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Synthesis and Anti-HIV Evaluation of 2′,3′-Dideoxy Imidazo- and ν-Triazolo[4,5-*d*]pyridazine Nucleosides†

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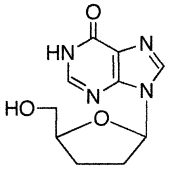
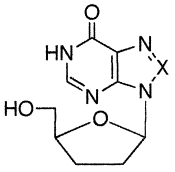
Abstract—The syntheses of the 2′-deoxy and 2′,3′-dideoxynucleosides of 2,8-diaza-3-deazainosine and the 2′,3′-dideoxynucleoside of 2-aza-3-deazainosine were achieved and the pathways leading to these novel nucleosides are described. The preparation of the 2′,3′-dideoxynucleoside (**1**) of 2-aza-3-deazainosine involved deoxygenation of the 2′-deoxy-3′-imidazolide intermediate with *n*-Bu_3SnH and AIBN. The latter nucleoside was synthesized from the known 2′-deoxy derivative of 2-aza-3-deazainosine. The three-step synthesis of **1** from the 2′-deoxy analogue was accomplished in 40% overall yield. Rather than synthesize the corresponding 2′,3′-dideoxynucleoside (**2**) of 2,8-diaza-3-deazainosine in the same manner, i.e. deoxygenation of the 2′-deoxynucleoside, a more cost-effective route was chosen. This pathway involved reductive cleavage of the 5′-protected, 2′,3′-thiocarbonate derivative to furnish a mixture of the 2′- and 3′-deoxy isomers. This mixture was not separated, but was deoxygenated by the aforementioned imidazolide method. Using this methodology, **2** was prepared in 23% overall yield from 2,8-diaza-3-deazainosine. Nucleosides **1** and **2** were evaluated for antiretroviral activity and were found to be inactive.

Introduction

The design and synthesis of nucleoside analogues as anti-HIV agents continues to provide potential clinical candidates and useful drugs (for reviews see refs 1–5).To date, the dideoxynucleosides have provided some of the most active agents in inhibiting reverse transcriptase. Among those approved for the treatment of AIDS are AZT (Retrovir), ddC (Hivid), d_4T (Zerit), and ddI (Videx).[1–5] In this group, the dideoxynucleoside of particular interest to us was ddI. We have been actively engaged in the synthesis of imidazo- and ν-triazolo[4,5-*d*]pyridazine nucleosides[6–8] and in both series the respective inosine analogue served as the key intermediate. Seela and co-workers have prepared a variety of modified purine-ring 2′,3′-dideoxynucleosides[9–11] and selected derivatives have shown significant inhibitory activity against HIV-1 reverse transcriptase as their *O*-5′-triphosphates.[12] Their pivotal contributions have demonstrated that modification in the five-membered ring portion of the purine moiety, i.e. removal of the N-7 atom and replacement with a methine[9,10] or replacement of the HC-8 methine with a nitrogen atom,[11] is allowed and does not alter inhibitory activity. On the other hand, the HN-1 is required for inhibition[9] and removal of this pyrrole-type nitrogen results in a drastic loss of activity. The 2′,3′-dideoxyinosine counterparts of the title ring systems satisfy the aforementioned structural requirements deemed necessary for potential inhibitory activity. Furthermore, 2-aza-3-deazainosine and 2,8-diaza-3-deazainosine are resistant to phosphorolytic cleavage by purine nucleoside phosphorylase (PNP).[7] This is an important feature, since ddI has been reported to be a substrate for PNP.[13] With these factors in mind, we prepared 2′,3′-dideoxy-2-aza-3-deazainosine (**1**) and 2′,3′-dideoxy-2,8-diaza-3-deazainosine (**2**) and evaluated their activity against human immunodeficiency virus.



ddI



1; 2-Aza-3-deaza ddI, X = CH
2; 2,8-Diaza-3-deaza ddI, X = N

Chemistry and Discussion

Recently we reported[6] an efficient synthesis of 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)imidazo[4,5-*d*]pyridazine-4(5*H*)-one (**4**) which can be used to prepare 2′,3′-

Key words: Imidazopyridazines; ν-triazolopyridazines; deoxynucleosides; ddI analogues; HIV.

