28** starting from DAMN and sugar derivatives clearly establishes the utility of DAMN adducts of sugars as starting materials for the preparation of novel nucleoside with the potential for useful pharmacological properties.[38,39,49] The multifaceted chemistry of DAMN provides the potential for the formation of a variety of heterocyclic adducts of sugars[18,26] and the synthetic methodology allows for almost complete freedom in the variation of the configuration at any center in the glycoside as well as in the ring size (furanose or pyranose) of the sugar moiety. An unexpected finding in the present study, the formation of the stable cyclic imidate **25**, may provide a route to selective substitution at the 2′-position, an area currently under investigation.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were measured in $(CD_3)_2SO$ on a Varian FT XL-200 unless stated otherwise. All chemical shifts are reported in ppm relative to Me_4Si as internal standard. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E and a Hewlett Packard 5987 and UV spectra on a Varian Cary 219. IR spectra were determined in Nujol on a Perkin-Elmer 298 spectrophotometer. Melting points were determined on a Mel-Temp apparatus. Thin-layer chromatography (TLC) was performed with Merck silica gel GC 254 on microscope slides or 20 × 20 cm glass plates. Column chromatography was performed with Baker 40–140 mesh silica gel. High-performance liq. chromatog. was carried out on a Whatman ODS-3 reverse-phase column (4.6 × 250 mm) with 0.01 M ammonium dihydrogen phosphate (pH 3.5)–methanol (4:1) as the mobile phase. The nucleosides were detected by their absorption at 254 nm. Methanol was dried by distillation from magnesium, anisole and dioxane by distillation from sodium. Triethyl orthoformate was distilled before use. Trimethylsilyl trifluoromethanesulfonate was obtained from Fluka and hexamethyldisilazene and chlorotrimethylsilane from Aldrich.

***N*-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)diaminomaleonitrile (3).** (a) To a solution of 1-bromo-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**2**),[35] obtained from 2.5 g (4.95 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**5**)[41] in dry dioxane (20 mL), was added diaminomaleonitrile (**1**) (0.3 g, 12 mmol), and the mixture was stirred at room temperature under argon for 24 h. A clear orange-red solution was formed from which some solid began separating. The dark colored reaction mixture was cooled and filtered. The residue was washed twice with dioxane (2 × 5 mL), and the filtrate was concentrated under reduced pressure. The dark colored syrup was triturated with chloroform (50 mL) and filtered. The residue was washed with chloroform. The combined filtrates were concentrated in a rotary evaporator and subjected to silica gel (60 g) column chromatography by using chloroform–acetone (9:1) as the eluent. Compound **3**, 1.2 g (44%), was isolated as a gummy solid which on trituration with anhydrous ether solidified. Crystallization from chloroform–hexane gave an analytically pure sample of **3**: mp 169–170 °C; UV_{max} (MeOH) 228 nm (ε 38 310), 302 nm (ε 11 830); IR 3420, 3320, 2200, 1720, 1600, 1260, 1100, 700 cm^{-1}; ^{1}H NMR δ 4.3–4.8 (m, 4, H-5′, H-4′, NH), 5.4 (dd, 1, $J_{1'2'}$ = 6.0 Hz, $J_{1'NH}$ = 8.0 Hz, H-1′), 5.6 (t, 1, $J_{1'2'}$ = 6.0 Hz, $J_{2'3'}$ = 6.0 Hz, H-2′), 5.84 (t, 1, $J_{2'3'}$ = 6.0 Hz, $J_{3'4'}$ = 6.0 Hz, H-3′), 6.26 (s, 2, NH_2), 7.4–8.2 (m, 15, aromatic).

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Anal. Calcd for $C_{30}H_{24}N_4O_7$: C, 65.21; H, 4.35; N, 10.15. Found: C, 65.18; H, 4.14; N, 10.01.

(b) A mixture of diaminomaleonitrile (2.7 g, 24 mmol), hexamethyldisilazane (25 mL, 118.5 mmol), and trimethylchlorosilane (2.5 mL, 19.7 mmol) in acetonitrile (40 mL) was heated to reflux under nitrogen for 3 h. The solvent was distilled, and the residue was dried overnight under high vacuum. The mass spectrum, (*m/e*) 252 (M^+), indicated the bis(trimethylsilyl) derivative was formed. To this residue was added 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (10 g, 19.8 mmol), and the mixture was dissolved in 100 mL of methylene chloride. The solution was cooled in an ice bath and to it was added dropwise trimethylsilyl trifluoromethanesulfonate (7.9 mL, 43.5 mmol) with stirring under a nitrogen atmosphere. The reaction was quenched after 2.5 h by pouring it into 500 mL of cold saturated sodium bicarbonate solution with simultaneous bubbling of nitrogen through the solution. The reaction mixture was extracted with chloroform, the organic phase was washed with water and dried over anhydrous Na_2SO_4. The dark brown solution thus obtained was concentrated to dryness and triturated with chloroform–acetone (19:1) and a solid crystallized. The solid was filtered, washed with cold chloroform, and dried to give 5.5 g (50%) of **3**: mp 169–170 °C. The filtrate was concentrated under reduced pressure and purified by silica gel flash chromatography using chloroform–acetone (19:1) as the eluent. Fractions containing **7** were combined and concentrated to give 3 g (24%) of **7** as an amorphous solid.

