A Convenient Synthesis of 1-(β-D-Ribofuranosyl)imidazo[4,5-*d*]pyridazin-4(5*H*)-one (2-Aza-3-deazainosine) and Its 2'-Deoxy Counterpart by Ring Closure of Imidazole Nucleosides

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Cyclization of methyl 5-formyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole-4-carboxylate (**5**) with 97% hydrazine in ethanol furnished 1-(β-D-ribofuranosyl)imidazo[4,5-*d*]pyridazin-4(5*H*)-one (**8**) in good yield. Likewise, ring closure of methyl 5-formyl-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)imidazole-4-carboxylate (**19**) using the same conditions provided 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)imidazo[4,5-*d*]pyridazin-4(5*H*)-one (**16**). This 2'-deoxyribonucleoside (**16**) was also obtained by deoxygenation of (**8**).

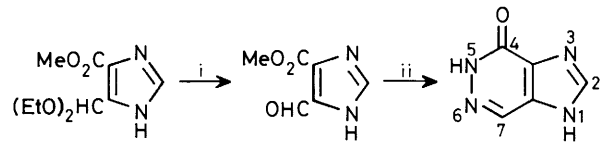
The imidazo[4,5-*d*]pyridazines[1] continue to attract attention as potential antimetabolites and, in fact, certain 4-substituted derivatives of this ring system have been shown to function as substrates/inhibitors of purine-requiring enzymes.[2] Although many mono- and di-substituted derivatives of this heterocycle have been prepared and tested, only a few nucleosides of this ring system are known.[3-6] The main reason for this is that the usual synthetic approach, *i.e.*, glycosylation of a suitable mono-substituted imidazo[4,5-*d*]pyridazine provides either the wrong isomer (N-6)[5] or poor[3] to moderate[6] yields of the desired N(1)-nucleoside. A detailed study[7] from our laboratory which focused on the site of alkylation of certain imidazo[4,5-*d*]-pyridazines showed that the preferred site was N-6. Cook and co-workers[5] also found this to be the case in their attempt to synthesize 1-(β-D-ribofuranosyl)imidazo[4,5-*d*]pyridazin-4(5*H*)-one (**8**) (Scheme 2) using the silyl derivative of imidazo[4,5-*d*]pyradizin-4(5*H*)-one (**3**) (Scheme 1). Based on these findings, Otter and co-workers[6] used an appropriately blocked imidazo[4,5-*d*]pyridazin-4-one which directed glycosylation to the imidazole portion of this heterocyclic system. Even under optimum conditions this novel procedure provided an equal mixture of the blocked N-1 and N-3 β-ribosides of (**3**).

It appeared that the most promising strategy which could lead to the desired 4-substituted N-1 nucleosides of this ring system (structurally similar to the 6-functionalized N-9 purine ribosides) would involve glycosylation of a 4,5-disubstituted imidazole and subsequent cyclization to the imidazo[4,5-*d*]-pyridazine ring. Such methodology was successfully employed[4,5] in the preparation of certain 4,7-substituted imidazo-[4,5-*d*]pyridazine nucleosides.

Access to the 4-substituted imidazo[4,5-*d*]pyridazine nucleosides *via* this procedure has been hampered due to a lack of a suitable imidazole synthon. Recently, however, two 4,5-di-substituted imidazoles [(**1**) and (**2**)] were described in the literature[8] and on glycosylation should provide the key imidazole nucleoside precursor required for ring closure. This report now addresses the use of these imidazoles in the preparation of imidazo[4,5-*d*]pyridazin-4-(5*H*)-one[9] and the title N(1)-ribosides of this heterocycle.

Chemistry and Discussion

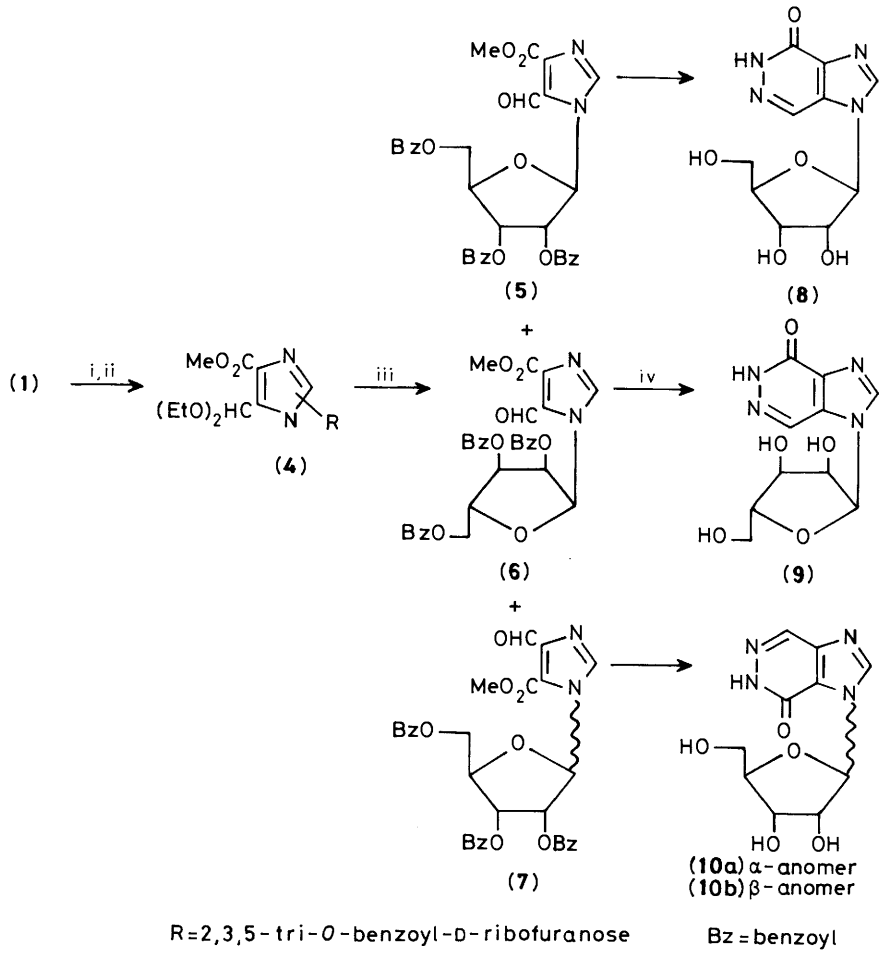
Treatment of (**2**) with anhydrous hydrazine in absolute ethanol afforded (**3**) in 78% yield. This heterocycle was identical (u.v., i.r., n.m.r.) to an authentic sample of (**3**) prepared by the cyclization of 4,5-diaminopyridazin-3-one[9] with triethyl orthoformate and acetic anhydride (Scheme 1). To the best of our knowledge, the ring closure of (**2**), represents the first example of a 4,5-disubstituted imidazole being cyclized directly to a 4-monosubstituted imidazo[4,5-*d*]pyridazine.