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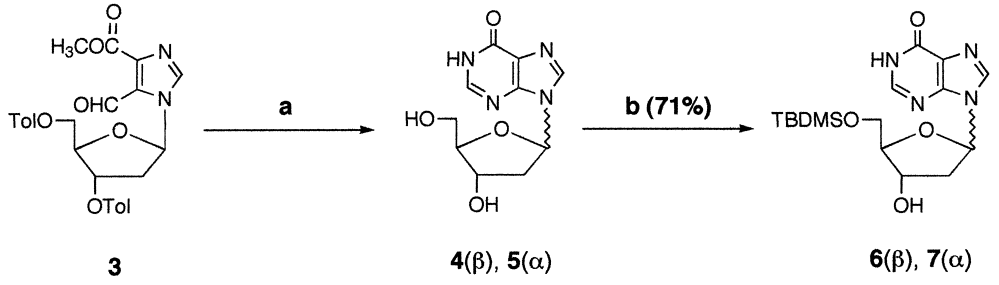
dideoxy-2-aza-3-deazainosine (**1**) in three steps. Nucleoside **4** was prepared by the ring closure of **3** with anhydrous hydrazine in ethanol as depicted in Scheme 1. The reaction proceeded in good yield,[14] but was always accompanied by a small amount of the α-anomer **5**. In our initial study,[6] we carefully checked the anomeric configuration of the nucleoside intermediates leading to **4** and established that both were beta (β). Therefore, we examined the reaction leading to **4** and found that anomerization was occurring after ring closure. Once cyclized, **4** is isolated as the hydrazino salt. Neutralization is then carried out using Amberlite IR-120 H^+ resin.[15] If the temperature is not controlled during neutralization, anomerization occurs and can be as high as 50%. This process can be minimized by rapidly neutralizing the salt at −5°C. The anomers were easily separated as their respective 5′-*O*-*tert*-butyldimethylsilyl (TBDMS) ethers (**6** and **7**) by fractional crystallization from methanol. The mixture of anomers (**4** and **5**) was regiospecifically 5′-silylated with *tert*-butyldimethylsilyl chloride (TBDMSCl) in dimethylformamide (DMF) to furnish 1-(5-*O*-*tert*-butyldimethylsilyl-2-deoxy-β-D-ribofuranosyl)imidazo[4,5-*d*]pyridazin-4(5*H*)-one (**6**) and 1-(5-*O*-*tert*-butyldimethylsilyl-2-deoxy-α-D-ribofuranosyl)imidazo[4,5-*d*]pyridazin-4(5*H*)-one (**7**) in a 70% yield. On standing in methanol, the α-anomer **7** readily crystallized out of solution. Nucleoside **7** was assigned as the α-anomer based on its characteristic splitting pattern in ^{1}H NMR spectrum.[6]

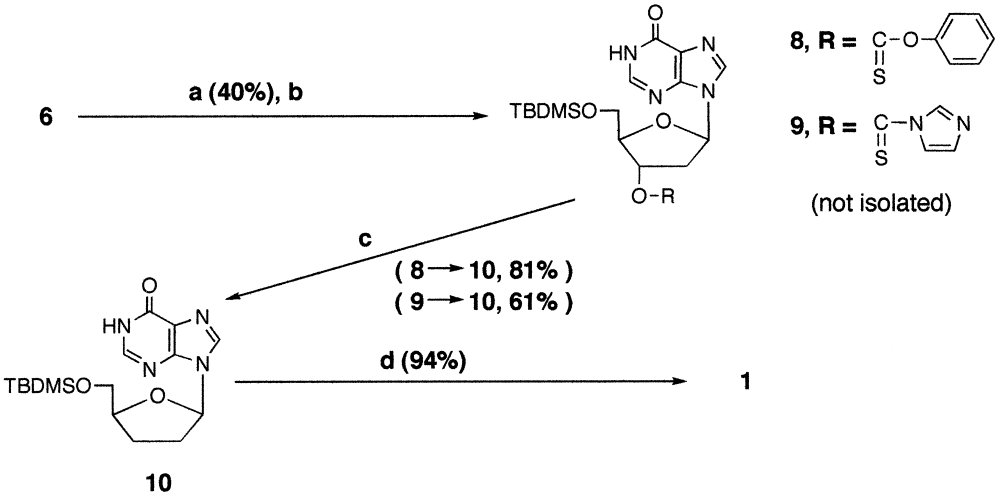
Next, the β-nucleoside **6**, isolated by fractional crystallization, was thioacylated[6] using phenyl chlorothionoformate to provide the 3′-*O*-phenoxythiocarbonyl analogue **8** (Scheme 2). This intermediate was then subjected to the Barton reduction[16] which furnished the 3′-deoxygenated nucleoside **10** in good yield. An alternate route to **10** involves the treatment of **6** with 1,1′-thiocarbonyldiimidazole (TCDI) in DMF to give the 3′-*O*-(1-imidazolylthiocarbonyl) analogue **9**. This derivative was used immediately without purification. It was treated with tri-*n*-butyltin hydride (for a deoxygenation procedure which avoids the use of *n*-Bu_3SnH or AIBN, see refs 17–19) in the presence of AIBN in dry toluene at reflux. This two-step, one-pot procedure provided **10** from **6** in an overall 61% yield. The 5′-*O*-TBDMS protected nucleoside (**10**) was deblocked with tetrabutylammonium fluoride (TBAF) in THF at room temperature for 1 h and the target nucleoside 1-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)imidazo[4,5-*d*]pyridazin-4 (5*H*)-one (**1**) was obtained in a 94% yield. This synthetic sequence afforded **1** in an overall 40% yield.

We now turned our attention to the synthesis of 2′,3′-dideoxy-2,8-diaza-3-deazainosine (**2**). Two pathways were envisaged. The first approach we adopted was similar to the synthetic sequence depicted in Scheme 2. This approach called for the preparation of the hitherto unknown 2′-deoxy analogue (**15**) of 1-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*d*]pyridazin-4-(5*H*)-one (**11**). The



3 **4**(β), **5**(α) **6**(β), **7**(α)

Scheme 1. Reagents: (a) 97% NH_2NH_2, abs. EtOH; (b) *t*-$BuSi(CH_3)_2Cl$, imidazole, DMF.