***N*-[D-*ribo*-2,3,5-Tri-*O*-benzoyl-4-*O*-(trimethylsilyl)-pentylidene]diaminomaleonitrile (7).** The bis(trimethylsilyl) derivative **4**, prepared from 5 g (46.3 mmol) of **1**, was dissolved in 150 mL of dichloromethane along with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**5**)[17] (10 g, 19.8 mmol). The solution was cooled in an ice bath, trimethylsilyl trifluoromethanesulfonate (**6**) (4.8 mL, 2.64 mmol) was added dropwise, and the mixture was stirred under nitrogen atmosphere for 2 h. Saturated sodium bicarbonate solution (500 mL) was then added, the mixture was extracted with chloroform, and the organic layer was washed with water (3 × 100 mL) and dried over anhydrous Na_2SO_4. The dark brown solution was evaporated to dryness under reduced pressure and the residue was purified by silica gel flash chromatography with chloroform–acetone (9:1) as the eluent. Fractions containing **7** were pooled and concentrated under reduced pressure to give **7** (11.4 g, 88%). Attempts to crystallize **7** were unsuccessful, but an analytical sample was prepared by precipitating from an etherial solution with hexane: UV_{max} (MeOH) 324 nm (ε 17 750), 230 nm (ε 34 443); IR (Nujol) 3440, 3320, 2230, 2200, 1720, 1610, 1260, 1110, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.1 (s, 9, $SiMe_3$) 4.3–4.6 (m, 3, H-4′, H-5′), 5.1 (br s, 2, NH_2), 5.84 (dd, 1, $J_{2'3'}$ = 3.6 Hz, $J_{3'4'}$ = 4.8 Hz, H-3′), 6.1 (dd, 1, $J_{1'2'} = J_{2'3'}$ = 3.6 Hz, H-2′), 7.3–8.0 (m, 15, aromatic), 8.0 (d, 1, $J_{1'2'}$ = 3.6 Hz, H-1′); mass spectrum, *m/e* 624 (M^+).

Anal. Calcd for $C_{33}H_{32}N_4O_4Si$: C, 63.42; H, 5.16; N, 8.99. Found: C, 63.07; H, 5.13; N, 8.89.

***N*-[D-*ribo*-3,5-Di-*O*-acetyl-2,4-bis-*O*-(trimethylsilyl)-pentylidene]diaminomaleonitrile (9).** The bis(trimethylsilyl) derivative **4**, prepared from 0.65 g (6 mmol) of DAMN, was dissolved in methylene chloride (25 mL) and filtered under anhydrous conditions. To the filtrate was added 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**8**)[10] (1.6 g, 5.0 mmol), and the solution was cooled to 0–5 °C. To this solution was added dropwise trimethylsilyl trifluoromethanesulfonate (0.3 mL, 1.65 mmol), and the mixture was stirred under nitrogen for 1.5 h. The reaction mixture was added carefully to a chilled solution of sodium bicarbonate (5 g, 50 mL) and extracted with chloroform. The organic phase was washed with water until the pH of the washings was 7, and the organic layer was then dried over anhydrous Na_2SO_4. The solution was concentrated to dryness and chromatographed on silica gel with chloroform–acetone (19:1) as the eluent. Fractions containing **9** were combined and evaporated under reduced pressure to give **9** (0.6 g, 47%) as a light brown syrup. Crystallization from carbon tetrachloride gave **9** as pale yellow needles: mp 114–115 °C; UV_{max} (MeOH) 321 nm; IR (Nujol) 3420, 3280, 3160, 2240, 2190, 1740, 1720, 1250, 1140, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (2 s, 18, 2 $SiMe_3$), 1.98 (2 s, 6, 2 CH_3COO), 4.06 (m, 3, H-4′, H-5′), 4.46 (dd, 1, $J_{1'2'}$ = 4 Hz, H-2′), 5.04 (dd, 1, $J_{3'4'}$ = 4 Hz, H-3′), 5.18 (br s, 2, NH_2), 7.72 (d, 1, $J_{1'2'}$ = 4 Hz, H-1′); mass spectrum, *m/e* 453 (M – CH_3), 408 (M – CH_3COOH), 335 (M – $CH_3COOSiMe_3$).

Anal. Calcd for $C_{19}H_{32}N_4O_6Si_2$: C, 48.71; H, 6.83; N, 11.96. Found: C, 48.94; H, 6.83; N, 12.24.

