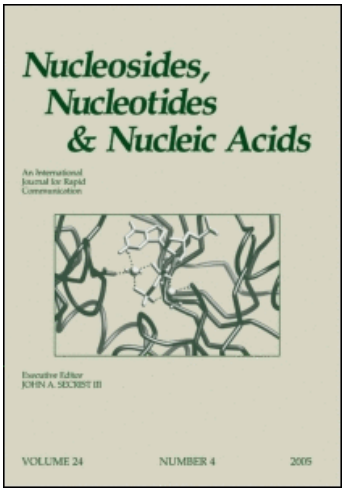

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Synthesis of 3-Aminoimidazo[4,5-*c*]pyrazole Nucleoside via the N-N Bond Formation Strategy as a [5:5] Fused Analog of Adenosine

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SYNTHESIS OF 3-AMINOIMIDAZO[4,5-*c*]PYRAZOLE NUCLEOSIDE VIA THE *N-N* BOND FORMATION STRATEGY AS A [5:5] FUSED ANALOG OF ADENOSINE

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□ *3-Amino-6-(β-D-ribofuranosyl)imidazo[4,5-c]pyrazole (***2***) was synthesized via an N-N bond formation strategy by a mononuclear heterocyclic rearrangement (MHR). A series of 5-amino-1-(5-O-tert-butyldimethylsilyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-4-(1,2,4-oxadiazol-3-yl)imidazoles (***6a-d***), with different substituents at the 5-position of the 1,2,4-oxadiazole, were synthesized from 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (AICA Ribose,* **3***). It was found that 5-amino-1-(5-O-tert-butyldimethylsilyl-2,3-O-isopropylidene-β-D-ribofuranosyl)-4-(5-methyl-1, 2,4-oxadiazol-3-yl)imidazole (***6a***) underwent the MHR with sodium hydride in DMF or DMSO to afford the corresponding 3-acetamidoimidazo[4,5-c]pyrazole nucleoside(s) (***7b*** *and/or* ***7a***) in good yields. A direct removal of the acetyl group from 3-acetamidoimidazo[4,5-c]pyrazoles under*

In honor and celebration of the life and career of John A. Montgomery.

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*numerous conditions was unsuccessful. Subsequent protecting group manipulations afforded the desired 3-amino-6-(β-D-ribofuranosyl)imidazo[4,5-c]pyrazole (**2**) as a 5:5 fused analog of adenosine (**1**).*

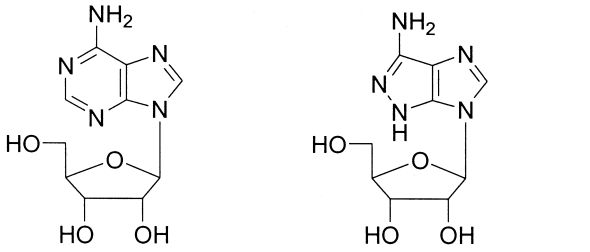
Keywords AICA riboside; Imidazo[4,5-c]pyrazole; Adenosine analog; Mononuclear heterocyclic rearrangements; Boulton-Katritzky rearrangement

INTRODUCTION

Our group has been interested in the synthesis of 5:5 bicyclic heterocycles that could serve as substitutes for the aglycons of certain 5:6 bicyclic nucleosides.[1,2] This ring contraction strategy has not yet been widely applied to the development of nucleoside analogs and only a few examples have been reported in the literature.[1–10] Using this approach, the removal of a carbon (C-2) from purine would lead to the imidazo[4,5-*c*] pyrazole ring system, a potential purine bio-isostere. This prompted us to initiate a study for the synthesis and biological evaluation of 3-amino-6-(β-D-ribofuranosyl)imidazo[4,5-*c*]pyrazole (**2**) as an adenosine (**1**) analog (Figure 1).

Only a few examples concerning the synthesis of imidazo[4,5-*c*]pyrazoles have been reported in the literature.[11–22] According to reported methods, construction of the imidazo[4,5-*c*]pyrazole ring system has used mostly pyrazole derivatives as starting materials.[11–13,16–21] An efficient synthetic route using imidazole derivatives has not been reported. We elected to investigate feasible synthetic methods for the formation of the imidazo[4,5-*c*] pyrazole ring system from imidazole derivatives to ensure that the desired substituents would be located at the *N*-6 position of the imidazo[4,5-*c*] pyrazole.

A literature survey has suggested that the most straightforward approach for the construction of heterocyclic ring systems with a [*c*]-face fused pyrazole involves a condensation of hydrazine with aromatic or heteroaromatic



Adenosine (**1**) 3-Amino-6-(β-D-ribofuranosyl)-imidazo[4,5-*c*]pyrazole (**2**)

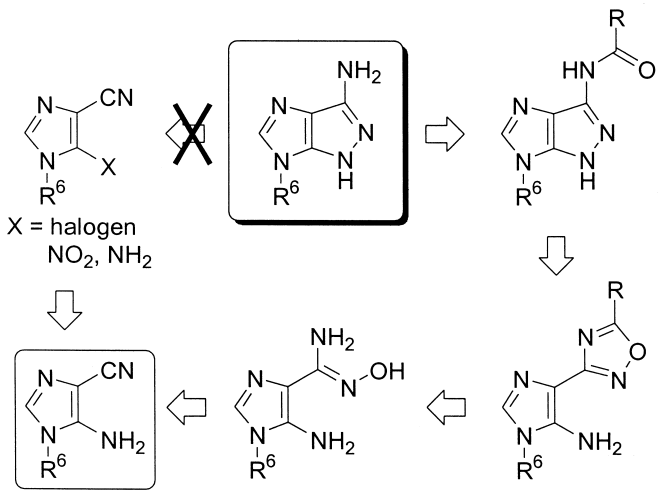
FIGURE 1 Proposed imidazo[4,5-*c*]pyrazole nucleoside and adenosine.

carboxylates or carbonitriles possessing an adjacent leaving group to afford the fused pyrazole rings. This approach has been widely used in the synthesis of [*c*]-fused pyrazole rings from various aromatic ring systems. However, this application toward the 5:5 bicyclic [*c*]-fused 3-aminopyrazole ring systems has been rarely reported in the literature.[23] Our preliminary studies based on this approach have been unsuccessful. When 5-chloro-1-(β-D-ribofuranosyl)imidazole-4-carbonitrile and 5-chloro-1-(β-D-ribofuranosyl) imidazole-4-carboxamide, prepared from a naturally occurring imidazole nucleoside, 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (AICA riboside, **3**),[24] were treated with hydrazine or methylhydrazine, the reaction mixture gave complex mixtures but the desired ring-closure products were not observed. This result prompted us to look for an alternative preparation of the imidazo[4,5-*c*]pyrazole ring system from pre-existing imidazole precursors.

It has been reported that the [*c*]-fused pyrazole ring can also be prepared directly by an *N-N* bond formation strategy. An aromatic or heteroaromatic compound bearing adjacent 1,2,4-oxadiazol-3-yl and amino groups can undergo a ring transformation [mononuclear heterocyclic rearrangement (MHR) (or Boulton-Katritzky rearrangement)][25] reaction to afford the [*c*]-fused 3-aminopyrazole.[26–32] This approach was initially used on π-electron deficient aromatic or heteroaromatic ring systems to furnish the [*c*]-fused 3-aminopyrazoles. D. Korbonits et al. demonstrated that 5-amino-1-phenyl-4-(5-phenyl-1,2,4-oxadiazol-3-yl)pyrazole would undergo the MHR to give the bicyclic pyrazolo[3,4-*c*]pyrazole ring.[29] Our group has previously applied this approach to synthesize 3-aminopyrazolo[3,4-*c*]pyrazole nucleosides as 5:5 bicyclic adenosine analogs.[1] The success in annulation of the pyrazolo[3,4-*c*]pyrazole ring system by the MHR has particularly prompted us to investigate the generality of this methodology and the possibility of using the methodology for the synthesis of the imidazo[4,5-*c*] pyrazole ring.[33] Based on the MHR approach, a retrosynthetic analysis of the target ring structure was derived from various 5-amino-4-(1,2,4-oxadiazol-3-yl)imidazoles which would be prepared from the readily available 1-substituted 5-amino-4-cyanoimidazole derivatives (Scheme 1). We now report on our studies which were designed to extend the application of the MHR approach for the preparation of 3-aminoimidazo[4,5-*c*]pyrazole derivatives.