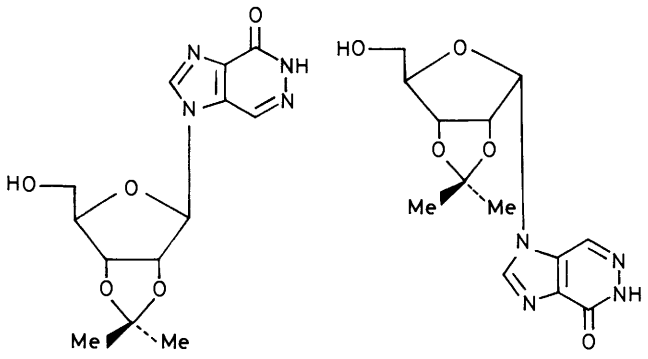
Scheme 1. *Reagents:* i, aq. AcOH; ii, H_2NNH_2, EtOH

Next, we turned our attention to the synthesis of (**8**). We elected to ribosylate (**1**) by the sodium salt glycosylation procedure.[10] The sodium salt of (**1**), produced *in situ* by sodium hydride in acetonitrile, was treated with a solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl iodide[11] in acetonitrile at 50 °C for 2 h (Scheme 2). After work up, the syrupy residue was purified by flash chromatography to provide (**4**) in 95% yield. Thin-layer chromatography and ^{1}H n.m.r. spectroscopy indicated (**4**) was a complex mixture of nucleosides. It was found that conversion of the acetal function on (**4**) to the aldehyde facilitated separation of this mixture. Silica gel, flash chromatography of the carboxaldehydes using hexane–ethyl acetate as eluant provided methyl 5-formyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole-4-carboxylate (**5**) (85%) as the major component,† the α-anomer (**6**) (3.8%) of (**5**), and an intimate mixture of the α- and β-anomers of methyl 4-formyl-1-(2,3,5-tri-*O*-benzoyl)-D-ribofuranosyl)imidazole-5-carboxylate (**7**) (5.6%). The site of ribosylation and the anomeric configuration of these imidazole nucleosides were subsequently confirmed by treating them with anhydrous hydrazine in absolute ethanol which effected cyclization to their respective imidazo[4,5-*d*]pyridazine nucleosides.

† This nucleoside was conveniently reduced with $NaBH_4$ to the 5-hydroxymethyl nucleoside which in turn was converted to the 5-chloromethyl analogue; a precursor to 3-deazaguanosine. For a similar sequence see, H. Tanaka, M. Hirayama, M. Suzuki, T. Miyasaka, A. Matsuda, and T. Ueda, *Tetrahedron*, 1986, **42**, 1971.



Scheme 2. *Reagents:* i, NaH, MeCN; ii, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, $(Me)_3SiI$, C_6H_6; iii, aq. AcOH; iv, H_2NNH_2, EtOH

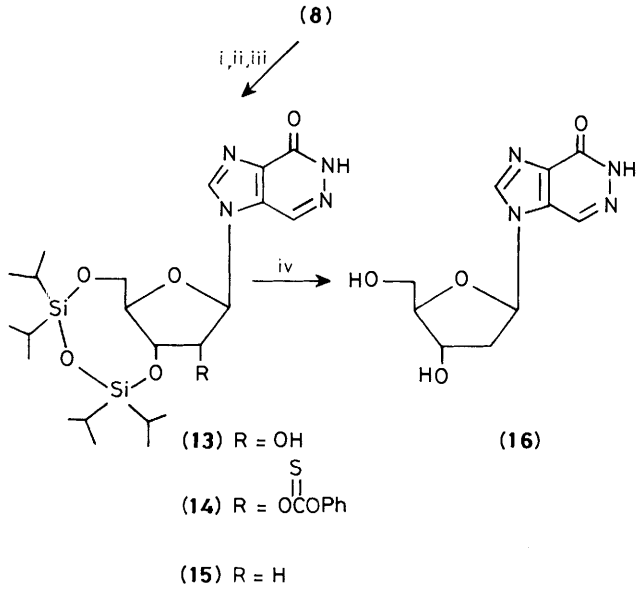


(11) (12)