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Scheme 2. Reagents: for compd. **8**, (a) $C_6H_5OC(S)Cl$, DMAP, TEA, CH_3CN; for compd. **9**, (b) TCDI, DMF; (c) *n*-Bu_3SnH, AIBN, toluene; (d) TBAF, THF.

latter nucleoside, i.e. the proposed starting material for **15**, was recently synthesized in our laboratory.[7] The preparative pathway leading to 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-*v*-triazolo[4,5-*d*]pyridazin-4(5*H*)-one (**15**) is illustrated in Scheme 3. The 5′-OH and 3′-OH of **11** are simultaneously protected using 1,3-dichloro-1,1,2,2-tetraisopropyl-disiloxane ($TIPDSiCl_2$) in pyridine to give **12** in an 83% yield. Thioacylation of **12** using phenyl chlorothionoformate in acetonitrile afforded the 2-*O*-phenoxthiocarbonyl **12** in good yield. Deoxygenation of **13** using tri-*n*-butyltin hydride in refluxing toluene in the presence of AIBN afforded the silylated 2′-deoxy nucleoside **14**. Standard deprotection of the silyl ether with TBAF afforded **15** in an overall 50% yield from **11.** This represents the first disclosure of the 2′-deoxy nucleoside in this series. At this point, we decided to select an alternate route to **2** which was shorter, i.e. avoided the generation and isolation of **15**, and more cost-effective. This procedure is illustrated in Scheme 4 and again employs nucleoside **11** as starting material. Treatment of **11** with *tert*-butyldimethylsilyl chloride in DMF provided the silyl ether **16** in good yield. Heating **16** with 1,1′-thiocarbonyldiimidazole (TCDI) in dry DMF at 80°C formed the desired cyclic thiocarbonate **17**. The reductive cleavage of **17** furnished an ca. 1:1 mixture of the 2′-deoxy (**18**) and 3′-deoxy (**19**) isomers. This pattern is consistent with the orginal report of Barton and Subramanian[16] on the radical-initiated reduction of nucleoside 2′,3′-thiocarbonates with *n*-Bu_3SnH in the presence of AIBN. The characteristic ^1H NMR spin patterns of the anomeric protons of these two nucleosides confirmed the assignment of this mixture as 1-(5-*O*-*tert*-butyldimethylsilyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-*v*-triazolo[4,5-*d*]pyridazin-4(5*H*)-one (**18**) and 1-5-*O*-*tert*-butyl-dimethylsilyl-3-deoxy-β-D-*erythro*-pentofuranosyl)-*v*-triazolo[4,5-*d*]pyridazin-4(5*H*)-one (**19**). The isomeric mixture can be treated in the same manner as **6** (Scheme 2) with TCDI. Like **9**, the respective intermediates **20** and **21** were not isolated or purified. Reduction and deprotection then gave **2** in 23% overall yield.

Biological Evaluation

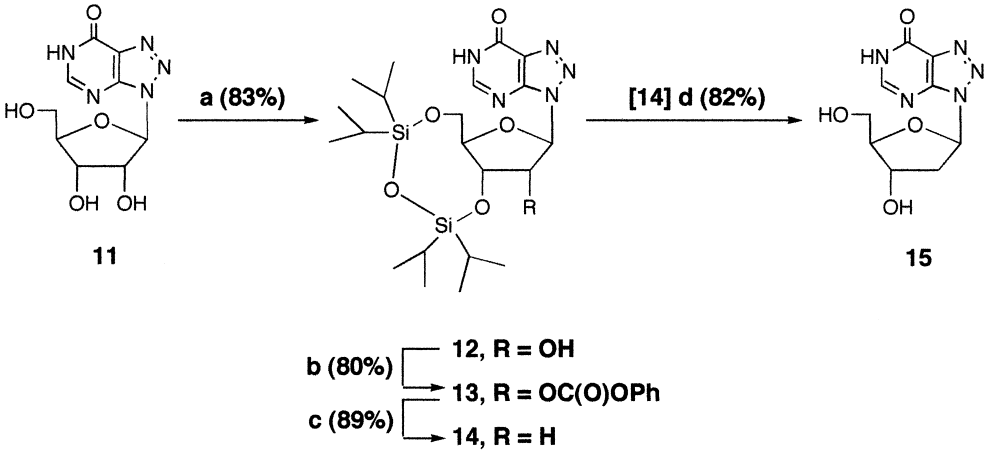
The 2′,3′-dideoxynucleosides **1** and **2** were evaluated in the National Cancer Institute in vitro Anti-AIDS Drug Discovery Program and screened against HIV-1 grown in CEM-SS cells. Their degree of activity was determined by the XTT assay[20]. Both of these nucleosides were found to be inactive at concentrations up to 2.00×10^{-4} M. It is worth mentioning that **1** and **2** were not cytotoxic in the concentration range, i.e. 6.00×10^{-8} to 2.00×10^{-4}, which they were tested.