RESULTS AND DISCUSSION

Naturally occurring 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (AICA riboside, **3**) was selected as the starting material to investigate the proposed annulation reactions from imidazole nucleosides. The sugar moiety was first protected with base-stable protecting groups to form



SCHEME 1

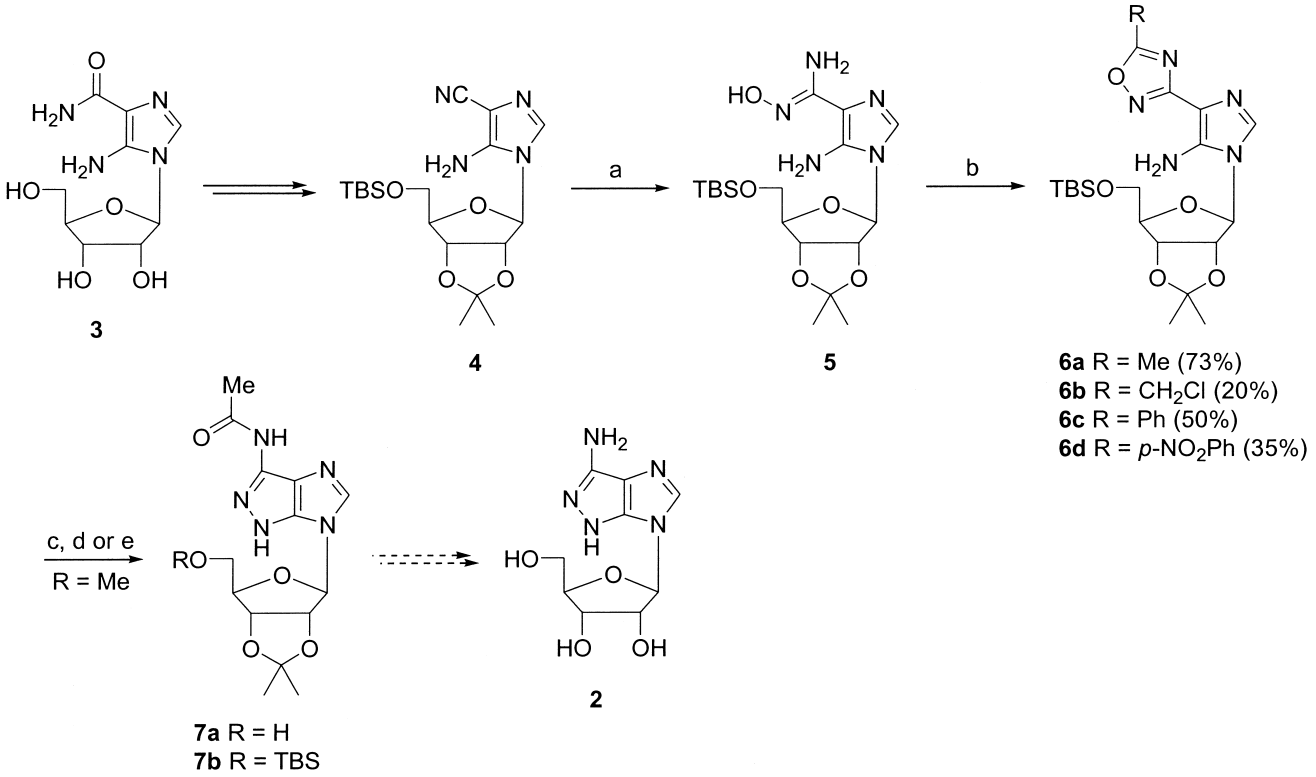
5-amino-1-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxamide.[34–36] Dehydration of the amide to the nitrile **4** was achieved using *p*-toluenesulfonyl chloride in pyridine in 90% yield. The dehydration by tosyl chloride was superior to the commonly used phosphorus oxychloride method[37] particularly in the presence of an acid-labile silicon protecting group. The reaction of **4** with hydroxylamine in ethanol at reflux temperature gave 5-amino-1-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxamidoxime (**5**) in 70% yield. The formation of the 1,2,4-oxadiazole ring from the amide oxime was accomplished in one pot by the D. Korbonits' method.[29] Treatment of **5** with ethyl acetate in an ethanolic solution of sodium ethoxide at reflux temperature afforded the corresponding 5-methyl-1,2,4-oxadiazole (**6a**) in 73% yield. The annulation of **6a** by MHR under the reported conditions[26,27,29,31] was unsuccessful in obtaining the desired imidazo[4,5-*c*]pyrazole derivative but accompanied by decomposition of the starting materials. It was subsequently found that the rearrangement of **6a** would proceed when it was heated from 75 to 100°C along with sodium hydride in DMSO. The desired ring transformation occurred in 15 minutes accompanied with desilylation to give the 3-acetamidoimidazo[4,5-*c*]pyrazole nucleoside **7a** in a good yield (<5 mmol scale, 50–74%). The chemical shift for the methyl groups had a significant upfield shift in the ^{1}H NMR from 2.59 ppm for **6a** to 2.07 ppm for **7a**. This shift indicated that the exocyclic methyl group of the 1,2,4-oxadiazole was transformed to the corresponding acetyl group. The amide NH peak of **7a** was also observed at 11.90 ppm by ^{1}H NMR. The reaction yield dropped lower (30–40%) when the reaction was scaled up (>5 mmol scale), possibly due to the decomposition of the product during

the prolonged vacuum distillation to remove the solvent. This procedure has limited the preparation of **7a**. Attempts to remove the acetyl group of **7a** by numerous basic conditions, including aqueous ammonium hydroxide, ammonia in methanol, hydrazine monohydrate, sodium methoxide in methanol and aqueous sodium hydroxide, were unsuccessful and the starting material can be recovered from the reactions[38] (Scheme 2).

A literature survey suggested that the installation of an electron-withdrawing group at the 5-position of the 1,2,4-oxadiazole ring would facilitate the MHR reaction.[29] In addition, a removal of the resulting acyl group on the exocyclic amino group would be more feasible. Both reasons have prompted us to introduce various electron-withdrawing groups at the 5-position of the 1,2,4-oxadiazole ring. Treatment of **5** with several ethyl carboxylates (i.e., ethyl benzoate, ethyl 4-nitrobenzoate, and ethyl chloroacetate) under the same reaction condition afforded the corresponding 5-subsituted 1,2,4-oxadiazoles **6b-d**. Attempts to introduce other groups using ethyl trifluoroacetate, ethyl trichloroacetate, or ethyl formate were unsuccessful. However, the annulation of **6b-d** by MHR under several conditions, including photo-induced MHR,[32] did not give the desired products.

The reaction conditions of the MHR for **6a** was only satisfied in microscale. A feasible multi-gram procedure for **7a** by changing the solvent from DMSO to DMF was employed for the subsequent investigation. The desired ring transformation occurred when **6a** was heated from 75 to 100°C with sodium hydride in DMF for 15 min. Two products were found in the reaction mixture which were not separated. The more polar product was identified to be the same as **7a** prepared under the NaH/DMSO conditions while the other compound **7b** was its 5′-*O*-*tert*-butyldimethylsilyl derivative. The ratio of two products (**7a**/**7b**) is about 1:1 based on the integration of the ^{1}H NMR spectrum. The partially desilylated product mixture was treated with tributyldimethylsilyl chloride to give a single product **7b** (55% overall yield from **6a**). Alternatively, the product mixture was treated with tetrabutylammonium fluoride to give **7a** (43% overall yield from **6a**) (Scheme 2). Although the overall yield of the reaction in DMF is lower than in DMSO, this modification allowed us to scale the reaction up to multi-grams.

After several unsuccessful attempts to remove the *N*-acetyl group from the nucleosides **7a-b**, we elected to study this reaction using a more available non-nucleoside model first in order to establish the reaction conditions that would remove the acetyl group from the 3-acetamidoimidazo[4,5-*c*]pyrazole derivatives. 3-Acetamido-1-benzylimidazo[4,5-*c*]pyrazole (**9**), a non-nucleoside analog of **7a-b**, was prepared from 5-amino-1-benzyl-4-cyanoimidazole[39,40] by the same route.[33] A removal of the acetyl group from **9** under basic or acidic conditions was also unsuccessful. An indirect approach for the removal of the acetyl group was then investigated. By introducing an



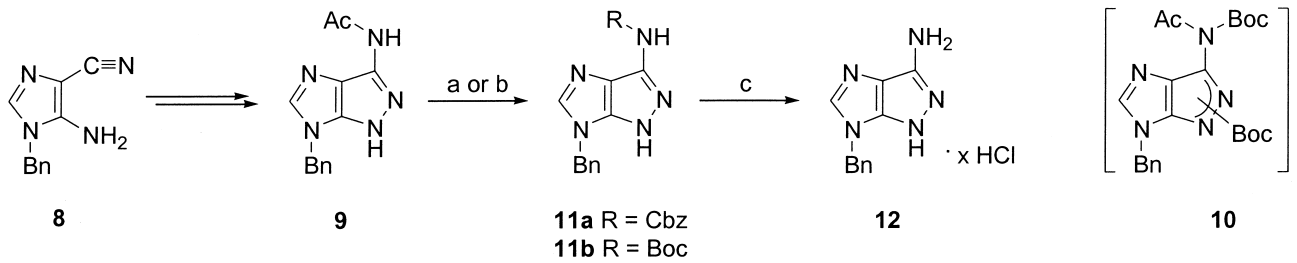
SCHEME 2 Reagents and conditions: (a) NH_2OH, EtOH, reflux, 90 min, 70%; (b) (i) Na/EtOH, rt; (ii) RCOOEt, EtOH, reflux; (c) NaH, DMSO, 75–100°C, 15 min, **7a**: 74% from **6a**; (d) (i) NaH, DMF, 75–100°C, 15 min; (ii) TBAF, THF, 0°C - rt, overnight, **7a**: 43% from **6a**; (e) (i) NaH, DMF, 75–100°C, 15 min; (ii) TBSCl, imidazole, *cat.* DMAP, DMF, rt, 8 h, **7b**: 55% from **6a**.

electron-withdrawing group resistant toward basic conditions at the amide nitrogen, the double-bond character of the amide bond would be decreased and should weaken the amide bond due to the lack of tautomerism. Basic hydrolysis/deacetylation should then be able to remove the acetyl group and yet retain the exchanged protecting group.[41] Two alkoxycarbonyl groups (Cbz and Boc) orthogonal to the acetyl group were selected for this investigation. Compound **9** was treated with benzyloxycarbonyl chloride in the presence of 4-dimethylaminopyridine and triethylamine as a base. Unexpectedly, the acetyl group was removed under the mild reaction conditions to provide the Cbz-protected 3-amino-1-benzylimidazo[4,5-*c*]pyrazole (**11a**). Attempts to remove the Cbz group under neutral or acidic hydrogenolysis were unsuccessful and resulted in complete decomposition of the starting materials. We then treated **9** with di-*tert*-butyl dicarbonate ($(Boc)_2O$) to give the di-*tert*-butyloxycarbonyl intermediate **10**. Compound **10** was subsequently deacetylated with methanolic ammonia to remove the acetyl group along with one of the Boc groups to afford the Boc-protected 3-amino-1-benzylimidazo[4,5-*c*]pyrazole (**11b**). Removal of the Boc group under various acidic conditions was investigated. The desired product **12** was isolated as a hydrochloride salt when **11b** was deprotected with hydrogen chloride in methanol (Scheme 3).