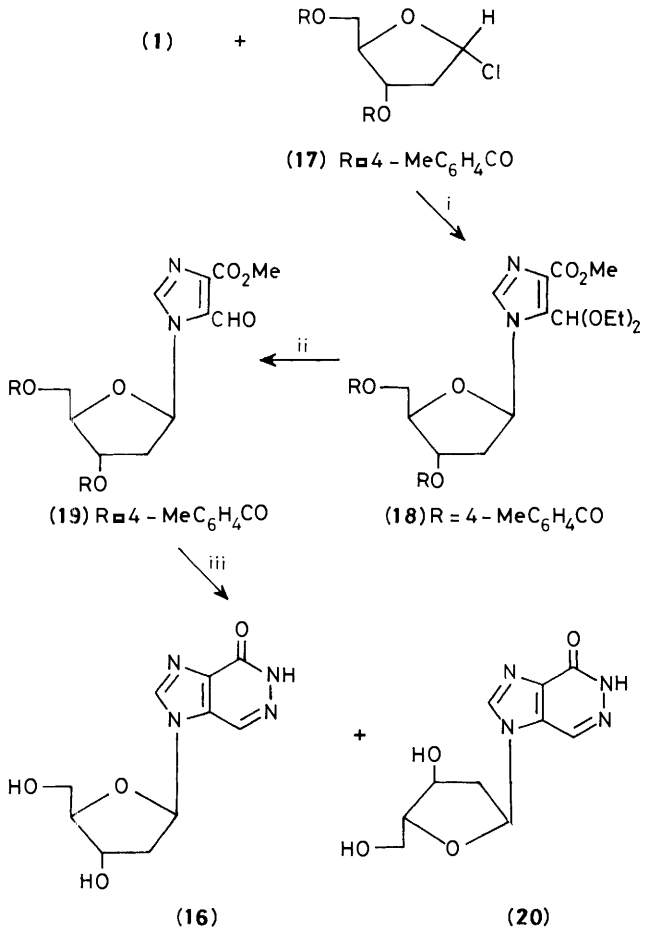
Thus, ring closure of (**5**) furnished the title nucleoside 1-(β-D-ribofuranosyl)imidazo[4,5-*d*]pyridazin-4(5H)-one (**8**) (2-aza-3-deazainosine) in 70% yield.* The ^{13}C and ^1H n.m.r. data, the u.v. data, and melting point of (**8**) were in good agreement with reported values.[6] It is worth mentioning that the structures of (**8**)[6] and (**10b**)[5,6] were rigorously established as β-N(1) and β-N(3), respectively. The assignment of (**9**), and therefore (**6**), was based on u.v. and ^1H n.m.r. data and chemical conversion to the 2′,3′-*O*-isopropylidene derivative (**12**). The u.v. data of (**9**) matched that of (**8**) which indicated that the ribosyl moiety was attached to N-1. The doublet for the anomeric proton (δ 6.48) in the ^1H n.m.r. spectrum [$(CD_3)_2SO$] of (**9**) appeared downfield to the doublet (δ 6.28) assigned to the anomeric proton in the spectrum of (**8**). This spectral feature is generally regarded as reasonable proof for the α-configuration.[13] Additional evidence for the α-configuration was furnished by the ^1H n.m.r. spectrum of (**12**). The observed difference in the chemical shifts (Δδ) of the isopropylidene methyl groups was δ 0.08 which is consistent with the criteria established for α-D-ribofuranosyl nucleosides.[14] It is noteworthy that the 2′,3′-*O*-isopropylidene derivative (**11**), which was prepared from (**8**), had a Δδ value for the methyl signals of δ 0.23; a value characteristic of the β-configuration.

The mixture of (**10a**) and (**10b**) obtained from (**7**) was tentatively assigned as the N(3)-anomers. This initial assignment was based on a comparison of the u.v. data of this mixture to that reported for authentic 3-(β-D-ribofuranosyl)imidazo-[4,5-*d*]pyridazin-4(5*H*)-one (**10b**).[5,6] The assignment was confirmed by fractional crystallization of this mixture from methanol to provide the near-pure β-anomer (**10b**) (*ca.* 90—92%). The ^1H n.m.r. and u.v. data of this material were in excellent agreement with those recorded in the literature.[5,6] The filtrate from this procedure was taken to dryness and the resulting solid was shown (^1H n.m.r.) to be a 1:1 mixture of the α- and β-anomers. This mixture enabled us to record the pertinent proton chemical shifts of the α-anomer (**10a**). Again

* We have also synthesized 1-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*d*]-pyridazin-4(5*H*)-one {$\delta_H[(CD_3)_2SO]$ 6.25 (1 H, d, *J* 4.5 Hz, 1′-H), 8.81 (1 H, s, 7-H), and 12.90 (1 H, s, NH)} from methyl 5-formyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*v*-triazole-4-carboxylate;[12] J. Bussolari and R. P. Panzica unpublished results.



Scheme 3. *Reagents and conditions:* i, $TIPDSiCl_2$, C_5H_5N, 25 °C; ii, PhOCSCl, $(C_2H_5)_3N$, DMAP, CH_3CN, 25 °C; iii, $(Bu)_3SnH$, AIBN, Toluene, reflux; iv, $(Bu)_4NF$, THF, 25 °C



Scheme 4. *Reagents and conditions:* i, NaH, MeCN; ii, 80% aq. AcOH, 25 °C; iii, NH_2NH_2, abs. EtOH

the u.v. data of this mixture matched those previously obtained in this study.

This efficient, three-step synthesis of (**8**) (58% overall yield) makes possible a ready source of this nucleoside and provides a synthon for other β-N(1) derivatives. One such analogue we felt would be of particular interest was (**16**), the 2′-deoxy derivative of (**8**). Our first synthetic approach to this nucleoside is depicted in Scheme 3 and involves deoxygenation of the 2′-position of (**8**). The 3′- and 5′-OH groups of (**8**) were protected by reaction with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane ($TIPDSiCl_2$) in pyridine at room temperature to provide the 3′,5′-cyclic disiloxanyl derivative (**13**) in near-quantitative yield.[15,16] Thioacylation of (**13**) gave the 2′-*O*-phenoxythiocarbonyl analogue (**14**) (80%) in good yield. Reduction of (**14**) with tributyltin hydride in the presence of α,α′-azoisobutyronitrile (AIBN) in refluxing toluene[16] furnished the 2′-deoxy compound (**15**) in 98% yield. Deprotection of (**15**) with tetrabutylammonium fluoride (TBAF) in dry tetrahydrofuran (THF) at room temperature for 20 min afforded the desired 1-(2-deoxy-β-D-*erythro*-pentofuranosyl)imidazo[4,5-*d*]pyridazin-4(5*H*)-one (**16**) in moderate yield. The ^1H n.m.r. spectrum of (**16**) displayed a pseudo triplet for the anomeric proton centered at δ 6.38 with a peak width of 13.5 Hz.