***N*-Formyl-*N*′-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)diaminomaleonitrile (12).** Monoformyldiaminomaleonitrile[19] (0.27 g, 2 mmol) was silylated by refluxing in hexamethyldisilazane (10 mL) and trimethylchlorosilane (1 mL) for 1 h under nitrogen. The solvents were distilled, the residue was dissolved in dry methylene chloride (10 mL), and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**5**)[17] (1 g, 2 mmol) was added followed by the addition of trimethylsilyl trifluoromethanesulfonate (**6**) (0.4 mL). The reactants were stirred at room temperature under nitrogen for 2.5 h. The reaction mixture was poured into 100 mL of chilled 10% sodium bicarbonate and extracted with chloroform. The organic phase was washed with water, dried over anhydrous Na_2SO_4, and concentrated, and the syrupy extract was purified by silica gel column chromatography with chloroform–acetone (19:1) as the eluent. Concentration of fractions containing **12** to dryness under reduced pressure gave 0.6 g (60%) as amorphous solid. An analytical sample was prepared by crystallization from methanol: mp 100–102 °C; UV_{max} (MeOH) 229 nm (ε 39 350), 280 nm (ε 17 300); IR 3400, 3300, 3200, 2200, 1720, 1630, 1260, 1120, 700 cm^{-1}; ^1H NMR δ 4.55 (m, 2, H-5′), 4.66 (m, 1, H-4′), 5.74 (m, 2, H-3′, H-2′), 6.1 (d, 1, $J_{1'2'}$ = 6.0 Hz, H-1′), 7.4–8.48 (m, 18, CHO, NH, aromatic).

Anal. Calcd for $C_{31}H_{24}N_4O_8 \cdot {}^1/_4H_2O$: C, 63.64; H, 4.19; N, 9.58. Found: C, 63.65; H, 4.38; N, 9.67.

4,5-Dicyano-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-imidazole (10). A solution of **3** (1.2 g, 1.8 mmol) in anisole (10 mL) and triethyl orthoformate (0.6 mL, 3.6 mmol) was heated to 90 °C for 1.5 h under nitrogen. To this reaction mixture was added sodium methoxide (16 mg, 0.3 mmol), and the reaction temperature was raised to 140 °c and maintained for 35 min. The solvents were distilled, and the residue was dried under high vacuum. The residue was purified by silica gel column chromatography with benzene–acetone (19:1) as the eluent. Compound **10** was isolated as an amorphous solid which crystallized from absolute ethanol to give 0.7 g (57%): mp 139–140 °C; UV_{max} (MeOH) 231 nm (ε 4910); IR 3100, 2240, 1715, 1600, 1280, 1130, 1080, 700 cm^{-1}; ^1H NMR δ 4.78 (m, 1, $J_{4'5'}$ = 4.8 Hz, $J_{5'a5'b}$ = –12.8 Hz, H-5′), 5.04 (m, 1, $J_{4'5'} = J_{3'4'}$ = 4.8 Hz, H-4′), 6.04 (dd, 1, $J_{2'3'}$ = 5.8 Hz, $J_{3'4'}$ = 4.8 Hz, H-3′), 6.14 (dd, 1, $J_{2'3'}$ = 5.8 Hz, $J_{1'2'}$ = 4.8 Hz, H-2′), 6.45 (d, 1, $J_{1'2'}$ = 4.8 Hz, H-1′), 7.7–8.1 (m, 15, aromatic), 8.78 (s, 1, H-2).

Anal. Calcd for $C_{31}H_{22}N_4O_7$: C, 66.19; H, 3.91; N, 9.96. Found: C, 66.25; H, 3.96; N, 9.86.

Acid-Catalyzed Cyclization of *N*-Formyl-*N*′-(2,3,5-tri-*O*-benzoyl-D-ribofuranosyl)diaminomaleonitrile (12) to 10. A solution of **12** (0.2 g, 0.34 mmol) in benzene (5 mL) containing acetic acid (0.5 mL) was heated to reflux for 10 h. The reaction mixture was concentrated to dryness and purified by preparative TLC with chloroform–acetone (4:1) as the eluent. Compound **10** was eluted (0.12 g, 63%) and crystallized from ethanol: mp 139–140 °C; IR and ^1H NMR data were identical with **10**.

Methyl 4-Cyano-1-(5′-*O*-benzoyl-β-D-ribofuranosyl)-imidazole-5-carboximidate (13). Anhydrous methanol (5 mL) was saturated with ammonia at 0 °C for 20 min and cooled to –40 °C. 4,5-Dicyano-1-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole (**10**) (0.14 g, 0.5 mmol) was added and the mixture stirred at –40 °C for 30 min. The solution was allowed to warm to 0 °C over a period of 2.5 h. The methanol was evaporated under reduced pressure at 0 °C, and the residue was purified by preparative silica gel TLC with ethyl acetate–acetonitrile (7:3) as the eluent. Crystallization from ethyl acetate afforded (**13**) (20 mg) as white fluffy crystals: mp 190 °C; UV_{max} (MeOH) 230 nm (ε 20 458), 250 nm (sh) (ε 11 097); IR (Nujol) 3500–3400 (br), 2220, 1700, 1640, 1100, 830 and 700 cm^{-1}; ^1H NMR δ 3.83, 3.86 (2 s, 3, OCH_3), 4.1–4.4 (m, 3, H-4′, H-5′), 4.6 (m, 2, H-2′, H-3′), 5.48, 5.6, 5.7, 5.94 (d, 2, $J_{2'OH} = J_{3'OH}$ = 6 Hz, 2′-OH, 3′-OH), 5.8, 6.62 (d, 1, $J_{1'2'}$ = 4.8 Hz, $J_{1'2'}$ = 2.5 Hz, H-1′), 7.4–8.4 (m, 6, aromatic, H-2), 9.06, 9.39 (2 s, 1, NH).