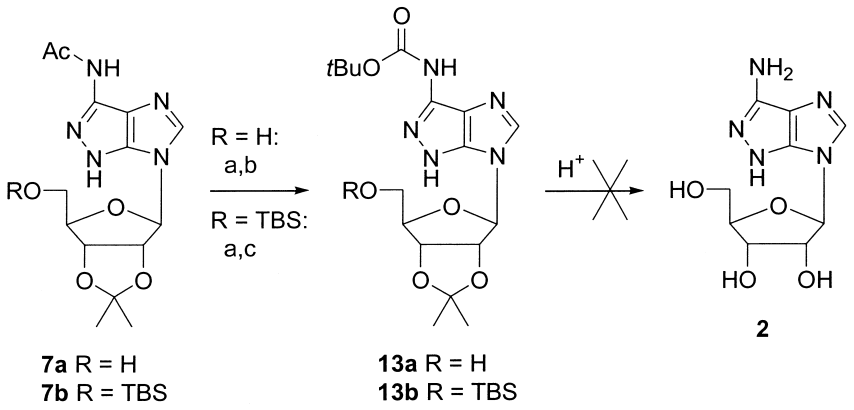
Compound **12** is unstable in solution possibly due to the high π-electron density on the ring atoms. However, our investigation has provided a feasible approach to remove the acetyl group from the 3-acetamidoimidazo[4,5-*c*]pyrazole derivatives. We anticipated that the nucleoside derivative of 3-aminoimidazo[4,5-*c*]pyrazole would be perhaps more stable since the anomeric carbon of the sugar is slightly electron-deficient which should provide some extra stabilization to the heterocycle. We then used the above approach for our nucleoside synthesis.

To apply our previous successful approach, compounds **7a-b** were treated with di-*tert*-butyl dicarbonate. The intermediates were not isolated but were subsequently deprotected by methanolic ammonia or sodium methoxide in methanol to give **13a-b**, respectively. The rest of the synthesis appeared to require only the removal of all the remaining acid-labile protecting groups from **13a-b**. However, the desired product **2** was not isolated after several attempts under various acidic conditions (Scheme 4).

We envisioned that this was due to the different reactivities of these protecting groups under acidic conditions. This unforeseen difficulty in the removal of these acid-labile protecting groups prompted us to revise the use of protecting groups in the synthesis. Elimination of the isopropylidene group from the synthesis, or the removal of the isopropylidene prior to the *N*-Boc group should overcome the problem. Our first attempt involved the use of acetyl esters to protect the sugar moiety, or to exclude the protecting group during the ring transformation step. 5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamidoxime[42] (**14**), directly prepare



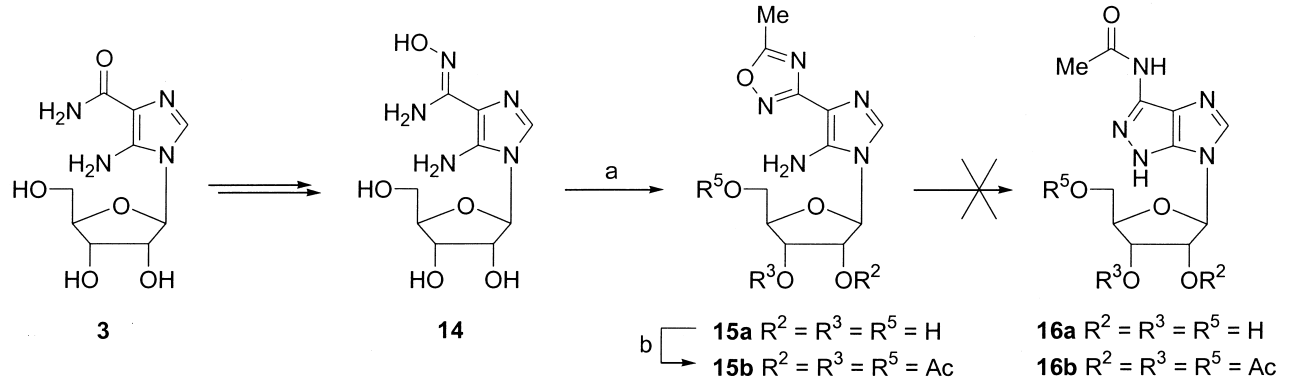
SCHEME 3 Reagents and conditions: (a) CbzCl, DMAP, Et_3N, CH_2Cl_2, 0°C - rt, 3 h, **11a**: 84%; (b) (i) $(Boc)_2O$, Et_3N, *cat.* DMAP, CH_2Cl_2, rt, 3 h, **10**: 90%; (ii) NH_3/MeOH, 60°C, 5 h, **11b**: 81%; (c) HCl/MeOH, rt, 3 h, 35%.



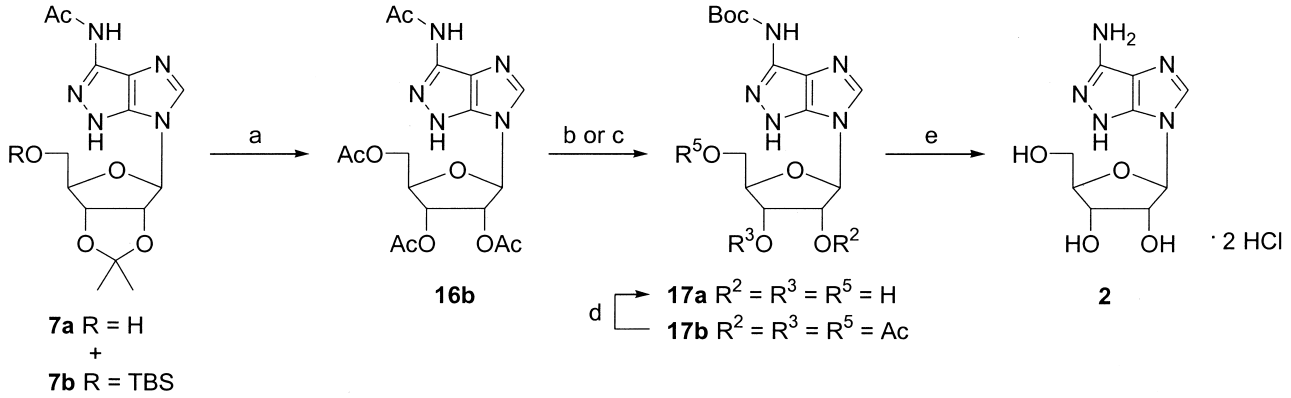
SCHEME 4 Reagents and conditions: (a) $(Boc)_2O$, Et_3N, *cat.* DMAP, CH_2Cl_2, rt; (b) MeONa/MeOH, reflux, **13a**: 43% from **7a**; (c) NH_3/MeOH, 60°C, 5 h, **13b**: 55% from **7b**.

from the corresponding nitrile (AICN riboside),[42,43] was reacted with ethyl acetate in an ethanolic solution of sodium ethoxide to afford the corresponding 5-methyl-1,2,4-oxadiazole **15a**. Compound **15a** was acetylated to give **15b** (40% yield from **14**). However, the ring transformations of **15a-b** by MHR under various conditions were unsuccessful (Scheme 5). The results showed that the unprotected 1,2,4-oxadiazole precursor **15a** and its triacetylated derivative **15b** were not compatible with the reaction conditions, or the ring transformation was being prevented by the deprotected sugar moiety.

Since we had previously used the acetonide in the ring transformation to obtain **7a-b**, this led us to remove the isopropylidene prior to adding the *N*-Boc group. A mixture of **7a-b** obtained from the MHR of **6a** was first treated with aqueous trifluoroacetic acid to remove the acid-labile isopropylidene and *tert*-bytyldimethylsilyl groups. This was followed by acetylation of the sugar to give 3-acetamido-6-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl) imidazo[4,5-*c*]pyrazole (**16b**) in 42% yield from **6a**. The Boc group was then introduced on the amide nitrogen followed by basic deacetylation with methanolic ammonia to give **17a**. Alternatively, the Boc group was introduced accompanied with the selective deacetylation at the 3-amino group by DMAP to afford **17b** in 72% yield from **16b**. The acetyl groups of **17b** were removed with methanolic ammonia to give **17a**. Compound **17a** was subsequently deprotected with hydrogen chloride in methanol to give the desired 3-amino-6-(β-D-ribofuranosyl)imidazo[4,5-*c*]pyrazole (**2**) as a hydrogen chloride salt in 24% yield from **16b** (Scheme 6). Attempts to neutralize the hydrogen chloride counterions by basic ion-exchange resin were unsuccessful. This suggested that the compound is unstable in a free base form because the 3-aminoimidazo[4,5-*c*]pyrazole core structure possesses a



SCHEME 5 Reagents and conditions: (a) (i) Na/EtOH, rt, 10 min; (ii) EtOAc, EtOH, reflux, 90 min; (b) Ac_2O, pyridine, rt, 24 h, 40% from **14**.