Conclusion

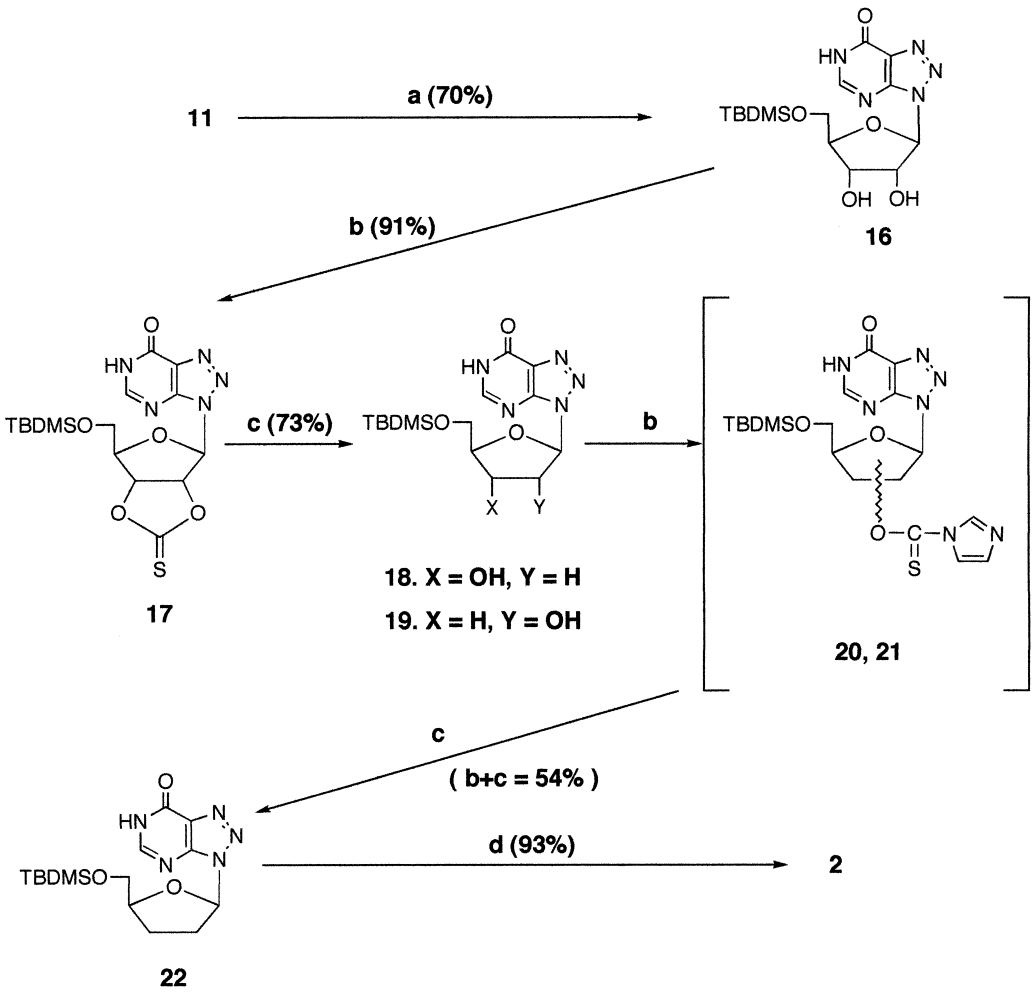
In conclusion, we have prepared the 2′,3′-dideoxynucleosides of 2-aza-3-deazainosine and 2,8-diaza-3-deazainosine. Our future research plans in this area include preparing the 5′-phosphonates[21] and the 5′-(difluoromethyl)phosphonates[22,23] of **1** and **2**. Phosphonate replacement is attractive since the carbon-phosphorus bond in phosphonates is not susceptible to enzymatic degradation by phosphatases, thus enhancing their physiological stability. Phosphonate esters are also less polar and this chemical feature gives rise to better cell permeability[24]. We anticipate that the 5′-phosphonate analogues of **1** and **2** will function as substrates for the nucleotide kinases and eventually be converted, in vivo, to their active 5′-triphosphate counterparts.

Experimental

Melting points were determined on a Buchi 535 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on either a Varian EM 390 or a Bruker AM-300 spectrometer, as indicated, using Me_4Si (TMS) as an internal standard. Optical rotations were measured on a Perkin–Elmer Model 141 automatic digital readout polarimeter. All moisture-sensitive reactions were performed using flame-dried glassware. Methylene chloride (CH_2Cl_2) and acetonitrile were dried over CaH_2 and distilled. Anhydrous THF was obtained by distillation over sodium benzophenone ketyl. Evaporations were performed under diminished pressure using a Buchi Rotary Evaporator unless stated otherwise. Davison silica gel (grade H, 60–200 mesh), purchased from Fisher Scientific, was used for flash column chromatography. A Chromatotron (centrifically



Scheme 3. Reagents: (a) TIPSiCl, pyridine; (b) $C_6H_5OC(S)Cl$, DMAP, TEA, CH_3CN; (c) *n*-Bu_3SnH, AIBN, toluene; (d) TBAF, THF.



Scheme 4. Reagents: (a) *t*-BuSi(CH_3)$_2$Cl, imidazole, DMF; (b) TCDI, DMF; (c) *n*-Bu_3SnH, AIBN, toluene; (d) TBAF, THF.

accelerated, preparative thin-layer, radial chromatograph), Model 7924 T was used to complete various separations as indicated. The 1.0 and 2.0 mm plates used were coated with silica gel PF254 containing $CaSO_4$. Thin-layer chromatography was performed on precoated silica gel plates (60-F254, 0.2 mm) manufactured by E.M. Science, Inc. and short-wave ultraviolet light (254 nm) was used to detect the UV absorbing compounds. All solvent proportions are by volume unless otherwise indicated. Elemental analyses were performed by MHW Laboratories, Phoenix, AR.