Anal. Calcd for $C_{18}H_{18}N_4O_6$: C, 55.95; H, 4.66; N, 14.50. Found: C, 56.02; H, 4.72; N, 14.42.

Methyl 4-Cyano-1-(β-D-ribofuranosyl)imidazole-5-carboximidate (14). A solution of **10** (0.4 g, 0.71 mmol) of dry methanol (12 mL) containing NaOMe (40 mg, 0.74 mmol) was

stirred at room temperature for 2 h under anhydrous conditions. The reaction mixture was cooled and filtered, and residue was washed with cold methanol and dried to give 0.11 g (55%) of **14**. An analytical sample of **14** was prepared by crystallization from MeOH: mp 185–186 °C dec; UV_{max} 247 nm (ϵ 10 500); IR 3300, 2220, 1645, 1530, 1200, 1100, 820 cm^{-1}; ^1H NMR δ 3.7 (m, 2, H-5′), 3.82, 3.86 (2 s, 3, OCH_3), 4.0 (m, 1, H-4′), 4.11 (m, 1, H-3′), 4.23 (m, 1, H-2′), 5.1–5.4 (m, 2, $J_{5'\text{-OH}} = J_{3'\text{-OH}} = 4.8$ Hz, 3′,5′-OH), 5.5, 5.74 (2 d, 1, $J = 4.8$ Hz, 2′-OH), 5.78, 6.52 (d, 1, $J_{1'2'} = 4.8$ Hz, $J_{1'2'} = 2.5$ Hz, H-1′), 8.44, 8.60 2 s, 1, H-2), 9.0, 9.3 (2 s, 1, NH); ^{13}C NMR 52.6, 53.6, 60.25, 60.73, 69.00, 69.88, 76.15, 76.44, 84.89, 86.12, 90.41, 90.8, 114.15, 114.62, 115.26, 116.08, 132.35, 133.13, 138.89, 140.09, 153.33, 156.38; mass spectrum, m/e 282 (M^+), 250, 208, 279, 132.

Anal. Calcd for $C_{11}H_{14}N_4O_5$: C, 46.80; H, 4.96; N, 19.86. Found: C, 46.90; H, 5.10; N, 19.78.

5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carbonitrile (15). To an ice cooled solution of sodium hypochlorite (1.9 mL, 5.25%) was added **14** (0.26 g, 0.92 mmol), and the mixture was stirred for 14 min, followed by the addition of 1.5 N NaOH (1 mL). The reactants were stirred at the same temperature for another 15 min and then heated to 75 °c under argon for 2.5 h. The pH of the reaction mixture dropped from 10 to 8. The reaction mixture was cooled, neutralized with dilute HCl, and freeze dried. The amorphous material (slightly pink in color) thus obtained was extracted with methanol (2 × 10 mL), filtered, and the filtrate was concentrated to a small volume in a rotary evaporator. Subsequent purification by preparative TLC with EtOAc–MeOH (7:3) yielded 0.12 g (55%) of **15** as gummy solid which crystallized from EtOH: mp 205 °C dec; UV_{max} (MeOH) 245 nm (ϵ 16 000), pH 2, 238 nm (ϵ 14 310); IR 3440, 3320, 3140, 2200, 1660, 1580, 1200, 1050 cm^{-1}; ^1H NMR δ 3.58 (m, 2, H-5′), 3.9 (dd, 1, $J_{3'4'} = 6.4$ Hz, $J_{4'5'} = 3.2$ Hz, H-4′), 4.03 (m, 1, H-3′), 4.23 (dd, 1, $J_{1'2'} = J_{2'3'} = J_{2'\text{OH}} = 6.4$ Hz, H-2′), 5.16 (d, 1, $J = 4.8$ Hz, 3′-OH), 5.3 (t, 1, $J = 6.4$ Hz, 5′-OH), 5.38 (d, 1, $J = 6.4$ Hz, 2′-OH), 5.46 (d, 1, $J_{1'2'} = 6.4$ Hz, H-1′), 6.34 (s, 2, NH_2), 7.4 (s, 1, H-2); ^{13}C NMR 60.87, 70.06, 72.92, 85.49, 87.86, 90.63, 117.18, 131.26, 147.49; mass spectrum, m/e 241 (M + 1), 240 (M^+), 186, 133.

Anal. Calcd for $C_9H_{12}N_4O_4$: C, 45.00; H, 5.00; N, 23.33. Found: C, 44.99; H, 5.07; N, 23.28.