SCHEME 6 Reagents and conditions: (a) (i) 90% aqueous TFA solution, rt, 1 h; (ii) Ac_2O, Et_3N, *cat.* DMAP, CH_2Cl_2, rt, 1 h, 64% from **6a**; (b) (i) $(Boc)_2O$, Et_3N, *cat.* DMAP, CH_2Cl_2, rt, 5 h; (ii) NH_3/MeOH, 60°C, 5 h; (c) $(Boc)_2O$, DMAP, THF, rt, 24 h, 72% from **16b**; (d) NH_3/MeOH, rt, 1 h; (e) HCl/MeOH, 0°C - rt, 1 h, 20% from **16b**.

relatively high electron density which was mainly contributed by the π-electrons on the ring atoms as well as the strong electron-donating character of the exocyclic amino group. The formation of a hydrochloride salt has substantially reduced the electron density from the ring and allowed us to purify and isolate the desired product in a stable formation. Furthermore, a comparison of structures and stabilities between the non-nucleoside model **12** and the 3-aminoimidazo[4,5-*c*]pyrazole nucleoside **2** indicated that the slightly electron-deficient character of the anomeric carbon on the sugar may have contributed some extra stabilization to the heterocycle.

EXPERIMENTAL SECTION

General Chemical Procedures

Melting points were taken on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained at 300 or 500 MHz with Bruker DPX300 or DRX500 spectrometers. The chemical shift values are reported in δ values (parts per million, ppm) relative to the standard chemical shift of tetramethylsilane (TMS). The coupling constant values are expressed in hertz (Hz). Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona, or by the Analytical Laboratory, Department of Chemistry, University of Michigan, Ann Arbor, Michigan. Mass spectrometry was performed by the Analytical Laboratory, Department of Chemistry, University of Michigan, Michigan. Thin-layer chromatography (TLC) was performed on silica gel GHLF-254 plates (Merck Reagents). Compounds on thin-layer chromatography were visualized by illumination under UV light (254 nm), or dipped into 10% methanolic sulfuric acid followed by charring on a hot plate. Solvent systems are expressed as a percentage of the more polar component with respect to total volume (v/v%). E. Merck silica gel (230–400 mesh) was used for flash column chromatography as described by Still et al.[49] Evaporations were carried out under reduced pressure (water aspirator) with the bath temperature below 50°C unless specified otherwise. Materials obtained from commercial suppliers were used without further purification.

5-Amino-1-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxamidoxime (5). To a solution of hydroxylamine hydrochloride (1.9 g, 27.3 mmol, 4 eq) and triethylamine (3.8 mL, 2.76 g, 27.3 mmol, 4 eq) in ethanol (60 mL) was added a solution of 5-amino-1-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carbonitrile[35] (**4**, 2.7 g, 6.83 mmol) in ethanol (20 mL). After the addition was completed, the reaction mixture was heated at reflux temperature for an additional 90 min. The reaction was monitored by TLC. After cooling to

room temperature, the solution was concentrated under reduced pressure. The residue was dissolved in EtOAc (100 mL), washed with H_2O, saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting oil was purified by flash column chromatography (Hex/EtOAc = 3:7) to give **5** (2.04 g, 4.78 mmol, 70%, Rf = 0.43 (Hex/EtOAc = 25:75)). The compound was recrystallized from EtOAc to give an analytical sample of **5** (1.23 g, 2.88 mmol, 42%). mp 144–146°C (EtOAc); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.90 (s, 1H, OH), 7.37 (s, 1H, 2-H), 5.77 (d, 2H, J = 3.1 Hz, 1′-H), 5.35 (bs, 2H, NH_2), 5.31 (bs, 2H, NH_2), 5.08 (dd, 1H, J = 3.1 and 6.3 Hz), 4.83 (dd, 1H, J = 3.3 and 6.3 Hz), 4.09 (dd, 1H, J = 4.3 and 7.7 Hz), 3.72–3.63 (m, 2H, 5′-H), 1.52 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 0.86 (s, 9H, 3 × CH_3), 0.04 (s, 6H, 2 × CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 151.0, 137.0, 128.4 (2-CH), 114.3, 112.9, 89.0 (1′-CH), 85.7 (CH), 83.7 (CH), 81.0 (CH), 63.7 (5′-CH_2), 27.8 (CH_3), 26.7 (3 × CH_3), 26.1 (CH_3), 18.9, −4.6 (2 × CH_3); MS (CI, NH_3) *m/z* 395 (53), 412 (69), 428 (100) (M+1); HRMS Calcd for $C_{18}H_{34}N_5O_5Si$: 428.2329. Found 428.2328. Anal. calcd for $C_{18}H_{33}N_5O_5Si$: C, 50.56; H, 7.78; N, 16.38. Found: C, 50.40; H, 7.99; N, 16.41.

5-Amino-1-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-4-(5-methyl-1,2,4-oxadiazol-3-yl)imidazole (6a). Compound **5** (2.14 g, 5 mmol) was added to an ethanolic solution of sodium ethoxide (230 mg of sodium (10 mmol, 2 eq) in 25 mL of ethanol). The solution was stirred at room temperature for 10 min. EtOAc (5 mL, 4.5 g, 51 mmol, 10.2 eq) and dry toluene (25 mL) were added and the reaction mixture was heated at reflux temperature with molecular sieve (4A) in a Dean-Stark apparatus for 1 h. After cooling to room temperature, the solution was neutralized with acetic acid (0.29 mL, 0.3 g, 5 mmol, 1 eq), and then concentrated under reduced pressure. The residue was partitioned between EtOAc (100 mL) and H_2O (35 mL). The organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography ($CHCl_3$/MeOH = 96:4, Rf = 0.3) to give **6a** (1.65 g, 3.65 mmol, 73%, Rf = 0.49 (Hex/EtOAc = 25:75)). The compound was recrystallized from EtOAc to give an analytical sample of **6a** (1.3 g, 2.88 mmol, 58%). mp 167–169°C (EtOAc); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.54 (s, 1H, 2-H), 5.89 (d, 1H, J = 2.7 Hz, 1′-H), 5.72 (bs, 2H, NH_2), 5.15 (dd, 1H, J = 2.7 and 6.2Hz, 2′-H), 4.87 (dd, 1H, J = 3.1 and 6.2 Hz), 4.13 (dd, 1H, J = 4.4 and 7.8 Hz), 3.70–3.64 (m, 2H, 5′-H), 2.59 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 0.87 (s, 9H, 3 × CH_3), 0.04 (s, 6H, 2 × CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 175.8, 164.7, 141.4, 130.5, 113.8, 107.1, 88.2, 85.8, 83.6, 80.8, 63.3, 27.3, 26.2, 25.7, 18.5, 12.3, −5.1 (2 × CH_3); MS (CI, NH_3) *m/z* 452 (100) (M+1); HRMS calcd for $C_{20}H_{34}N_5O_5Si$: 452.2329. Found 452.2318.

Anal. calcd for $C_{20}H_{33}N_5O_5Si$: C, 53.19; H, 7.37; N, 15.51. Found: C, 52.84; H, 7.35; N, 15.50.

5-Amino-1-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-4-(5-chloromethyl-1,2,4-oxadiazol-3-yl)imidazole (6b). Compound **6b** (0.489 g, 1.01 mmol, 20%, Rf = 0.38 ($CHCl_3$/MeOH = 97:3)) was prepared from **5** (2.14 g, 5 mmol) using an ethanolic solution of sodium ethoxide (0.23 g of sodium (10 mmol, 2 eq) in 35 mL of ethanol), then ethyl chloroacetate (10.8 mL, 12.26 g, 100 mmol, 20 eq) and dry toluene (25 mL) by the method described for **6a**, and purified by flash column chromatography ($CHCl_3$/MeOH = 98:2). An analytical sample of **6b** was obtained by recrystallization from EtOAc (0.098 g, 0.2 mmol, 4%). mp 150–152°C (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27 (s, 1H, 2-H), 5.68 (d, 1H J = 3.4 Hz, 1′-H), 5.19 (bs, 2H, NH_2), 5.02 (dd, 1H, J = 3.4 and 6.7 Hz), 4.97 (dd, 1H, J = 3.8 and 6.7 Hz), 4.72 (s, 2H, CH_2Cl), 4.22–4.20 (m, 1H), 3.99 (dd, 1H, J = 2.3 and 11.5 Hz, 5′-H), 3.88 (dd, 1H, J = 2.0 and 11.5 Hz, 5′-H), 1.62 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 0.94 (s, 9H, 3 × CH_3), 0.15 (s, 3H, CH_3), 0.13 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.4, 165.5, 140.6, 131.5 (2-CH), 115.5, 109.7, 91.8 (5′-CH), 85.4 (CH), 83.6 (CH), 79.2 (CH), 62.9 (5′-CH_2), 33.9 (CH_2Cl), 27.7(CH_3), 26.4 (3 × CH_3), 25.7 (CH_3), 19.0, −5.0 (CH_3), −5.1 (CH_3); MS (CI, NH_3) m/z 452 (29), 486 (100) (M+1), 488 (47) (M+3); HRMS calcd for $C_{20}H_{33}ClN_5O_5Si$: 486.1940. Found 486.1931. Anal. calcd for $C_{20}H_{32}ClN_5O_5Si$: C, 49.42; H, 6.64; N, 14.41. Found: C, 49.40; H, 6.70; N, 14.37.