1-(5-*O*-*tert*-Butyldimethylsilyl-2-deoxy-β-D-*erythro*-pentofuranosyl)imidazo[4,5-*d*]pyridazin-4(5*H*)-one (6). A mixture containing the anomers **4,5**[6] (2.20 g, 8.62 mmol), imidazole (1.29 g, 18.9 mmol), and *tert*-butyldimethylsilyl chloride in dry DMF (10 mL) was stirred under N_2 for 12 h. The reaction mixture was concentrated under vacuum and the residue was purified by flash column chromatography using ethyl acetate:methanol (19:1) as the eluent to give a mixture of compounds **6** and **7** (2.27 g, 71%) as a white solid. Recrystallization of this intimate mixture from methanol gave pure **6** (2.00 g, 67%): mp 171–172°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ −0.01 (s, 6H, Si(CH_3)$_2$), 0.81 (s, 9H, Si(CH_3)$_3$), 2.35–2.55 (m, 2H, H-2′), 3.65–3.82 (m, 2H, H-5′), 3.92 (q, 1H, J = 6.94 Hz, J = 3.53 Hz, H-4′), 4.32–4.37 (m, 1H, H-3′), 5.41 (d, 1H, J = 4.06 Hz, D_2O exchangeable, O*H*), 6.36 (t, 1H, J = 6.39 Hz, H-1′), 8.46 (s, 1H, H-2), 8.54 (s, 1H, H-7), 12.70 (s, 1H, D_2O exchangeable, N*H*). Anal. calcd for $C_{16}H_{26}N_4O_4Si$: C, 52.44; H, 7.15; N, 15.29. Found: C, 52.38; H, 7.27; N, 15.64.

1-(5-*O*-*tert*-Butyldimethylsilyl-3-*O*-phenoxythiocarbonyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-imidazo[4,5-*d*]pyridazin - 4(5*H*) - one (8). A solution of **6** (0.40 g, 1.09 mmol), dimethylaminopyridine (0.15 g, 1.19 mmol), phenylchlorothionoformate (0.45 mL, 3.26 mmol), and triethylamine (2 mL) in anhyd acetonitrile (10 mL) was stirred at room temperature for 5 h. The reaction mixture was poured over cracked ice/water (50 mL), and the water solution extracted with ethyl acetate (3×60 mL). The organic layers were combined, dried over anhyd like Na_2SO_4, and concentrated. The residue was purified by flash column chromatography using ethyl acetate:CH_2Cl_2 (3:2) as the eluent to give **8** (0.22 g, 40% yield) as a yellow foam: mp 84–86°C; ^{1}H NMR ($CDCl_3$) δ 0.15 (s, 6H, Si(CH_3)$_2$), 0.90 (s, 9H, Si(CH_3)$_3$), 2.68–2.90 (m, 2H, H-2′), 3.89–4.10 (m, 2H, H-5′), 4.40–4.54 (m, 1H, H-4′), 5.73–5.90 (m, 1H, H-3′), 6.30 (dd, 1H, J = 5.7 Hz, J = 8.8 Hz H-1′), 6.93–7.48 (m, 5H, C_6H_5), 8.12 (s, 1H, H-2), 8.49 (s,

1H, H-7), 11.73 (s, 1H, D_2O exchangeable, N*H*). Anal. calcd for $C_{23}H_{30}N_4O_5SSi$; C, 54.96; H, 6.02; N, 11.14. Found: C, 55.05; H, 5.87; N, 10.91.

1-(5-*O*-*tert*-Butyldimethylsilyl-2,3-dideoxy-β-D-*glycero*-pentofuranosyl)imidazo[4,5-*d*]pyridazin-4(5*H*)-one (10). Method A. Compound **8** (0.10 g, 0.20 mmol) was dissolved in dry toluene (5 mL) and heated to reflux as a solution of tri-*n*-butyltin hydride (0.5 mL) and α,α′-azobisisobutyronitrile (AIBN, 5 mg) in toluene (2 mL) was added dropwise. After the addition was completed, the reaction was stirred at reflux for 4 h and then cooled to room temperature and concentrated. Purification of the crude product by flash column chromatography using CH_2Cl_2:ethyl acetate (1:1) as the eluent afforded **10** (0.06 g, 81% yield) as a white solid: mp 49–50 °C sinters, 92–94°C; ^{1}H NMR ($CDCl_3$) δ 0.17 (s, 6H, Si (CH_3)$_2$), 0.88 (s, 9H, Si(CH_3)$_2$), 1.90–2.61 (m, 4H, H-2′, H-3′), 3.49–3.91 (m, 2H, H-5′), 4.02–4.30 (m, 1H, H-4′), 6.02 (dd, 1H, J = 4.0 Hz, J = 6.0 Hz, H-1′), 8.13 (s, 1H, H-2), 8.23 (s, 1H, H-7), 11.32 (bs, 1H, D_2O exchangeable, N*H*). Anal. calcd for $C_{16}H_{26}N_4O_3Si$: C, 54.83; H, 7.48; N, 15.99. Found: C, 54.49; H, 7.55; N, 15.73.