5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (16). A solution of **15** (0.18 g, 0.75 mmol) in 1.5 N NaOH (2 mL) was heated to 100 °C under argon for 2.5 h. The reaction mixture was cooled, neutralized with dilute HCl, and concentrated to dryness under high vacuum. The residue was extracted with dry methanol (2 × 10 mL), and the insoluble salts were filtered and concentrated. Preparative TLC of the concentrate with EtOAc–MeOH (6:4) afforded 0.14 g (72%) of **16** as semisolid. Crystallization from methanol yielded an analytical sample: mp 213–214 °,c dec (lit.[50] mp 213–214 °C); UV_{max} pH 7 and 1 N NaOH, 265 nm (ϵ 12 400), 1 N HCl, 245 nm (ϵ 8670), 265 nm (ϵ 10 320) [lit.[50] pH 7.05 and 13, 267 nm (ϵ 12 800) pH 1, 246 and 267 nm]; ^1H NMR δ 3.6 (m, 2, H-5′), 3.9 (m, 1, H-4′), 4.06 (m, 1, H-3′), 4.3 (dd, $J_{1'2'} = 6.5$ Hz, $J_{2'3'} = J_{2'\text{-OH}} = 6.0$ Hz, H-2′), 5.18 (d, 1, $J = 6.0$ Hz, 3′-OH), 5.26 (t, 1, $J = 6.0$ Hz, 5′-OH), 5.4 (d, 1, $J = 6.5$ Hz, 3′-OH), 5.48 (d, 1, $J_{1'2'} = 6.5$ Hz, H-1′), 5.96 (s, 2, NH_2), 6.76 (br, 2, $CONH_2$), 7.34 (s, 1, H-2). The IR, UV, and ^1H NMR spectra were identical with an authentic sample.[24]

D-Ribopyranosyldiaminomaleonitrile (17). (a) To a solution of D-ribose (1.5 g, 10 mmol) in 20 mL of methanol and 0.2 mL acetic acid was added diaminomaleonitrile (**1**) (1.08 g, 10 mmol). The reaction was allowed to proceed at room temperature for 24 h, concentrated to dryness, and crystallized from ethanol to give 1.29 g (51%) of **17**: mp 125 °C dec; UV_{max} (CH_3OH) 302 nm (ϵ 15 700); IR (Nujol) 3333, 2212, 1623, 1602 cm^{-1}; ^1H NMR δ 5.80 (1 H, d, $J = 1$ Hz, H-1′, α-anomer) 5.55 (1 H, d, $J = 10$ Hz, H-1′, β-anomer).

Anal. Calcd for $C_9H_{12}N_4O_4$: C, 45.00; H, 5.04; N, 23.32. Found: C, 44.70; H, 5.02; N, 23.26.

(b) A mixture of diaminomaleonitrile (**1**) (0.22 g, 2 mmol) and D-ribose (0.30 g, 2 mmol) was stirred 48 h at pH 6.0 in aqueous phosphate buffer. A 10–20% yield of D-ribopyranosyldiaminomaleonitrile (**17**) was formed as shown by TLC. Only trace amounts of **17** were detected when the reaction was performed at pH 7 and pH 8.

***N*-(2′,3′,4′-Tri-*O*-acetyl-D-ribopyranosyl)diaminomaleonitrile (18).** To a solution of 10 mL of pyridine and 10 mL of acetic anhydride cooled to 0–5 °C was added D-ribopyranosyldiaminomaleonitrile (**17**) (1.96 g, 8 mmol) and the mixture was allowed to stand for 2 h. The reaction mixture was poured into ice water and extracted into 100 mL of $CHCl_3$. The organic layer was washed with four 150-mL portions of 0.1 N HCl and one 150-mL portion of H_2O, dried over $MgSO_4$, and concentrated to a gummy residue in vacuo. The product was purified by elution from a silica gel column with 7:3 benzene–ethyl acetate and concentrated to give 1.46 g (49%) of an anomeric mixture of triacetates as shown by two spots on silica gel TLC and a ^1H NMR with multiple CH_3CO signals at δ 2.0.

α- and β-Anomers of 4,5-Dicyano-1-(2′,3′,4′-tri-*O*-acetyl-D-ribopyranosyl)imidazole (19 and 20). Procedure A. To a stirred solution of **18** (1.10 g, 3 mmol) in 2 mL of anisole at 90–100 °C was added triethyl orthoformate (0.85 mL, 4.5 mmol) and heating was continued for 1 h. Then 0.02 g of sodium methoxide was added to the solution, and the temperature was raised to 150–155 °C and maintained at that temperature for 20 min.[9] The cooled reaction mixture was eluted from a silica gel column with varying proportions of benzene–ethyl acetate. The β-anomer (**19**) was eluted first and crystallized from ethanol to give 0.13 g (11%): mp 169–170 °C; UV_{max} (CH_3OH) 244 nm (ϵ 10 300); IR (Nujol) 2242, 1751, 1739, 1473, 1364, 1239, 1224, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.98 (t, 1, $J_{4'5'b} = 10.8$ Hz, $J_{5'a5'b} = -11.4$ Hz, H-5′b), 4.18 (dd, 1, $J_{4'5'a} = 6.0$ Hz, H-5′a), 5.18 (m, 2, H-2′, H-4′), 5.65 (d, 1, H-1′, $J_{1'2'} = 8.4$ Hz), 5.82 (m, 1, H-3′), 7.88 (s, 1, H-2); ^{13}C NMR 169.95, 169.20, 168.68 (CO), 142.26 (C-2), 122.85 (C-4), 111.98, 110.79, 108.06 (C-5 and two nitrile carbons), 81.85 (C-1′), 68.68, 67.30, 65.25, 63.24 (C-2′, C-3′, C-4′, and C-5′), 20.37, and 20.04 (CH_3); mass spectrum, m/e 376 (M^+).