In an effort to prepare (**16**) on a larger scale and by a more cost efficient route, we explored the synthetic pathway depicted in Scheme 4. This approach involves direct ribosylation of the sodium salt of (**1**). Thus, condensation of (**1**) with 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentafuranosyl chloride (**17**)[17] furnished after chromatography a 70% yield of (**18**). Treatment of (**18**) with 20% aqueous acetic acid gave a near-quantitative yield of (**19**). Ring closure of (**19**) with anhydrous hydrazine in ethanol provided (**16**) and a small amount of the α-anomer (**20**). The assignment of (**20**) as the α-anomer of (**16**) was based on the characteristic spin pattern observed for the anomeric proton in the ^1H n.m.r. spectrum. This proton appeared as a doublet of doublets ('quartet') centered at δ 6.39 with coupling constants of 2.6 Hz and 7.3 Hz which is in close agreement with data published for 2-deoxy-α-D-*erythro*-pentofuranosyl nucleosides.[13]

We were somewhat surprised by the appearance of (**20**), as the sodium salt glycosylation procedure is considered to be stereospecific.[10] After careful examination of the ^1H n.m.r. spectra of (**17**), (**18**), and (**19**) all of which indicated only one compound was present, we surmized that anomerization occurred after glycosylation. A possible explanation is that anomerization occurred during the conversion of (**18**) to (**19**) on large-scale runs. This interesting aspect is under further investigation in our laboratory.

In conclusion, this general synthetic procedure, *i.e.*, glycosylation of methyl 5(4)-diethoxymethylimidazole-4(5)-carboxylate (**1**) with an appropriate sugar *via* the sodium salt method and subsequent ring closure, now provides an ample supply of 1-(β-D-ribofuranosyl)imidazo[4,5-*d*]pyridazin-4(5)-one (**8**) and its 2′-deoxy counterpart (**16**). It is envisaged that these nucleosides will serve as synthons for the preparation of other 4-substituted imidazo[4,5-*d*]pyridazine nucleosides.

Experimental

M.p.s were determined with a Thomas-Hoover apparatus. U.v. absorption spectra were recorded with a Beckman DU-64 spectrophotometer. ^1H N.m.r. spectra were obtained with Varian EM-390 and Bruker AM-300 spectrometers using deuteriochloroform and $(CD_3)_2SO$ as solvents and Me_4Si as an internal standard. ^{13}C N.m.r. spectra were recorded with a Bruker AM-300 spectrometer. Normal operating conditions involved a 20° pulse flip angle. Optical rotations were determined with a Perkin-Elmer Model 141 automatic digital readout polarimeter. Silica gel (60—200 mesh) suitable for chromatographic use was purchased from Fisher Scientific Company. EM Silica Gel (grade 60, 60 Å) was employed for

flash column chromatography. Thin layer chromatography was run on precoated (0.2 mm) silica gel 60 F-254 plates manufactured by EM Laboratories, Inc., and short-wave ultraviolet light (254 nm) was used to detect the u.v. absorbing spots. All solvent proportions are quoted by volume. Evaporations were performed under diminished pressure at 40 °C with a Buchi Rotovapor unless otherwise stated.

Imidazo[4,5-d]*pyridazin*-4(5H)-*one* (**3**).—A mixture of methyl 5(4)-formylimidazole-4(5)-carboxylate (**2**)[8] (1.54 g, 1.0 mmol) and anhydrous hydrazine (1 ml; 98%) in absolute ethanol (25 ml) was heated at reflux for 24 h. The reaction mixture was allowed to cool and the excess solvent was removed *in vacuo*. The resulting solid was covered with water and carefully acidified to pH 4 with 0.1M hydrochloric acid. The white solid was collected by filtration, washed with cold water, and air-dried to give (**3**) (1.02 g, 75%). This compound was identical in all respects to an authentic sample prepared according to Martin and Castle.[9]

Methyl 1-(2,3,5-*Tri*-O-*benzoyl*-D-*ribofuranosyl*)-5-(*diethoxymethyl*)*imidazole*-4-*carboxylate* and *Methyl* 1-(2,3,5-*Tri*-O-*benzoyl*-D-*ribofuranosyl*)-4-(*diethoxymethyl*)*imidazole*-5-*carboxylate* (**4**).—*Method* 1. To a solution of methyl 5(4)-(diethoxymethyl)imidazole-4(5)-carboxylate (**1**)[8] (10.0 g, 44 mmol) in acetonitrile (200 ml) was added sodium hydride (60% in oil; 2.0 g, 50 mmol) and the mixture was stirred at room temperature under a nitrogen atmosphere for 30 min. At this point, a solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide[18] [from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (22.5 g, 45 mmol)] in acetonitrile was added dropwise over a period of 10 min. The reaction mixture was stirred at 50 °C for 4 h, filtered, and the filtrate concentrated. The resulting syrup was purified by flash chromatography using hexane–ethyl acetate (7:3) as eluant to give (**4**) (21 g, 70%) as a foam, m.p. 65—67 °C (Found: C, 64.15; H, 5.5; N, 4.05. $C_{36}H_{36}N_2O_{11}$ requires C, 64.28; H, 5.39; N, 4.16%); $\delta_H(CDCl_3)$ 0.9—1.3 (6 H, m, OCH_2Me), 3.4—3.9 (7 H, m, OMe and OCH_2Me), 4.6—4.8 (3 H, m, 4′-H and 5′-H), 5.75—6.0 (2 H, m, 2′-H and 3′-H), 6.35 [1 H, s, $CH(OEt)_2$], 6.75 (1 H, d, *J* 4.5 Hz, 1′-H), 7.15—7.50 (10 H, m, ArH), and 7.70—8.10 (6 H, m, ArH and 2-H).