5-Amino-1-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-4-(5-phenyl-1,2,4-oxadiazol-3-yl)imidazole (6c). Compound **6c** (1.11 g, 2.17 mmol, 50%, Rf = 0.4 ($CHCl_3$/MeOH = 97:3)) was prepared from **5** (1.85 g, 4.33 mmol) using an ethanolic solution of sodium ethoxide (0.299 g of sodium (13 mmol, 3 eq) in 45 mL of ethanol), and then ethyl benzoate (5 mL, 5.26 g, 34.99 mmol, 8.1 eq) by the method described for **6a**, and purified by flash column chromatography ($CHCl_3$/MeOH = 98:2). An analytical sample of **6c** was obtained by recrystallization from Hex/EtOAc (0.683 g, 1.33 mmol, 30%). mp 175–177°C (Hex/EtOAc); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.22–8.19 (m, 2H, Ph), 7.74–7.62 (m, 3H, Ph), 7.57 (s, 1H, 2-H), 5.94 (d, 1H, J = 2.7 Hz, 1′-H), 5.91 (bs, 2H, NH_2), 5.17 (dd, 1H, J = 2.7 and 6.2 Hz), 4.88 (dd, 1H, J = 3.1 and 6.2 Hz), 4.14 (dd, J = 4.6 and 7.9 Hz), 3.67 (d, 2H, J = 4.8 Hz, 5′-H), 1.54 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 0.86 (s, 9H, 3 × CH_3), 0.04 (s, 6H, 2 × CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 179.2, 170.5, 147.1, 138.7 (CH), 135.8 (CH), 135.1 (CH), 133.6 (CH), 129.2, 119.0, 111.9, 93.3 (1′-CH), 91.1 (CH), 88.8 (CH), 86.0 (CH), 68.5 (5′-CH_2), 32.5 (CH_3), 31.4 (3 × CH_3), 30.8 (CH_3), 23.7, −0.2 (2 × CH_3); MS (CI, NH_3) m/z 91 (66), 514 (100) (M+1); HRMS calcd for

$C_{25}H_{36}N_5O_5Si$: 514.2486. Found 514.2466. Anal. calcd for $C_{25}H_{35}N_5O_5Si$: C, 58.46; H, 6.87; N, 13.63. Found: C, 58.31; H, 6.60; N, 13.67.

5-Amino-1-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-4-[5-(*p*-nitrophenyl)-1,2,4-oxadiazol-3-yl]imidazole (6d). Compound **6d** (0.87 g, 1.56 mmol, 35%) was prepared from **5** (1.9 g, 4.45 mmol) using an ethanolic solution of sodium ethoxide (0.205 g of sodium (8.9 mmol, 2 eq) in 25 mL of ethanol), and then ethyl *p*-nitrobenzoate (2.61 g, 13.35 mmol, 3 eq) by the method described for **6a**, and purified by flash column chromatography (Hex/EtOAc = 4:6, Rf = 0.34). An analytical sample of **6d** was obtained by recrystallization from EtOAc (0.497 g, 0.89 mmol, 20%). mp 208–210°C (EtOAc); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.51–8.43 (m, 4H, Ph), 7.59 (s, 1H 2-H), 5.99 (bs, 2H, NH_2), 5.96 (d, 1H, J = 2.8 Hz, 1′-H), 5.18 (dd, 1H, J = 2.7 and 6.2 Hz), 4.89 (dd, 1H, J = 3.1 and 6.2 Hz), 4.14 (dd, 1H, J = 4.7 and 7.8 Hz), 3.68–3.66 (m, 2H, 5′-H), 1.55 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 0.86 (s, 9H, 3 × CH_3), 0.04 (s, 6H, 2 × CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 172.8, 166.0, 150.7, 142.7, 131.1 (CH), 130.4 (CH), 129.8, 125.4 (CH), 114.2, 106.7, 88.5 (1′-CH), 86.4 (CH), 84.1 (CH), 81.3 (CH), 63.8 (5′-CH_2), 27.7 (CH_3), 26.7 (3 × CH_3), 26.1 (CH_3), 18.9, −4.6 (2 × CH_3); MS (CI, NH_3) *m/z* 531 (50), 559 (59), 561 (100) (M+3); HRMS calcd for $C_{25}H_{35}N_6O_7Si$: 559.2337. Found 559.2335. Anal. calcd for $C_{25}H_{34}N_6O_7Si$: C, 53.75; H, 6.13; N, 15.04. Found: C, 53.75; H, 6.19; N, 14.96.

3-Acetamido-6-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazo[4,5-*c*]pyrazole (7a). [Method A]. Sodium hydride (60% in mineral oil, 83.3 mg, 2 mmol, 2 eq) was placed in a 25 mL round bottom flask equipped with a rubber septum and an inert gas (argon) inlet. Dimethylsulfoxide (10 mL) was added and the mixture was stirred at room temperature. After the gas evolution ceased, the reaction mixture was heated in a 75°C oil bath and **6a** (0.452 g, 1 mmol) was added to the mixture. The reaction temperature was gradually raised to 100°C in 15 min. The reaction was then cooled to room temperature and neutralized with acetic acid (0.12 mL, 0.12 g, 2 mmol, 2 eq). The solvent was removed by vacuum distillation (0.1 mmHg, 55–60°C). The residue was partitioned between $CHCl_3$ (100 mL) and H_2O (40 mL). The organic layer was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by flash column chromatography ($CHCl_3$/MeOH = 95:5, Rf = 0.21) to give **7a** (0.25 g, 0.74 mmol, 74%). An analytical sample of **7a** was obtained by recrystallization from EtOAc (0.12 g, 0.37 mmol, 37%).

[Method B]. Sodium hydride (60% in mineral oil, 0.483 g, 12.08 mmol, 2.5 eq) was placed in a 200 mL round bottom flask equipped with a rubber

septum and an inert gas (argon) inlet. *N*,*N*-Dimethylformamide (50 mL) was added and the mixture was stirred at room temperature. The suspension mixture was heated in a 75°C oil bath and **6a** (2.18 g, 4.83 mmol) was added to the mixture. The reaction temperature was gradually raised to 100°C in 15 min. The reaction was then cooled to room temperature and neutralized with acetic acid (0.7 mL, 0.725 g, 12.08 mmol, 2.5 eq). The solvent was evaporated in vacuo. The residue was partitioned between $CHCl_3$ (200 mL) and H_2O (75 mL). The aqueous layer was further extracted with $CHCl_3$ (150 mL). The organic portions were washed with H_2O, saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure to dryness. The residue was purified by flash column chromatography ($CHCl_3$/MeOH = 97:3) to give a mixture of products (1.38 g, Rf: **7b** = 0.25, **7a** = 0.19 ($CHCl_3$/MeOH = 96:4). **7b**/**7a** ~1:1 from ^{1}H NMR) that were used without further purification. To a solution of the mixture of **7a**/**7b** (~3.81 mmol) in THF (30 mL) was added 1 M tetrabutylammonium fluoride solution (2 mL, 1 M TBAF in THF) and the solution was stirred at room temperature for 12 h. The solvent was removed under reduced pressure. The residue was partitioned between $CHCl_3$ (150 mL) and H_2O (50 mL), the aqueous layer was further extracted with $CHCl_3$ (100 mL). The organic portions were washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to dryness. The residue was purified by flash column chromatography ($CHCl_3$/MeOH = 96:4) to give **7a** (0.696 g, 2.06 mmol, 43% from **6a**). An analytical sample of **7a** was obtained by recrystallization from EtOAc.

mp 215–217°C (EtOAc); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.90 (bs, 1H, NH), 11.18 (bs, 1H, NH), 7.59 (s, 1H, 5-H), 5.96 (d, 1H, J = 2.8 Hz, 1′-H), 5.34 (dd, 1H, J = 2.8 and 6.1 Hz, 2′-H), 5.11 (t, 1H, J = 5.7 Hz, 5′-OH), 4.91 (dd, 1H, J = 2.0 and 6.1 Hz), 4.15 (dt, 1H, J = 2.0 and 5.8 Hz), 3.41 (t, 2H, J = 5.7 Hz, 5′-H), 2.07 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 169.4, 141.9, 135.4 (5-CH), 134.7, 132.1, 113.9, 91.7 (1′-CH), 86.7 (CH), 83.6 (CH), 82.4 (CH), 62.4 (5′-CH_2), 27.8 (CH_3), 26.0 (CH_3), 23.7 (CH_3); MS (FAB+) *m/z* 123 (43), 136 (57), 137 (42), 165 (61), 166 (93), 337 (45), 338 (100) (M+1); HRMS calcd for $C_{14}H_{20}N_5O_5$: 338.1464. Found 338.1473. Anal. calcd for $C_{14}H_{19}N_5O_5$: C, 49.85; H, 5.68; N, 20.76. Found: C, 49.66; H, 5.72; N, 20.75.