Anal. Calcd for $C_{16}H_{16}N_4O_7$: C, 51.07; H, 4.29; N, 14.89. Found: C, 50.84; H, 4.24; N, 14.67.

The α-anomer (**20**) was eluted second and was recrystallized from water to give 0.37 g (32%) of product: mp 151–152 °C; UV_{max} 244 nm (ϵ 12 000); IR (Nujol) 2232, 1748, 1727, 1364, 1252, 1244, 1209, 1107 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.0 (dd, 1, $J_{5'a5'b} = -13.2$ Hz, 5′b), 4.34 (dd, 1, 5′a), 5.26 (m, 1, $J_{4',5a'} = 2.0$ Hz, $J_{4',5b'} = 1.2$ Hz, $J_{3'4'} = 3.6$ Hz, H-4′), 5.34 (t, 1, $J_{2'3'} = J_{3'4'} = 3.6$ Hz, H-3′), 5.48 (m, 1, H-2′), 5.77 (d, 1, $J_{1'2'} = 2.4$ Hz, H-1′), 7.98 (s, 1, H-2); ^{13}C NMR 169.94, 169.56, 169.05 (CO), 141.68 (C-2), 122.98 (C-4), 112.15, 111.04, 108.29 (C-5 and 2 -CN), 83.33 (C-1′), 67.71, 67.50, 66.52, 65.41 (C-2′, C-3′, C-4′, and C-5′), 20.59 and 20.22 (CH_3); mass spectrum, m/e 376 (M^+).

Anal. Calcd for $C_{16}H_{16}N_4O_7$: C, 51.07; H, 4.29. Found: C, 50.95; H, 4.42.

In this procedure, if the heating at 90–100 °C was reduced to 20 min and the temperature was quickly (20 min) raised to 150 °C after the addition of sodium methoxide, the β-anomer was obtained in 37% yield and the α-anomer in 15% yield.

Procedure B. An intimate mixture of 4,5-dicyanoimidazole (**23**)[9] (1.5 g, 5 mmol) and 1,2,3,4-tetra-*O*-acetyl-D-ribopyranose (**24**) (1.59 g, 5 mmol) was rapidly heated to 190–195 °C, 0.01 g of chloroacetic acid was added to the melt, and a vacuum was applied to the mixture for 5 min. The warm solid was dissolved in benzene and purified by chromatography on silica gel. A 26% yield of **19** and a 2% yield of **20** was obtained.

4-Cyano-1-(β-D-ribopyranosyl)imidazole 5,2′-Lactim 25. Anhydrous ammonia was passed into ice cooled methanol (10 mL) for 20 min. To this solution was added **19** (1 g, 2.66 mmol) and it was stirred at 0 °C for 1 h. Methanol was evaporated with a rotary evaporator and the residue was triturated with methanol (2 mL) and water (0.5 mL). The mixture was cooled and the white solid which separated, was filtered, washed with methanol, and finally dried in a desiccator which yielded 0.47 g (71%) **25** as white powder: mp 190–191 °C dec; UV_{max} (MeOH) 259 nm (ϵ 8670); IR 3530, 2220, 1660, 1650, 1570, 1560, 1120, and 1040 cm^{-1}; ^1H NMR δ 3.9 (m, 3, H-5′ and H-4′), 4.02 (br s, 1, H-3′), 4.1 (dd, 1, $J_{1'2'} = 10.0$ Hz, H-2′), 5.2 (d, 1, $J = 6.0$ Hz, 4′-OH), 5.72 (d, 2, $J_{1'2'} = 10.0$ Hz, H-1′, 3′-OH), 8.2 (s, 1, H-2), 9.12 (s, 1, NH), $(CD_3)_2SO$–D_2O, 5.68 (d, 1, $d_{1,2} = 9.6$ Hz, H-1′); ^{13}C NMR 65.28, 66.04, 67.16, 76.73, 77.93, 113.44, 114.22, 127.36, 136.54, 149.49; mass

(50) Greenberg, G. R.; Spilman, E. L. *J. Biol. Chem.* **1956**, *219*, 411–422.

spectrum, m/e 250 (M^+), 205, 180, 161, and 133.

Anal. Calcd for $C_{10}H_{10}N_4O_4$: C, 48.00; H, 4.00; N, 22.40. Found: C, 48.05; H, 4.06; N, 22.28.