Method B. A solution of **6** (0.34 g, 0.87 mmol) and 1,1′-thiocarbonyldiimidazole (0.47g, 2.63 mmol) and dry DMF (5 mL) was stirred at room temperature for 20 h under N_2. The mixture was poured into cold H_2O (ca. 5 mL) and the aq solution was extracted with ethyl acetate (2×20 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and then concentrated. Crude **9** was dissolved in dry toluene (6 mL) and heated to reflux while a solution of tri-*n*-butyltin hydride (0.5 mL) and AIBN (5 mg) in toluene (2 mL) was added dropwise. The reaction was stirred at reflux for 5 h, cooled to room temperature, and concentrated. The oily residue was purified by flash column chromatography using ethyl acetate as the eluent to give **10** (0.19 g, 61% yield) having physical data identical in all respects to that obtained by Method A.

1-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)imidazo[4,5-*d*]pyridazin-4(5*H*)-one (1). Tetrabutylammonium fluoride (TBAF, 0.2 mL, 1 M solution in THF) was added dropwise to a solution of **10** (0.10 g, 0.29 mmol) in dry THF (5 mL) and stirred at room temperature under N_2 for 2 h. The solvent was evaporated to give the crude product which was dissolved in H_2O (3 mL), washed with CH_2Cl_2 (2×10 mL), and then lyophilized. The product was purified by flash column chromatography using ethyl acetate as the eluent to give **1** (0.05 g, 94% yield) as a white solid: mp 252 °C dec; $[\alpha]_D^{25}$ −30.6° (*c* 0.88, DMF); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.93–2.03 (m, 2H, H-3′), 2.33–2.50 (m, 2H, H-2′), 3.41–3.48 (m, 1H, H-5′), 3.54–3.61 (m, 1H, H-5′), 4.11–4.19 (m, 1H, H-4′), 4.97 (t, 1H, J = 5.28 Hz, D_2O exchangeable, O*H*), 6.27 (dd, 1H, J = 6.37 Hz, J = 3.31 Hz, H-1′), 8.53 (s, 1H, H-2), 8.55 (s, 1H, H-7). Anal. calcd for $C_{10}H_{12}N_4O_3$: C, 50.67; H, 5.44; N, 23.64. Found: C, 50.48; H, 5.21; N, 23.46.

1-{3,5-O-(1,1,3,3-Tetraisopropyldisiloxanyl)-β-D-ribofuranosyl}-ν-triazolo[4,5-*d*]pyridazin-4(5*H*)-one (12). To a solution containing **11**[7] (2.10 g, 7.8 mmol) and anhyd pyridine (20 mL) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (2.70 mL, 8.6 mmol). The reaction mixture was stirred at room temperature under N_2 for 6 h. Cold water (50 mL) was then added to the reaction mixture and the aq solution was extracted with CH_2Cl_2 (3×60 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by flash column chromatography using CH_2Cl_2: methanol (19:1) as the eluent to afford **12** (3.31 g, 83% yield) as a white foam: mp 80 °C sinters, 87–88 °C; ^{1}H NMR ($CDCl_3$) δ 0.98, 1.07 (2s, 28H, *i*-Pr), 3.85–4.35 (m, 3H, H-5′, H-4′), 4.63–4.91 (m, 2H, H-3′, H-2′), 6.32 (s, 1H, H-1′), 8.55 (s, 1H, H-7), 12.09 (bs, 1H, D_2O exchangeable, N*H*). Anal. calcd for $C_{21}H_{37}N_5O_6Si_2$: C, 49.29; H, 7.29; N, 13.68. Found: C, 49.50; H, 7.47; N, 13.36.

1-{2-*O*-Phenoxythiocarbonyl-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxanyl)-β-D-ribofuranosyl}-ν-triazolo[4,5-*d*]pyridazin-4(5*H*)-one (13). A solution containing **12** (1.74 g, 3.40 mmol), dimethylaminopyridine (0.46 g, 3.7 mmol), phenyl chlorothionoformate (1.00 mL, 7.0 mmol), triethylamine (5 mL) and anhyd acetonitrile (30 mL) was stirred at room temperature for 5 h as for the preparation of **8**. The usual work up followed by flash column chromatography using CH_2Cl_2:methanol (9:1) as the eluent afforded **13** (1.76 g, 80% yield) as a white solid: mp 83–84 °C; ^{1}H NMR ($CDCl_3$) δ 0.99, 1.09 (2s, 28H, *i*-Pr), 3.91–4.34 (m, 3H, H-4′, H-5′), 4.88–5.08 (m, 1H, H-3′), 6.47 (d, 1H, J = 4.5 Hz, H-2′), 6.52 (s, 1H, H-1′), 6.98–7.51 (m, 5H, C_6H_5), 8.51 (s, 1H, H-7), 11.73 (bs, 1H, D_2O exchangeable, N*H*). Anal. calcd for $C_{28}H_{41}N_5O_7SSi_2$: C, 51.91; H, 6.38; N, 10.81. Found: C, 52.08; H, 6.27; N, 10.82