3-Acetamido-6-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazo[4,5-*c*]pyrazole (7b). The partially desilylated product mixture **7a** and **7b** (0.612 g, Rf: **7b** = 0.21, **7a** = 0.15 ($CHCl_3$/MeOH = 96.5:3.5); **7b** = 0.24, **7a** = 0.07 (Hex/EtOAc = 2:8). **7b**/**7a** ~1:1 from ^{1}H NMR) was prepared from **6a** (0.903 g, 2 mmol) using sodium hydride (60% in mineral oil, 0.16 g, 4 mmol, 2 eq), and *N*,*N*-dimethylformamide

(20 mL) by the method described for **7a** in **[Method B]**, and purified by flash column chromatography ($CHCl_3$/MeOH = 97:3) to give a mixture of products that were used without further purification. To a solution of the mixture of **7a**/**7b** (~1.6 mmol), imidazole (0.122 g, 1.79 mmol), and 4-dimethylaminopyridine (22 mg, 0.18 mmol) in DMF (15 mL) was added *tert*-butyldimethylsilyl chloride (0.27 g, 1.79 mmol) and the solution was stirred at room temperature for 8 h. The reaction was quenched by the addition of EtOH, and the mixture was concentrated in vacuo. The residue was partitioned between EtOAc (100 mL) and H_2O (35 mL), the aqueous layer was further extracted with EtOAc (2 × 100 mL). The organic portions were washed with saturated aqueous $NaHCO_3$ solution, saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to dryness. The residue was purified by flash column chromatography ($CHCl_3$/MeOH = 97:3) to give **7b** (0.494 g, 1.09 mmol, 55% from **6a**). The compound was recrystallized from Hex/EtOAc to give an analytical sample of **7b** (0.207 g, 0.46 mmol, 23% from **6a**). mp 70–74°C (dec) (Hex/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.04 (bs, 1H, NH), 9.40 (bs, 1H, NH), 7.47 (s, 1H, 5-H), 5.98 (d, 1H, J = 1.8 Hz, 1′-H), 5.40 (dd, 1H, J = 1.7 and 6.0 Hz), 4.93 (dd, 1H, J = 1.7 and 6.0 Hz), 4.39–4.37 (m, 1H), 3.67 (dd, 1H, J = 5.0 and 10.9 Hz, 5′-H), 3.63 (dd, 1H, J = 5.8 and 10.9 Hz, 5′-H), 2.26 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 0.84 (s, 9H, 3 × CH_3), −0.01 (s, 3H, CH_3), −0.04 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.2, 142.1, 134.1 (5-CH), 133.8, 131.8, 114.3, 92.2 (1′-CH), 87.6 (CH), 84.6 (CH), 82.3 (CH), 63.2 (5′-CH_2), 27.5 (CH_3), 26.2 (3 × CH_3), 25.7 (CH_3), 24.1 (CH_3), 18.7, −5.1 (CH_3), −5.2 (CH_3); MS (FAB+) *m/z* 129 (45), 452 (100) (M+1); HRMS calcd for $C_{20}H_{34}N_5O_5Si$: 452.2329. Found 452.2324. Anal. calcd for $C_{20}H_{33}N_5O_5Si$: C, 53.19; H, 7.37; N, 15.51. Found: C, 53.48; H, 7.49; N, 15.50.

3-Benzyloxycarbonylamino-6-benzylimidazo[4,5-*c*]pyrazole (11a). To a mixture of **9**[33] (0.31 g, 1.21 mmol), 4-dimethylaminopyridine (0.193 g, 1.58 mmol, 1.3 eq) and triethylamine (0.22 mL, 0.16 g, 1.58 mmol, 1.3 eq) in dichloromethane (13 mL) at 0°C was added benzyl chloroformate (0.35 mL, 0.414 g, 2.43 mmol, 2 eq) dropwise. After the addition, the reaction mixture was allowed to warm to room temperature with continuous stirring for 3 h. Ethanol (5 mL) was added, and then the solvents were removed under reduced pressure. The resulting residue was dissolved in $CHCl_3$ and the solution was washed with H_2O, saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure to dryness. The resulting oil was purified by flash column chromatography ($CHCl_3$/MeOH = 97.5:2.5) to give **11a** (0.355 g, 1.02 mmol, 84%, Rf = 0.2 ($CHCl_3$/MeOH = 97:3)). The compound was recrystallized from methanol to give an analytical sample of **11a** (0.236 g, 0.68 mmol, 56%). mp 185–189°C

(dec) (MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.79 (bs, 1H, NH), 10.53 (bs, 1H, NH), 7.54 (s, 1H, 5-H), 7.40–7.25 (m, 10H, 2 × Ph), 5.24 (s, 2H, CH_2), 5.16 (s, 2H, CH_2); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.6, 140.5, 138.3, 137.3, 135.3 (CH), 135.0, 134.2, 129.4 (CH), 129.3 (CH), 128.9 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 67.0 (CH_2), 49.0 (CH_2); MS (CI, NH_3) *m/z* 330 (100), 348 (92) (M+1); HRMS calcd for $C_{13}H_{14}N_5O$: 348.1460. Found: 348.1470. Anal. calcd for $C_{13}H_{13}N_5O$: C, 65.69; H, 4.93; N, 20.16. Found: C, 65.46; H, 4.96; N, 20.05.

(1 or 2)-(*tert*-Butyloxycarbonyl)-3-[(*tert*-butyloxycarbonyl)amino]-6-benzylimidazo[4,5-*c*]pyrazole (10). To a mixture of **9**[33] (0.511 g, 2 mmol), triethylamine (0.62 mL, 0.445 g, 4.4 mmol, 2.2 eq) and 4-dimethylaminopyridine (24.4 mg, 0.2 mmol, 0.1 eq) in dichloromethane (20 mL) was added di-*tert*-butyl dicarbonate (0.96 g, 4.4 mmol, 2.2 eq) in one portion. The reaction mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure. The resulting oil was dissolved in EtOAc, washed with H_2O, saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (Hex/EtOAc = 4:6, Rf = 0.31) to give **10** (0.823 g, 1.81 mmol, 90%). The compound was recrystallized from EtOAc to give an analytical sample of **10** (0.527 g, 1.16 mmol, 58%). mp 154–155°C (dec) (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46 (s, 1H, 5-H), 7.34–7.24 (m, 5H, Ph), 5.36–5.24 (m, 2H, CH_2), 2.63 (s, 3H, CH_3), 1.65 (s, 9H, 3 × CH_3), 1.37 (s, 9H, 3 × CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.5, 151.2, 146.9, 137.5, 137.4 (CH), 135.8, 135.3, 133.4, 129.3 (CH), 128.7 (CH), 127.9 (CH), 86.1, 84.6, 49.6 (CH_2), 28.3 (3 × CH_3), 28.2 (3 × CH_3), 26.2 (CH_3); MS (FAB+) *m/z* 91 (55), 213 (35), 256 (100), 356 (37), 456 (31) (M+1); HRMS calcd for $C_{23}H_{30}N_5O_5$: 456.2247. Found 456.2245; Anal. calcd for $C_{23}H_{29}N_5O_5$: C, 60.65; H, 6.42; N, 15.37. Found: C, 60.30; H, 6.38; N, 15.36.

3-[(*tert*-Butyloxycarbonyl)amino]-6-benzylimidazo[4,5-*c*]pyrazole (11b). Compound **10** (0.296 g, 0.65 mmol) was dissolved in methanolic ammonia (13 mL) and the solution was placed in a stainless steel vessel and sealed. The reaction mixture was heated at 60°C for 5 h. After cooling to room temperature, the solvent was removed under reduced pressure. The resulting residue was recrystallized from Hex/EtOAc to give **11b** (0.143 g, 0.46 mmol, 71%). mp 193–195°C (dec) (Hex/EtOAc); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.64 (bs, 1H, NH), 10.08 (bs, 1H, NH), 7.51 (s, 1H, 5-H), 7.35–7.26 (m, 5H, Ph), 5.25 (s, 2H, CH_2), 1.46 (s, 9H, 3 × CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 153.0, 140.1, 137.5, 134.2 (CH), 134.0, 133.3, 128.5 (CH), 127.6 (CH), 127.3 (CH), 79.8, 48.1 (CH_2), 28.0 (3 × CH_3); MS (CI, NH_3) *m/z* 214 (53), 240 (100), 314 (58) (M+1); HRMS calcd for $C_{16}H_{20}N_5O_2$ (M+1):

314.1617. Found 314.1614. Anal. calcd for $C_{16}H_{19}N_5O_2$: C, 61.33; H, 6.11; N, 22.35. Found: C, 61.18; H, 6.12; N, 22.59.