Method 2. To a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (22.5 g, 45 mmol) in dry benzene (150 ml), under nitrogen, and contained in an equalizing dropping funnel was added iodotrimethylsilane[11] (9 ml, 64.3 mmol). The mixture was swirled for 10 min at room temperature and then it was added dropwise to a stirred suspension of the sodium salt of (**1**) [from (**1**) (10 g, 44 mmol) as described in Method 1] in MeCN (200 ml) under nitrogen. During the addition, the reaction temperature was maintained at room temperature and when the addition was complete it was raised to 50 °C and kept there for 2 h. The reaction mixture was then allowed to cool, the small amount of precipitated solid removed by filtration, and the filtrate concentrated under diminished pressure to a syrup. The syrup was purified in the same manner as described in Method 1 to furnish (**4**) (27.9 g, 95%) as a foam.

Methyl 1-(2,3,5-*Tri*-O-*benzoyl*-β-D-*ribofuranosyl*)-5-*formylimidazole*-4-*carboxylate* (**5**), *Methyl* 1-(2,3,5-*Tri*-O-*benzoyl*-α-D-*ribofuranosyl*)-5-*formylimidazole*-4-*carboxylate* (**6**) *and Methyl* 3-(2,3,5-*Tri*-O-*benzoyl*-D-*ribofuranosyl*)-5-*formylimidazole*-4-*carboxylate* (**7**).—A solution of (**4**) (50 g, 74.3 mmol) in 80% aqueous acetic acid (200 ml) was stirred at room temperature for 15 h. The solution was then poured into ice-water (1 l) and the precipitated solid extracted with methylene chloride (4 × 100 ml). The organic layer was washed with water (3 × 150 ml), dried (Na_2SO_4), and evaporated to dryness. The resulting residue was flash chromatographed over silica gel with hexane–ethyl acetate (7:3) as eluant to provide (**5**) (39.3 g, 85%), m.p. 144—146 °C (from methanol) (Found: C, 64.0; H, 4.7; N, 4.6. $C_{32}H_{26}N_2O_9$ requires C, 64.21; H, 4.38; N, 4.68%); $\delta_H(CDCl_3)$ 3.90 (3 H, s, CO_2Me), 4.75 (3 H, m, 4′-H and 5′-H), 5.65—5.80 (2 H, m, 2′-H and 3′-H), 6.85 (1 H, d, *J* 4.5 Hz, 1′-H), 7.1—7.50 (10 H, m, ArH), and 7.75—8.0 (7 H, m, CHO, ArH, and 2-H).

Continued elution gave (**6**) (1.75 g, 3.8%), m.p. 67—70 °C (from methanol) (Found: C, 64.4; H, 4.65; N, 4.35. $C_{32}H_{26}N_2O_9$ requires C, 64.21; H, 4.38; N, 4.68%); $\delta_H(CDCl_3)$ 3.80 (3 H, s, CO_2Me), 4.6—4.80 (3 H, m, 4′-H and 5′-H), 5.70—5.85 (2 H, m, 3′-H and 2′-H), 6.75 (1 H, d, *J* 4.5 Hz, 1′-H), 7.1—7.50 (10 H, m, ArH), and 7.70—8.10 (7 H, m, CHO, ArH, and 2-H).

The last material eluted off the column was the mixture of N(3)-α and -β anomers (**7**) (2.62 g, 5.7%), m.p. 60—65 °C (Found: C, 64.0; H, 4.5; N, 4.55. $C_{32}H_{26}N_2O_9$ requires C, 64.21; H, 4.38; N, 4.68%); $\delta_H(CDCl_3)$ 3.70 and 3.75 (6 H, 2s, α and β CO_2Me), 5.55—5.75 (6 H, m, 4′-H and 5′-H), 5.60—5.75 (4 H, m, 2′-H and 3′-H), 6.65 (1 H, d, *J* 6.5 Hz, 1′-H), 7.00—7.40 (20 H, m, ArH), and 7.65—8.00 (14 H, m, CHO, ArH, and 2-H).

1-(β-D-*Ribofuranosyl*)*imidazo*[4,5-d]*pyridazin*-4(5H)-*one* (**8**).—To a solution of (**5**) (10 g, 16 mmol) in absolute ethanol (100 ml) was added anhydrous hydrazine (2.3 ml, 70 mmol) and the mixture was heated at reflux for 24 h. The solution was allowed to cool and then concentrated *in vacuo*. The resulting residue was chromatographed over silica gel using dichloromethane–methanol (8:2) to furnish the monohydrazine salt of (**8**); {$\delta_H[(CD_3)_2SO]$ 3.70 (2 H, br s, 5′-H), 4.00—4.30 (3 H, m, 2′-H, 3′-H, and 4′-H), 5.30—5.80 (8 H, br s, 2′,3′,5′-OH, and $N_2H_5^+$), 5.90 (1 H, d, *J* 6.5 Hz, 1′-H), 8.45 (1 H, s, 2-H), and 8.86 (1 H, s, 7-H)}. An aqueous solution (*ca.* 100 ml) of the hydrazine salt was carefully adjusted to pH 5 using amberlite IR-120 (H^+) resin. The resin was removed by filtration, washed with water (2 × 20 ml), and the combined filtrate and wash evaporated to dryness *in vacuo*. Crystallization of the resulting solid from methanol afforded the title compound (**8**) as a hemi-methanolate (3.04 g, 70%), m.p. 200—202 °C (lit.,[6] 200—202 °C) (Found: C, 44.7; H, 4.9; N, 20.05. $C_{10}H_{12}N_4O_5 \cdot 0.5\ CH_3OH$ requires C, 44.36; H, 4.96; N, 19.71%); $[\alpha]_D^{25}$ −38.3° (*c* 0.965 in H_2O); $\lambda_{max.}$(pH 1) 244 (ε 7 906), 251 (7 236), and 275 nm (8 629); $\lambda_{max.}(H_2O)$ 244 (ε 7 638), 252 (6 968), and 266 nm (8 442) [lit.,[6] (pH 7) 245 (4 840), 253 (4 800), and 269 nm (4 700)]; $\lambda_{max.}$(pH 11) 245 (ε 7 504), 252 (7 021), and 277.5 nm (8 844) [lit.,[6] (pH 12) 253 (ε 4 900) and 282 nm (5 300)]; $\delta_H[(CD_3)_2SO]$ 3.70 (2 H, m, 5′-H), 4.0—4.30 (3 H, m, 2′-H, 4′-H, and 5′-H), 4.6—5.20 (3 H, br s, OH), 5.90 (1 H, d, *J* 6.0 Hz, 1′-H), 8.50 (1 H, s, 2-H), 8.64 (1 H, s, 7-H), and 13.82 (1 H, s, NH); $\delta_C[(CD_3)_2SO]$ 61.1 (C-5′), 70.1 (C-3′), 75.3 (C-2′), 86.5 (C-4′), 89.6 (C-1′), 127.4 (C-7), 131.7 (C-7a), 136.8 (C-3a), 142.4 (C-2), and 158.1 (C-4).