Methyl 4-Cyano-1-(β-D-ribopyranosyl)imidazole-5-carboximidate (26). To an ice-cooled methanol (25 mL) solution presaturated with ammonia for 1 h was added **19** (2.5 g, 6.65 mmol) and the mixture was stirred at room temperature for 30 min. Methanol was removed in a rotary evaporator, and the residue was dissolved in methanol (5 mL) and water (0.5 mL) and heated at 60 °C for 6 h. The reaction mixture was cooled and the solid which separated was filtered, washed with methanol, and dried. Recrystallization from methanol gave 1.1 g (59%) of **26** as white crystalline material: mp 168–170 °C; UV_{max} (H_2O) 244 nm (ε 9410); IR 2230, 1650, 1340, 1100, 1050 cm^{-1}; NMR δ 3.66 (m, 3, H-5′, H-4′), 3.80, 3.86 (2 s, 3, OCH_3), 3.9 (m, 1, H-2′), 4.02 (br s, 1, H-3′), 4.91, 5.0 (d, 1, J = 6.4 Hz, 4′-OH), 5.16, 5.29 (d, 1, J = 4 Hz, 3′-OH), 5.2, 5.6 (d, 1, J = 7.2 Hz, 2′-OH), 5.46, 6.4 (d, 1, $J_{1'2'}$ = 9.6 Hz, H-1′), 8.30, 8.35 (2 s, 1, H-2), 9.0, 9.2 (2 s, 1, NH); ^{13}C NMR 51.72, 52.09, 64.17, 65.01, 65.25, 67.99, 68.01, 68.27, 69.68, 80.17, 81.37, 112.04, 112.97, 113.62, 113.96, 131.60, 132.16, 138.57, 139.07, 151.70, 155.05; mass spectrum, m/e 282 (M^+) 250, 180, 149, 118, 73.

Anal. Calcd for $C_{11}H_{11}N_4O_5$: C, 46.80; H, 4.96; N, 19.86. Found: C, 46.72; H, 5.04; N, 19.78.

The filtrates from **26** were combined, concentrated, and cooled to give methyl 5-cyano-1-(β-D-ribopyranosyl)imidazole-4-carboximidate (**32**), the yield of which was variable: mp 179–180 °C; UV_{max} (MeOH) 248 nm (ε 13 270); IR 3400–3100 (br), 2230, 1650, 1540, 1500 cm^{-1}; ^1H NMR δ 3.7 (m, 3, H-5′, H-3′), 3.86 (s, 3, OCH_3), 3.94 (m, 1, H-2′), 4.02 (br s, 1, H-4′), 5.0 (br s, 1, 3′-OH), 5.31 (d, 1, 4′-OH, J = 3.6 Hz), 5.42 (d, 1, 2′-OH, J = 7.0 Hz), 5.44 (d, 1, J = 9.2 Hz, H-1′), 8.4 (s, 1, H-2), 8.72 (s, 1, NH); ^{13}C NMR 53.02, 65.37, 66.27, 69.06, 70.89, 83.45, 101.92, 110.48, 141.13, 141.22, 160.83; mass spectrum (CI), m/e 283 (M + 1), 265, 251, 133.

Anal. Calcd for $C_{11}H_{14}N_4O_5$: C, 46.80; H, 4.96; N, 19.86. Found: C, 46.73; H, 4.99; N, 19.77.

Silylation of Imidates 14 and 26. Each imidate (0.18 mmol) was heated to reflux in acetonitrile with hexamethyldisilazane (9.5 mmol) and tirmethylchlorosilane (3.9 mmol) under nitrogen for 4 h. The solvent was evaporated under reduced pressure to give the tetrasilyl derivatives. A pale yellow solid was obtained from **26**: mp 100 °C; mass spectrum, m/e 570 (M^+), 555 (M^+ – 15); ^1H NMR ($CDCl_3$) δ 3.64 (s, 3, OCH_3), 5.36 (d, $J_{1'2'}$ = 8.4 Hz, H-1′), 7.53 (s, 1, H-2). A syrup was obtained from **14**: mass spectrum, m/e 570 (M^+), 555 (M^+ – 15); ^1H NMR ($CDCl_3$) δ 3.66 (s, 3, OCH_3), 5.70 (d, 1, $J_{1'2'}$ = 4.0 Hz, H-1′), 8.06 (s, 1, H-2).

4,5-Dicyano-1-(β-D-ribopyranosyl)imidazole (29). To a suspension of methyl 4-cyano-1-(β-D-ribopyranosyl)imidazole-5-carboximidate (**26**) (0.3 g, 1.06 mmol) in acetonitrile (10 mL) was added a solution of KF (120 mg, 2.06 mmol) and 18-crown-6 (60 mg, 0.21 mmol) in acetonitrile (2 mL) and the mixture heated to reflux under nitrogen for 2 h with stirring. The solution was concentrated to dryness, the residue was purified by silica gel preparative TLC with 25% MeOH in EtOAc as the eluent. The major UV absorbing band was eluted, concentrated, and crystallized from EtOAc to give **29** (0.12 g, 47%) as white crystals: mp 179–180 °C; UV_{max} (MeOH) 244 nm (ε 12 500); IR (Nujol) 3470, 2250, 2230 cm^{-1}; NMR δ 3.7 (m, 3, H-2′, H-5′), 4.00 (m, 1, H-3′), 5.02 (m, 1, 4′-OH), 5.33 (d, 1, J = 4 Hz, 3′-OH), 5.47 (d, 1, J = 4.8 Hz, 2′-OH), 5.5 (d, 1, J = 7.2 Hz, H-1′), 8.54 (s, 1, H-2); mass spectrum, m/e 250 (M^+).

Anal. Calcd for $C_{10}H_{10}N_4O_4$: C, 48.00; H, 4.00; N, 22.40. Found: C, 47.96; H, 4.09; N, 22.27.