3-Amino-6-benzylimidazo[4,5-*c*]pyrazole (12). Compound **11b** (0.626 g, 2 mmol) was dissolved in a mixture of concentrated hydrochloric acid and ethanol (20 mL, 1:1 (v/v)). The mixture was stirred at room temperature for 3 h. The solvents were removed under reduced pressure and the resulting residue was recrystallized from isopropanol to give **12** as a hydrochloride salt (0.174 g, 0.7 mmol, 35%). mp 131–134°C (dec) (isopropanol); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.80 (s, 1H, 5-H), 7.40–7.20 (m, 5H, Ph), 5.38 (s, 2H, CH_2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 150.6, 137.1, 134.5, 132.2, 129.7, 129.0, 128.6, 122.3, 49.9; MS (FAB+) *m/z* 91 (73), 136 (55), 154 (67), 214 (100) (M+1); MS (ESI) *m/z* 214 (100) (M+1); HRMS calcd for $C_{11}H_{12}N_5$: 214.1093. Found 214.1085.

3-[(*tert*-Butyloxycarbonyl)amino]-6-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazo[4,5-*c*]pyrazole (13a). To a solution of **7a** (0.337 g, 1 mmol), triethylamine (1.4 mL, 1.01 g, 10 mmol, 10 eq), and 4-dimethylaminopyridine (12.2 mg, 0.1 mmol, 0.1 eq) in dichloromethane (10 mL) at room temperature was added di-*tert*-butyl dicarbonate (2.18 g, 10 mmol, 10 eq). The solution was stirred at room temperature for 2 h. The solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$. The solution was washed with H_2O, saturated aqueous Na_2CO_3 solution, saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to dryness. The resulting residue was purified by flash column chromatography ($CHCl_3$/MeOH = 100:0–98:2) to give a product mixture (Rf = 0.38 ($CHCl_3$/MeOH = 98:2), 0.33 (Hex/EtOAc = 6:4)) that was used without further purification. The product mixture was dissolved in methanol (20 mL). To the solution was added sodium methoxide (0.216 g, 4 mmol) in one portion. The solution was heated at reflux temperature for 2 h. After cooling to room temperature, saturated aqueous NH_4Cl solution (3 mL) was added and the solvents were removed under reduced pressure. The resulting oil was purified by flash column chromatography ($CHCl_3$/MeOH = 97:3, Rf = 0.25) to give **13a** (89.9 mg, 0.23 mmol, 23% from **7a**). The compound was recrystallized from Hex/EtOAc to give an analytical sample of **13a** (42.1 mg, 0.11 mmol, 11% from **7a**). mp 216–218°C (dec) (Hex/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.79 (bs, 1H, NH), 8.36 (bs, 1H, NH), 7.36 (s, 1H, 5-H), 6.83 (bs, 1H, 5′-OH), 5.79 (d, 1H, J = 4.1 Hz, 1′-H), 5.10 (d, 1H, J = 5.6 Hz), 4.94 (t, 1H, J = 4.8 Hz), 4.52 (s, 1H), 4.00 (d, 1H, J = 13.1 Hz, 5′-H), 3.81 (d, 1H, J = 13.2 Hz, 5′-H), 1.66 (s, 3H, CH_3), 1.56 (s, 9H, 3 × CH_3), 1.39 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.9, 142.3, 134.4, 133.1 (5-CH), 131.0, 114.0, 94.9 (1′-CH), 86.6 (CH), 85.2 (CH), 83.1, 82.1 (CH), 63.6 (5′-CH_2), 28.6 (3 × CH_3), 28.0 (CH_3), 25.7

(CH_3); MS (CI, NH_3) *m/z* 190 (60), 296 (100), 322 (71), 396 (94) (M+1); HRMS calcd for $C_{17}H_{26}N_5O_6$: 396.1883. Found 396.1889. Anal. calcd for $C_{17}H_{25}N_5O_6 \cdot 0.5\ H_2O$: C, 50.49; H, 6.48; N, 17.32. Found: C, 50.51; H, 6.53; N, 17.67.

3-[(*tert*-Butyloxycarbonyl)amino]-6-(5-*O*-*tert*-butyldimethylsilyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazo[4,5-*c*]pyrazole (13b). To a solution of **7b** (3.3 g, 7.3 mmol), triethylamine (3.1 mL, 2.22 g, 21.9 mmol, 3 eq), and 4-dimethylaminopyridine (0.178 g, 1.46 mmol, 0.2 eq) in dichloromethane (70 mL) at room temperature was added di-*tert*-butyl dicarbonate (4.78 g, 21.9 mmol, 3 eq). The solution was stirred at room temperature for 5 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc (150 mL). The solution was washed with H_2O, saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to dryness. The resulting solid was dissolved in methanolic ammonia (70 mL) and the solution was transferred to a stainless steel vessel. The vessel was sealed and heated at 60°C for 5 h. After cooling to room temperature, the solution was transferred to a round-bottom flask and the solvent was removed under reduced pressure. The resulting oil was purified by flash column chromatography ($CHCl_3$/MeOH = 98:2) to give **13b** (2.05 g, 4.01 mmol, 55%, Rf = 0.43 ($CHCl_3$/MeOH = 97:3), 0.31 (Hex/EtOAc = 5:5)). The compound was recrystallized from Hex/EtOAc to give an analytical sample of **13b** (1.5 g, 2.95 mmol, 40%). mp 182–184°C (dec) (Hex/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.66 (bs, 1H, NH), 8.31 (bs, 1H, NH), 7.46 (s, 1H, 5-H), 5.96 (d, 1H, J = 2.0 Hz, 1′-H), 5.36 (dd, 1H, J = 1.7 and 5.9 Hz), 4.94 (dd, 1H, J = 2.0 and 6.1 Hz), 4.41–4.39 (m, 1H), 3.71 (dd, 1H, J = 5.9 and 11.0 Hz, 5′-H), 3.67 (dd, 1H, J = 5.0 and 11.0 Hz, 5′-H), 1.61 (s, 3H, CH_3), 1.56 (s, 9H, 3 × CH_3), 1.41 (s, 3H, CH_3), 0.83 (s, 9H, 3 × CH_3), −0.02 (s, 3H, CH_3), −0.05 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.0, 142.5, 133.8, 133.3 (5-CH), 131.6, 114.1, 91.9 (1′-CH), 87.6 (CH), 84.7 (CH), 82.9, 82.2 (CH), 63.7 (5′-CH_2), 28.6 (3 × CH_3), 27.5 (CH_3), 26.2 (3 × CH_3), 25.7 (CH_3), 18.7, −5.10 (CH_3), −5.13 (CH_3); MS (ESI) *m/z* 532 (100) (M+Na); HRMS calcd for $C_{23}H_{39}N_5O_6Si \cdot Na$: 532.2567. Found 532.2573. Anal. calcd for $C_{23}H_{39}N_5O_6Si$: C, 54.20; H, 7.71; N, 13.74. Found: C, 54.12; H, 7.95; N, 13.97.

5-Amino-4-(5-methyl-1,2,4-oxadiazol-3-yl)-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (15b). 5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamidoxime[42] (**14**, 5.46 g, 20 mmol) was added to an ethanolic solution of sodium ethoxide (1.84 g of sodium (80 mmol, 4 eq) in 125 mL of ethanol). The solution was stirred at room temperature for 10 min. EtOAc (30 mL, 27.1 g, 307 mmol, 15 eq) was added and the reaction mixture was heated at reflux temperature for 90 min. After cooling to room temperature,

the solution was neutralized with acetic acid (4.60 mL, 4.8 g, 80 mmol, 4 eq), and then concentrated under reduced pressure to dryness. To the residue was added pyridine (125 mL) and the mixture was stirred at 0°C. Acetic anhydride (9.45 mL, 10.21 g, 100 mmol, 5 eq) was added dropwise to the mixture maintaining the temperature at 0°C. After the addition, the reaction mixture was allowed to warm to room temperature with continuous stirring for 24 h. Another portion of acetic anhydride (0.95 mL, 1.02 g, 10 mmol, 0.5 eq) was added to the solution. After the mixture was stirred at room temperature for 30 min, ethanol (10 mL) was added to quench the reaction. The solvents were removed under reduced pressure. The residue was partitioned between EtOAc (200 mL) and H_2O (75 mL). The organic layer was washed with H_2O, saturated aqueous $NaHCO_3$ solution, saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography ($CHCl_3$/MeOH = 98:2) to give **15b** (3.37 g, 7.96 mmol, 40% from **14**, Rf = 0.3 ($CHCl_3$/MeOH = 97:3)). The compound was recrystallized from EtOAc to give an analytical sample of **15b** (2.4 g, 5.67 mmol, 28% from **14**). mp 164–166°C (EtOAc); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.61 (s, 1H, 2-H), 5.94 (d, 1H, J = 6.4 Hz, 1′-H), 5.78 (bs, 2H, NH_2), 5.61 (t, 1H, J = 6.3 Hz), 5.35–5.33 (m, 1H), 4.33–4.28 (m, 3H), 2.59 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.06 (s, 6H, 2 × CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 176.3, 170.9, 170.3, 170.1, 165.0, 141.9, 131.1 (2-CH), 107.6, 84.9 (1′-CH), 80.2 (CH), 72.7 (CH), 70.5 (CH), 63.9 (5′-CH_2), 21.4 (CH_3), 21.3 (CH_3), 21.1 (CH_3), 12.8 (CH_3); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40 (s, 1H, 2-H), 5.76 (d, 1H, J = 5.1 Hz, 1′-H), 5.58 (t, 1H, J = 5.3 Hz), 5.38 (t, 1H, J = 5.3 Hz), 5.05 (bs, 2H, NH_2), 4.49 (dd, 1H, J = 2.7 and 12.4 Hz, 5′-H), 4.44–4.42 (m, 1H), 4.39 (dd, 1H, J = 1.9 and 12.4 Hz, 5′-H), 2.63 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.15 (s, 3H, CH_3); MS (EI, 70 eV) *m/z* 97 (64), 139 (100), 165 (40), 259 (50), 423 (21) (M+); HRMS calcd for $C_{17}H_{21}N_5O_8$: 423.1390. Found: 423.1382. Anal. calcd for $C_{17}H_{21}N_5O_8$: C, 48.23; H, 5.00; N, 16.54. Found: C, 48.04; H, 4.92; N, 16.41.