These proton and carbon chemical shifts are in good agreement with those reported in reference 6.

1-(α-D-*Ribofuranosyl*)*imidazo*[4,5-d]*pyridazin*-4(5H)-*one* (**9**).—In the same manner as for (**8**), the title compound was prepared by cyclization of (**6**) (1.0 g, 1.6 mmol) with anhydrous hydrazine in ethanol. Work up and crystallization afforded (**9**) (295 mg, 68%), m.p. 185—190 °C dec. (methanol) (Found: C, 44.05; H, 4.75; N, 19.45. $C_{10}H_{12}N_4O_5 \cdot 0.5\ CH_3OH$ requires C, 44.36; H, 4.96; N, 19.71%); $[\alpha]_D^{25}$ + 29.4 (*c* 0.5 in MeOH); $\lambda_{max.}$(pH 1) 242 (ε 7 906), 252 (7 102), and 274 nm (8 174); $\lambda_{max.}(H_2O)$ 245 (ε 4 874), 253 (6 502), and 272 nm (4 502); $\lambda_{max.}$(pH 11) 244 (ε 7 638), 252 (6 968), and 276.5 nm (8 442); $\delta_H[(CD_3)_2SO]$ 3.58 (2 H, m, 5′-H), 4.17—4.37 (3 H, m, 2′-H, 3′-H, and 4′-H), 5.00 (1 H, t, OH), 5.33 (1 H, d, OH), 5.65 (1 H, d, OH), 6.33 (1 H, d, *J* 6 Hz, 1′-H), 8.40 (1 H, s, 2 H), 8.45 (1 H, s, 7-H), and 12.67 (1 H, s, NH); $\delta_C[(CD_3)_2SO]$ 61.0 (C-5′), 70.4 (C-

3'), 71.6 (C-2'), 85.1 (C-1'),* 86.9 (C-4'),* 128.1 (C-7), 132.5 (C-7a), 135.8 (C-3a), 143.3 (C-2), and 158.2 (C-4).

3-(β-D-*Ribofuranosyl*)*imidazo*[4,5-d]*pyridazin*-4(5H)-*one* (**10b**) *and* 3-(α-D-*Ribofuranosyl*)*imidazo*[4,5-d]*pyridazin*-4(5H)-*one* (**10a**).—In the same manner as for (**8**), the title compounds were prepared by using anhydrous hydrazine and absolute ethanol. Thus, ring closure of (**7**) (1.0 g, 1.6 mmol) provided after work-up (**10a**) and (**10b**) (305 mg, 70%). Fractional crystallizations from methanol gave 100 mg of near pure (**10b**) (*ca.* 90—92%), m.p. 190 °C, slow decomp. (lit.,[5] >120 °C, decomp.) (Found: C, 44.5; H, 5.05; N, 19.9. $C_{10}H_{12}N_4O_5$·0.5 CH_3OH requires C, 44.36; H, 4.96; N, 19.71%); δ_H[$(CD_3)_2SO$] (**10b**) 6.30 (1 H, d, *J* 5.5 Hz, 1'-H), 8.35 (1 H, s, 2-H), and 8.70 (1 H. s, 7-H). This ^1H n.m.r. data is in good agreement with the literature[5,6] values. δ_H[$(CD_3)_2SO$] (**10a**) 6.70 (1 H, d, *J* 5.5 Hz, 1'-H), 8.32 (1 H, s, 2-H), and 8.46 (1 H, s, 7-H); $\lambda_{max.}$(pH 1) 266 nm (ε 8 254); $\lambda_{max.}$(H_2O) 260 nm (ε 5 842); $\lambda_{max.}$(pH 11) 265 nm (ε 8 844).

1-(2,3-O-*Isopropylidene*-β-D-*ribofuranosyl*)*imidazo*[4,5-d]*pyridazin*-4(5H)-*one* (**11**).—The title compound was prepared according to the procedure of Cook *et al.*,[5] and the yield was not optimized. Isopropylidenation of (**8**) (300 mg, 1.05 mmol) was carried out with dry acetone (5 ml) and 2,2-dimethoxypropane (2.5 ml). This mixture was cooled to 0 °C and 70% perchloric acid (112 mg, 0.75 mmol) was added dropwise with stirring. The stirred reaction mixture was allowed to warm to room temperature and kept at this temperature for 2 h. The reaction was then cooled (ice-bath) and a 10% sodium carbonate solution (7 ml) was slowly added. The resulting suspension was filtered, the filtrate evaporated under diminished pressure, and the residue chromatographed over silica gel using dichloromethane–methanol (9:1) as eluant to give (**11**) (150 mg, 46%), m.p. 174—176 °C; δ_H[$(CD_3)_2SO$] 1.34 (3 H, s, Me), 1.57 (3 H, s, Me), 3.50 (2 H, m, 5'-H), 4.27 (1 H, dd, 4'-H), 4.98 (1 H, dd, 2'-H or 3'-H), 5.15 (1 H, t, 5'-OH, D_2O exchangeable), 5.2 (1 H, dd, 2'-H or 3'-H), 6.28 (1 H, d, *J* 1.1 Hz, 1'-H), 8.54 and 8.56 (2 H, 2s, 2-H, and 7-H), and 12.78 (1 H, s, NH).