1-{2-Deoxy-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxanyl)-β-D-*erythro*-pentofuranosyl)-ν-triazolo[4,5-*d*]pyridazin-4(5*H*)-one (14). To a solution of **13** (0.32 g, 0.49 mmol) and anhyd toluene (15 mL) stirred at room temperature, under N_2, was added tri-*n*-butyltin hydride (1.5 mL) and AIBN (15 mg). The mixture was heated at reflux for 4 h, cooled to room temperature and then concentrated. Purification of the residue by flash column chromatography using CH_2Cl_2:ethyl acetate (9:1) as the eluent gave **14** (0.22 g, 89% yield) as a white foam: mp 80–85 °C; ^{1}H NMR ($CDCl_3$) δ 0.87–1.09 (m, 28H, *i*-Pr), 2.57–3.33 (m, 2H, H-2′), 3.80–4.07 (m, 3H, H-5′, H-4′), 4.63–4.93 (m, 1H, H-3′), 6.50 (dd, 1H, J = 6.5 Hz, H-1′) 8.53 (s, 1H, H-7), 11.40 (s, 1H, D_2O exchangeable, N*H*). Anal. calcd for $C_{21}H_3N_5O_5Si_2$: C, 50.88; H, 7.52; N, 14.13. Found: C, 51.07; H, 7.58; N, 14.20.

1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-ν-triazolo[4,5-*d*]pyridazin-4(5*H*)-one (15). To a solution of **14** (0.45 g, 0.91 mmol) in dry THF (10 mL) was added TBAF (1.0 mL, 1 M solution in THF) and the resulting mixture was stirred at room temperature for 40 min. The mixture was then poured over cracked ice/water (50 mL), the aq solution washed with CH_2Cl_2 (3×60 mL) and then lyophilized. Purification of the resulting residue on a Chromatotron (2.0 mm plate) using ethyl acetate:methanol (9:1) as the eluent followed by recrystallization from methanol afforded pure **15** (0.190 g, 82% yield) as crystalline prisms: mp 145–146°C; ^{1}H NMR (DMSO-d_6) δ 2.27–2.60, 2.73–3.07 (m, 2H, H-2′, H-2″), 3.23–3.50 (m, 2H, H-5′, H-5″), 3.82–4.00 (m, 1H, H-4′), 4.28–4.50 (m,

1H, H-3′), 4.72 (t, 1H, $J=5.0$ Hz, D_2O exchangeable, O*H*), 5.33 (d, 1H, $J=4.5$ Hz, D_2O exchangeable, O*H*), 6.20 (t, 1H, $J=6$ Hz, H-1′), 8.69 (s, 1H, H-7), 11.95 (s, 1H, D_2O exchangeable, N*H*). Anal. calcd for $C_9H_{11}N_5O_4$: C, 42.69; H, 4.38; N, 27.66. Found: C, 42.73; H, 4.53; N, 27.76.

1-(5-*O*-*tert*-Butyldimethylsilyl-β-D-ribofuranosyl)-ν-triazolo[4,5-*d*]pyridazin-4(5*H*)-one (16). To a solution containing **11** (1.07 g, 3.97 mmol) and imidazole (0.68 g, 9.92 mmol), in anhyd DMF (10 mL) under N_2 was added *tert*-butyldimethylsilyl chloride (0.72 g, 4.76 mmol). The reaction mixture was then stirred at room temperature for 20 h. The solvent was removed in vacuo and the resulting residue purified by flash column chromatography using CH_2Cl_2:methanol (19:1) as the eluent to yield **16** (1.06 g, 70% yield) as a white foam: mp 88–89 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ −0.02 (s, 6H, Si(C*H*$_3$)$_2$), 0.72 (s, 9H, Si(C*H*$_3$)$_3$), 3.63–3.88 (dq, 2H, H-5′, H-5″), 4.06–4.26 (m, 3H, H-4′, H-3′), 4.69–4.77 (m, 1H, H-2′), 5.34 (d, 1H, $J=6$ Hz, D_2O exchangeable, O*H*), 5.79 (d, 1H, $J=6.0$ Hz, D_2O exchangeable, O*H*), 6.31 (d, 1H, $J=4.4$ Hz, H-1′), 8.77 (s, 1H, H-7). Anal. calcd for $C_{15}H_{25}N_5O_5Si$: C, 46.98; H, 6.57; N, 18.26. Found: C, 46.90; H, 6.65; N, 17.87.

1-(5-*O*-*tert*-Butyldimethylsilyl-2,3-*O*-thionocarbonyl-β-D-ribofuranosyl)- ν-triazolo[4,5-*d*]pyridazin-4(5*H*)-one (17). A solution containing **16** (1.03 g, 2.69 mmol) and 1,1′-thiocarbonyldiimidazole (0.62 g, 3.49 mmol) in anhyd DMF (10 mL) was heated to 80 °C under N_2 for 4 h. The solvent was removed in vacuo and the resulting residue was purified by flash column chromatography using CH_2Cl_2:ethyl acetate (4:1) as the eluent. Recrystallization of the product from CH_2Cl_2 afforded pure **17** (1.14 g, 91% yield) as a white solid: mp 279–280 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ −0.22 (s, 3H, Si(C*H*$_3$)$_2$), −0.17 (s, 3H, Si(C*H*$_3$)$_2$), 0.67 (s, 9H, Si(C*H*$_3$)$_3$), 3.80 (dq, 2H, H-5′, H-5″), 4.79 (t, 1H, H-4′), 5.84 (d, 1H, $J=6.6$ Hz, H-3′), 6.53 (d, 1H,$J=7.2$ Hz, H-2′), 7.16 (s, 1H, H-1′), 8.78 (s, 1H, H-7). Anal. calcd for $C_{16}H_{23}N_5O_5SiS$: C, 45.16; H, 5.45; N, 16.46; S, 73. Found: C, 44.97; H, 5.29; N, 16.20; S, 7.23.