5-Amino-1-(β-D-ribopyranosyl)imidazole-4-carbonitrile (27). To an ice-cooled solution of sodium hypochlorite (2 mL, 5.25%) was added **26** (0.28 g, 1 mmol) and the mixture was stirred for 30 min; the addition of 1.5 N NaOH (1 mL) followed and the solution stirred for another 30 min at the same temperature. A clear solution was obtained which was then heated to 85 °C under argon for 2.5 h. The solution was cooled, carefully neutralized with 2 N HCl, and freeze-dried to give an orange-red powder. It was washed with 2 × 10 mL of dry methanol and filtered. The TLC (EtOAc–MeOH (7:3)) of the filtrate showed one major UV absorbing compound. The filtrate was concentrated to dryness under reduced pressure and the residue was purified by preparative TLC using EtOAc–MeOH (7:3) as the eluant to give 0.11 g (48%). Crystallization from MeOH–ether gave **27** as a white hygroscopic powder: mp 135–140 °C; UV_{max} (MeOH) 245 nm; pH 2, 237 nm; IR 3300 (br), 2200, 1630, 1575, 1040 cm^{-1}; NMR δ 3.56 (m, 2, H-5′), 3.7 (m, 1, H-4′), 3.83 (m, 1, H-2′), 3.98 (br s, 1, H-3′), 4.85 (br s, d, 1, J = 4 Hz, 4′-OH), 5.08 (d, 2, J = 8 Hz, 2′- and 3′-OH), 5.13 (d, 1, $J_{1'2'}$ = 8 Hz, H-1′), 6.2 (br s, 2, NH_2), 7.32 (s, 1, H-2); ^{13}C NMR 64.86, 66.38, 68.29, 71.10, 79.66, 90.1, 117.33, 130.81, 148.17; mass spectrum, m/e 241 (M^+), 240 (M^+), 186, 169, 108, 73.

Anal. Calcd for $C_9H_{12}N_4O_4 \cdot 2.5H_2O$: C, 37.89; H, 5.96; N, 19.65. Found: C, 37.93; H, 6.00; N, 19.52.

5-Amino-1-(β-D-ribopyranosyl)imidazole-4-carboxamide (28). A solution of **27** (0.2 g, 0.83 mmol) in 1.5 N NaOH (2.5 mL) was heated to 100 °C under argon for 2 h. The solution was cooled, neutralized with 2 N HCl, and freeze-dried. The residue thus obtained was triturated with methanol and filtered. The filtrate was concentrated on a rotary evaporator and purified by TLC with EtOAc–MeOH (6:4) to give 0.1 g (50%) of **28** as a gummy solid. It was crystallized from ethanol: mp 215 °C dec; UV_{max} (H_2O) 267 nm (ε 9680), pH 2, 243 nm (ε 7070), 263 nm (ε 7880); IR 3300 (br), 1640, 1550, 1040 cm^{-1}; NMR δ 3.5–3.7 (m, 3, H-5′ and H-4′), 3.8 (m, 1, H-2′), 4.0 (m, 1, H-3′), 4.88 (d, 1, J = 5.2 Hz, 4′-OH), 5.0–5.2 (m, 3, $J_{1'2'}$ = 9.6 Hz, H-1′, 2′-OH, 3′-OH), 5.76 (s, 2 NH_2), 6.7 (br, 2, $CONH_2$), 7.2 (s, 1, H-2); $(CD_3)_2SO$–D_2O 5.20 (d, 1 H, $J_{1'2'}$ = 9.6 Hz, H-1′); ^{13}C NMR 64.91, 66.49, 68.52, 71.14, 79.6, 112.27, 128.06, 143.37, 166.66; mass spectrum, m/e 258 (M^+) 186, 169, 126, 109, 73.

Picrate Salt. To a hot solution of 20 mg of **28** in alcohol was added a solution of 25 mg of picric acid in alcohol. The yellow solid which separated was filtered, washed with alcohol, and dried. Crystallization from water furnished the salt as golden yellow flakes (10 mg): 185 °C dec.

Anal. Calcd for $C_{15}H_{17}N_7O_{12}$: C, 36.96; H, 3.51; N, 20.1. Found: C, 36.85; H, 3.59; N, 20.06.

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Registry No. 1, 1187-42-4; 2, 16205-60-0; 3, 94619-71-3; 4, 61022-58-0; 5, 6974-32-9; 7, 94644-70-9; 8, 13035-61-5; 9, 94619-72-4; 10, 94619-73-5; 11, 94619-74-6; 12, 94619-75-7; 13, 94619-76-8; 14, 94619-77-9; 15, 23192-64-5; 16, 2627-69-2; 17 (α isomer), 70042-22-7; 17 (β isomer), 70042-23-8; 18 (α isomer), 70042-24-9; 18 (β isomer), 70042-25-0; 19, 70042-27-2; 14 (TMS deriv), 94619-85-9; 20, 70042-26-1; 23, 1122-28-7; 24, 4627-30-9; 25, 94619-78-0; 26, 94619-79-1; 26 (TMS deriv), 94619-84-8; 27, 94619-80-4; 28, 64044-31-1; 28 picrate, 94619-81-5; 29, 94619-82-6; 32, 94619-83-7; monoformyldiaminomaleonitrile, 53144-01-7; triethyl orthoformate, 122-51-0; D-ribose, 50-69-1.