1-(2,3-O-*Isopropylidene*-α-D-*ribofuranosyl*)*imidazo*[4,5-d]*pyridazin*-4(5H)-*one* (**12**).—Isopropylidenation of (**9**) (100 mg, 0.35 mmol) was carried out in the same manner described for (**11**) and provided (**12**) (39 mg) in 36% yield, m.p. 127—129 °C; δ_H[$(CD_3)_2SO$] 1.13 (3 H, s, Me), 1.21 (3 H, s, Me), 3.61 (2 H, m, 5'-H), 4.48 (1 H, s, 4'-H), 4.93—4.97 (1 H, m, 2'-H or 3'-H), 5.25 (1 H, m, 2'-H or 3'-H), 6.48 (1 H, d, *J* 1.4 Hz, 1'-H), 8.34 and 8.40 (2 H, 2s, 2-H, and 7-H), and 11.4 (1 H, s, NH).

1-[3,5-O-(1,1,3,3-*Tetraisopropyldisiloxanyl*)-β-D-*ribofuranosyl*]*imidazo*[4,5-d]*pyridazin*-4(5H)-*one* (**13**).—To a solution of (**8**) (2.0 g, 7.04 mmol) in dry pyridine (20 ml) was added $TIPDSiCl_2$ (2.5 g, 8 mmol) and the mixture was stirred at room temperature for 3 h in a nitrogen atmosphere. Cold water (500 ml) was added to the solution and the mixture was extracted with dichloromethane (3 × 100 ml), dried (Na_2SO_4), and concentrated. Column chromatography of the residue on silica gel with dichloromethane–methanol (98:2) as eluant gave the title compound (3.55 g, 98.6%) as a white foam. This material could be crystallized by dissolving it in a minimal amount of dichloromethane and adding hexane (*ca.* 3:1, hexane–dichloromethane), m.p. 125—130 °C (Found: C, 51.65; H, 7.75; N, 10.8. $C_{22}H_{38}N_4O_6Si_2$ requires C, 51.74; H, 7.50; N, 10.97%); δ_H($CDCl_3$) 0.95—1.15 (28 H, m, Pr^i), 3.85—4.70 (5 H, m, 2'-, 3'-, 4'-, and 5'-H), 6.05 (1 H, s, 1'-H), 8.25 (1 H, s, 2-H), 8.40 (1 H, s, 7-H), and 11.90 (1 H, s, NH).

1-[2-O-*Phenoxythiocarbonyl*-3,5-O-(1,1,3,3-*tetraisopropyldisiloxanyl*)-β-D-*ribofuranosyl*]*imidazo*[4,5-d]*pyridazin*-4(5H)-*one* (**14**).—Compound (**13**) (1.3 g, 2.95 mmol), *N,N*-dimethylaminopyridine (0.4 g, 3.27 mmol), phenyl chlorothionoformate (0.82 g, 6 mmol) and triethylamine were dissolved in acetonitrile (30 ml). The mixture was stirred for 5 h at room temperature while under a nitrogen atmosphere. The reaction mixture was then poured into ice-water (200 ml) and extracted with dichloromethane (3 × 100 ml). The organic layer was washed with water (2 × 100 ml), dried (Na_2SO_4) and concentrated (<40 °C) *in vacuo*. The residue was placed on a silica gel column and the column eluted with dichloromethane–methanol (98:2) to provide (**14**) (1.485 g, 80%) as a foam, m.p. 95—100 °C [dichloromethane–hexane, *ca.* (3:1)] (Found: C, 53.85; H, 6.5; N, 8.5. $C_{29}H_{42}N_4O_7SSi_2$ requires C, 53.85; H, 6.55; N, 8.66%); δ_H($CDCl_3$) 1.0—1.20 (18 H, m, Pr^i), 4.10—4.30 (3 H, m, 4'-H, and 5'-H), 4.63—4.80 (1 H, dd, 3'-H), 5.85 (1 H, d, 2'-H), 6.17 (1 H, s, 1'-H), 7.00—7.50 (5 H, m, ArH), 8.35 (1 H, s, 2-H), 8.45 (1 H, s, 7-H), and 11.4 (1 H, s, NH).

1-[2-*Deoxy*-3,5-O-(1,1,3,3-*tetraisopropyldisiloxanyl*)-β-D-*ribofuranosyl*]*imidazo*[4,5-d]*pyridazin*-4(5H)-*one* (**15**).—A solution of tributyltin hydride (3 ml) and α,α'-azoisobutyronitrile (AIBN, 20 mg) in dry toluene (10 ml) was added to a stirred solution of (**14**) (800 mg, 1.24 mmol) in refluxing toluene (20 ml). The reaction mixture was held at reflux temperature for 3 h while under a nitrogen atmosphere. The mixture was then concentrated *in vacuo* and the residue was chromatographed on a silica gel column using dichloromethane–methanol (97:3) as eluant. The fractions containing pure product were pooled and evaporated to afford (**15**) (600 mg, 98%) as a foam, m.p. 85–90 °C (Found: C, 53.35; H, 7.6; N, 11.3. $C_{22}H_{38}N_4O_5Si_2$ requires C, 53.42; H, 7.74; N, 11.53%); δ_H($CDCl_3$) 1.0—1.15 (28 H, m, Pr^i), 2.65 (2 H, m, 2'-H), 3.90—4.10 (3 H, m, 4'-H, and 5'-H), 4.65 (1 H, q, 3'-H), 6.25 (1 H, dd, *J* 3 Hz and 7 Hz, 1'-H), 8.13 (1 H, s, 2-H), 8.30 (1 H, s, 7-H), and 12.1 (1 H, s, NH).