1-(5-*O*-*tert*-Butyldimethylsilyl-3-deoxy-β-D-*erythro*-pentofuranosyl)-ν-triazolo[4,5-*d*]pyridazin-4(5*H*)-one (18) and 1-(5-*O*-*tert*-butyldimethylsilyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-ν-triazolo[4,5-*d*]pyridazin-4(5*H*)-one (19). Compound **17** (0.91 g, 2.15 mmol) was heated to reflux in dry toluene (20 mL) while a solution containing tri-*n*-butyltin hydride (1.00 mL) and AIBN (30 mg) in toluene (2 mL) was added dropwise. The reaction was stirred at reflux for 4 h, cooled, concentrated and then purified by flash column chromatography using CH_2Cl_2:ethyl acetate (3:1) as the eluent to give ca. 1:1 intimate mixture of **18** and **19** (0.58 g, 73% yield) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ −0.07 (s, 6H, Si(C*H*$_3$)$_2$), −0.04 (s, 3H, Si(C*H*$_3$)$_2$), −0.03 (s, 3H, Si(C*H*$_3$)$_2$), 0.76 (s, 9H, Si(C*H*$_3$)$_3$), 0.79 (s, 9H, Si(C*H*$_3$)$_3$), 2.15–2.22 (m, 1H), 2.29–2.38 (m, 1H), 2.73–2.81 (m, 1H), 3.08–3.16 (m, 2H), 3.60–3.94 (m, 4H), 4.25 (q, 1H), 4.71–4.78 (m, 1H), 5.36 (d, 1H), 6.35 (s, 1H, H-1′), 6.64 (t, 1H, $J=5.7$ Hz, H-1′), 8.67 (s, 1H), 8.70 (s, 1H), 11.14 (bs, 1H), 11.22 (bs, 1H). Anal. calcd for $C_{15}H_{25}N_5O_4Si$; C, 49.03; H, 6.86; N, 19.06. Found: C, 49.23; H, 6.95; N, 18.95.

1-(5-*O*-*tert*-Butyldimethylsilyl-2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-ν-triazolo[4,5-*d*]pyridazin-4(5*H*)-one (22). A solution of isomers **18** and **19** (0.22 g, 0.61 mmol) and TCDI (0.32 g, 1.18 mmol) in dry DMF (5 mL) was stirred for 20 h at room temperature under N_2. The mixture was concentrated in vacuo, dissolved in CH_2Cl_2 (20 mL), and washed with H_2O (2×10 mL). The aqueous phase was washed with ethyl acetate (10 mL) and the organic phases were combined, dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in dry toluene (5 mL) and heated to reflux as a solution of *n*-Bu_3SnH (0.5 mL) and AIBN (5 mg) in dry toluene (2 mL) was added dropwise. The reaction was stirred at reflux for 3 h, cooled, and concentrated. The oily residue was purified by flash column chromatography using CH_2Cl_2: ethyl acetate (4:1) as the eluent to provide **22** (0.12 g, 54% yield) as a waxy solid: mp 92–94 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ –0.09 (s, 6H, Si(C*H*$_3$)$_2$), 0.76 (s, 9H, Si(C*H*$_3$)$_3$), 2.03–2.18 (m, 2H, H-3′), 2.55–2.68 (m, 1H, H-2′), 3.21–3.30 (m, 1H, H-2″), 3.51–3.87 (dq, 2H, $J_{5',5''}=11.42$, $J_{5',4'}=3.15$, $J_{5'',4'}=4.39$ Hz, H-5′, H-5″), 4.40–4.48 (m, 1H, H-4′), 6.40 (dd, 1H, $J=6.3$ Hz, $J=1.9$ Hz, H-1′), 8.65 (s, 1H, H-7), 10.41 (s, 1H, D_2O exchangeable, N*H*). Anal. calcd for $C_{15}H_{25}N_5O_3Si$; C, 51.25; H, 7.17; N, 19.93. Found: C, 51.46; H, 7.27; N, 19.71.

1-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-ν-triazolo[4,5-*d*]pyridazin-4(5*H*)-one (2). Tetrabutylammonium fluoride (TBAF, 0.5 mL, 1 M solution in THF) was added dropwise to a solution of **22** (0.10 g, 0.29 mmol) in dry THF (5 mL) and stirred at room temperature under N_2 for 2 h. Reaction work up and purification as for the synthesis of **1** gave **2** (0.05 g, 93% yield) as a white solid: mp 140–142 °C dec.; $[\alpha]_D^{25}$ −44.7° (*c* 0.98, abs EtOH); ^{1}H NMR (MeOH-d_4) δ 1.96–2.30 (m, 2H, H-3′, H-3″), 2.55–2.70, 3.00–3.15 (2m, 2H, H-2′, H-2″), 3.40–3.74 (m, 2H, H-5′), 4.30–4.43 (m, 1H, H-4′), 6.54 (dd, 1H, $J=6.6$ Hz, $J=1.6$ Hz, H-1′), 8.69 (s, 1H, H-7). Anal. calcd for $C_{10}H_{12}N_4O_3$: C, 45.57; H, 4.67; N, 29.52. Found: C, 45.35; H, 4.71; N, 29.47.

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