3-Acetamido-6-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazo[4,5-*c*]pyrazole (16b). The partially desilylated product mixture **7a** and **7b** (ratio ~1:1, 6.04 g, approximately 15 mmol, prepared from 16.6 mmol of **6a**) was dissolved in 90% aqueous trifluoroacetic acid (100 mL) and stirred at 0°C for 1 h. The solvents were removed in vacuo. The residue was co-evaporated with MeOH (2 × 50 mL) to give the crude intermediate as an oil. A mixture of the intermediate, triethylamine (21.5 mL, 15.5 g, 153.1 mmol, 10 eq), and 4-dimethylaminopyridine (0.561 g, 4.59 mmol, 0.3 eq) in dichloromethane (140 mL) was added acetic anhydride (5.65 mL, 6.1 g, 59.7 mmol, 3.9 eq) dropwise. After the addition, the reaction mixture was stirred at room temperature for an additional 1 h. The solvent

was removed under reduced pressure. The residue was dissolved in $CHCl_3$, washed with saturated aqueous Na_2CO_3 solution, saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4, and then the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography ($CHCl_3$/MeOH = 97:3) to give **16b** (oil, 4.46 g, 10.53 mmol, 64% from **6a**, Rf = 0.3 ($CHCl_3$/MeOH = 95:5), 0.2 (EtOAc)). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.03 (bs, 1H, NH), 9.16 (bs, 1H, NH), 7.39 (s, 1H, 5-H), 5.94–5.91 (m, 2H), 5.82 (t, 1H, J = 4.9 Hz), 4.49–4.42 (m, 2H), 4.34 (dd, 1H, J = 5.2 and 11.5 Hz, 5′-H), 2.25 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.06 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.1, 170.1, 169.8, 169.3, 142.3, 134.4 (5-CH), 134.1, 131.7, 87.9 (1′-CH), 80.2 (CH), 73.9 (CH), 71.2 (CH), 63.9 (CH_2), 24.0 (CH_3), 21.1 (CH_3), 21.0 (CH_3), 20.8 (CH_3); MS (ESI) *m/z* 97 (34), 139 (40), 166 (30), 259 (48), 424 (100) (M+1), 446 (58) (M+Na); HRMS calcd for $C_{17}H_{22}N_5O_8$: 424.1468. Found 424.1460.

3-[(*tert*-Butyloxycarbonyl)amino]-6-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl) imidazo[4,5-*c*]pyrazole (17b). To a mixture of **16b** (0.55 g, 1.3 mmol) and 4-dimethylaminopyridine (0.524 g, 4.29 mmol, 3.3 eq) in THF (18 mL) was added di-*tert*-butyl dicarbonate (0.851 g, 3.9 mmol, 3 eq) in one portion. The reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure. The resulting oil was dissolved in $CHCl_3$ (50 mL), washed with 1 N hydrochloric acid solution (15 mL), saturated aqueous Na_2CO_3 solution, saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by flash column chromatography ($CHCl_3$/MeOH = 98:2–97:3) to give **17b** (oil, 0.45 g, 0.934 mmol, 72% from **16b**, Rf = 0.36 ($CHCl_3$/MeOH = 97:3)). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 11.92 (bs, 1H, NH), 10.09 (bs, 1H, NH), 7.63 (s, 1H, 5-H), 6.08 (d, 1H, J = 5.5 Hz, 1′-H), 5.82 (t, 1H, J = 5.5 Hz), 5.56 (t, 1H, J = 4.9 Hz), 4.39 (dd, 1H, J = 3.8 and 11.9 Hz, 5′-H), 4.32 (dd, 1H, J = 4.4 and 8.8 Hz), 4.17 (dd, 1H, J = 5.2 and 11.9 Hz, 5′-H), 2.12 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 1.47 (s, 9H, 3 × CH_3); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 171.0, 170.3, 170.1, 154.0, 141.1, 135.9 (5-CH), 135.4, 132.5, 87.0 (1′-CH), 80.8, 80.0 (CH), 73.0 (CH), 71.1 (CH), 63.7 (CH_2), 28.8 (3 × CH_3), 21.4 (CH_3), 21.2 (CH_3), 21.1 (CH_3); MS (ESI) *m/z* 504 (100) (M+Na); HRMS calcd for $C_{20}H_{27}N_5O_9$·Na: 504.1706. Found 504.1719.

3-Amino-6-(β-D-ribofuranosyl)imidazo[4,5-*c*]pyrazole (2). To a mixture of **16b** (4.46 g, 10.53 mmol), triethylamine (5.2 mL, 3.73 g, 36.87 mmol, 3.5 eq) and 4-dimethylaminopyridine (0.386 g, 3.16 mmol, 0.3 eq) in dichloromethane (110 mL) was added di-*tert*-butyl dicarbonate (6.9 g, 31.6 mmol, 3 eq) in one portion. The reaction mixture was stirred at room

temperature for 5 h. The solvent was removed under reduced pressure. The resulting oil was dissolved in $CHCl_3$, washed with H_2O, saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to dryness. The residue was dissolved in methanolic ammonia (40 mL) and the solution was placed in a stainless steel vessel and sealed. The reaction mixture was heated at 60°C for 5 h. After cooling to room temperature, the solvent was removed under reduced pressure to give a crude product of **17a** which was left in vacuum for 24 h at room temperature to remove a trace amount of solvents. The resulting residue was dissolved in a saturated hydrogen chloride solution in methanol and the solution was stirred at 0°C for 1 h. The solvent was removed under reduced pressure to dryness. The resulting residue was recrystallized from ethanol to give **2** as a hydrochloride salt. (0.725 g, 2.09 mmol, 20% from **16b**). mp 121–123°C (dec) (EtOH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.78 (s, 1H, 5-H), 5.70 (d, 1H, $J = 6.2$ Hz, 1′-H), 4.25 (t, 1H, $J = 5.6$ Hz), 4.06 (dd, 1H, $J = 2.9$ and 4.8 Hz), 3.96 (dd, 1H, $J = 3.3$ and 6.4 Hz), 3.66 (dd, 1H, $J = 3.7$ and 12.0 Hz, 5′-H), 3.61 (dd, 1H, $J = 3.6$ and 12.0 Hz, 5′-H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 149.7, 133.4 (5-CH), 132.3, 119.4, 89.4 (1′-CH), 86.0 (CH), 74.7 (CH), 70.4 (CH), 61.2 (5′-CH_2); MS (FAB) *m/z* 136 (71), 154 (100), 176 (67), 256 (51) (M+1); HRMS calcd for $C_9H_{14}N_5O_4$: 256.1046. Found 256.1035. MS (ESI) *m/z* 256 (100) (M+1); HRMS calcd for $C_9H_{14}N_5O_4$: 256.1046. Found 256.1046. Anal. calcd for $C_9H_{13}N_5O_4 \cdot 2\ HCl \cdot 1\ H_2O$: C, 31.23; H, 4.95; N, 20.23. Found: C, 31.25; H, 4.96; N, 20.19.

CONCLUSION

The title compound, 3-amino-6-(β-D-ribofuranosyl)imidazo[4,5-*c*]pyrazole (**2**), was synthesized via an *N-N* bond formation strategy by mononuclear heterocyclic rearrangement (MHR). This investigation has successfully extended the use of the MHR to the imidazo[4,5-*c*]pyrazole ring system which was not achievable by the widely used hydrazine annulation approach. A direct removal of the acetyl group from 3-acetamidoimidazo[4,5-*c*]pyrazoles under several acidic and basic conditions was unsuccessful. However, we have successfully removed the acetyl group by a protecting-group interconversion approach which allowed *tert*-butyloxycarbonyl and benzyloxycarbonyl groups to replace the acetyl group under mild reaction conditions. This approach was applied to accomplish the synthesis of the desired 3-amino-6-(β-D-ribofuranosyl)imidazo[4,5-*c*]pyrazole (**2**) as a hydrochloride salt. This 3-aminoimidazo[4,5-*c*]pyrazole nucleoside is a close structural 5:5 fused analog of adenosine.

Compound **2** was evaluated for activity against two herpesviruses, herpes simplex virus type 1 (HSV-1) and human cytomegalovirus (HCMV), in a plaque reduction assay and an ELISA, respectively, as we have described

previously.[2] Cytotoxicity was determined in both stationary human foreskin fibroblasts (HFF cells) and in growing KB cells. No activity was observed at the highest concentration tested (100 μM) against HCMV and HSV-1. Similarly, no cytotoxicity was observed in either cell line at concentrations up to and including 100 μM.[44–48] We conclude that, although **2** is an isostere of adenosine and of related ribosides that have potent anti-cancer and antiviral activities, the target compound is neither cytotoxic nor active against two herpesviruses.

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