1-(2-*Deoxy*-β-D-erythro-*pentofuranosyl*)*imidazo*[4,5-d]*pyridazin*-4(5H)-*one* (**16**).—*Method* 1. To a solution of (**15**) (800 mg, 1.62 mmol) in dry THF (20 ml) was added a 1M solution of tetrabutylammonium fluoride (TBAF; 2 ml, 2 mmol) in THF. The mixture was stirred at room temperature for 20 min and then poured into cold water (100 ml). This solution was extracted with dichloromethane (3 × 50 ml) and the aqueous layer was concentrated *in vacuo* and chromatographed on a silica gel column. The column was eluted with dichloromethane–methanol (8:2) to furnish (**16**) (210 mg, 51.4%), m.p. >250 °C [ethanol–water (3:1)] (Found: C, 47.25; H, 5.1; N, 21.9. $C_{10}H_{12}N_4O_4$ requires C, 47.63; H, 4.80; N, 22.22%); $[\alpha]_D^{25}$ −23° (*c* 0.5 in H_2O); δ_H[$(CD_3)_2SO$] 2.35—2.54 (2 H, m, 2'-H and 2''-H), 3.58 (2 H, m, 5'-H, and 5''-H), 3.91 (1 H, m, 4'-H), 4.40 (1 H, m, 3'-H), 5.08 (1 H, t, 5'-OH, D_2O exchangeable), 5.40 (1 H, d, 3'-OH, D_2O exchangeable), 6.38 (1 H, t, 1'-H), 8.57 (1 H, s, 2-H), 8.64 (1 H, s, 7-H), and 12.75 (1 H, s, NH); δ_C†[$(CD_3)_2SO$] 40.8 (C-2'), 61.2 (C-5), 70.2 (C-3'), 85.7 (C-1'), 88.2 (C-4'), 127.4 (C-7), 131.7 (C-7a), 136.6 (C-3a), 142.2 (C-2), and 158.0 (C-4).

Method 2. By a procedure similar to that which provided (**8**),

* The C-1' and C-4' carbon chemical shifts were assigned according to F. Seela and W. Bussman, *Nucleosides, Nucleotides*, 1985, **4**, 391.

† The resonance line sequence (from downfield to upfield) for the carbon atoms of the 2'-deoxy-β-D-*erythro*-pentofuranosyl moiety of *N*-nucleosides has been established as: C-4', C-1', C-3', C-5', C-2' see H. Bazin, X.-X. Zhou, C. J. Welch, T. Pathak, A. Nyilas, and J. Chattopadhyaya, *Chem. Scr.*, 1986, **26**, 17. The assignments for the 2'-deoxy-α-D-*erythro*-pentofuranosyl moiety of (**20**) are tentative.

nucleoside (**19**) (1.8 g, 3.55 mmol) was treated with anhydrous hydrazine (1.5 ml) in absolute ethanol (25 ml) and the mixture was heated to reflux for 24 h. The reaction was allowed to cool to room temperature and the excess solvent was removed *in vacuo*. The residue was dissolved in water (50 ml), neutralized, and thoroughly washed with dichloromethane (5 × 100 ml). The water layer was evaporated to dryness and the residue was flash chromatographed over silica gel using dichloromethane–methanol (9:1) as eluant to furnish (**16**) (450 mg, 50.2%). This nucleoside was identical in all respects to (**16**) obtained in Method 1.

In addition to (**16**) a small amount of 1-(2-deoxy-α-D-*erythro*-pentofuranosyl)imidazo[4,5-*d*]pyridazin-4(5*H*)-one (**20**) (30 mg, 3.3%) was obtained. This nucleoside had the following physical constants, m.p. >250 °C (slow decomp.); $[\alpha]_D^{25}$ +53.8 (*c* 0.5 in H_2O); δ_H[$(CD_3)_2SO$] 2.32 (1 H, ddd, 2′-H), 2.72 (1 H, ddd, 2″-H), 3.46 (2 H, m, 5′-H and 5″-H), 4.12 (1 H, m, 4′-H), 4.32 (1 H, m, 3′-H), 4.92 (1 H, br s, OH, D_2O exchangeable), 5.42 (1 H, br d, OH, D_2O exchangeable), 6.39 (1 H, dd, *J* 2.6 Hz and 7.3 Hz, 1′-H), 8.47 (1 H, s, 2′-H), 8.55 (1 H, s, 7-H), and 12.73 (1 H, s, NH); δ_C[$(CD_3)_2SO$] 40.6 (C-2′), 61.6 (C-5′), 70.6 (C-3′), 86.4 (C-1′), 89.1 (C-4′), 127.2 (C-7), 131.8 (C-7a), 136.5 (C-3a), 142.6 (C-2), and 158.2 (C-4).

Methyl 1-(2-*Deoxy*-3,5-*di*-O-p-*toluoyl*-β-D-erythro-*pentofuranosyl*)-5-(*diethoxymethyl*)*imidazole*-4-*carboxylate* (**18**).—In the same manner as for (**4**) (Method 1), the title compound (**18**) was prepared by using (**1**) (2.0 g, 8.77 mmol), NaH (60% in oil; 0.4 g, 10 mmol), acetonitrile (50 ml) and 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranosyl chloride (**17**) (3.54 g, 8.77 mmol). The chlorodeoxy sugar (**17**) was added portionwise over a period of 1 h. When addition was complete, the reaction mixture was allowed to stir at room temperature for 2 h. The reaction mixture was then filtered, concentrated, and the residue purified by flash chromatography using dichloromethane–methanol (99:1) as eluant. This procedure provided the title compound (**18**) (3.2 g, 70%), m.p. 44—46 °C (Found: C, 64.3; H, 6.45; N, 4.8. $C_{31}H_{36}N_2O_9$ requires C, 64.12; H, 6.25; N, 4.82%); $\delta_H(CDCl_3)$ 1.15—1.35 (6 H, m, OCH_2Me), 2.39 and 2.42 (6 H, 2 s, C_6H_4Me), 2.85 (2 H, m, 2′- and 2″-H), 3.45—3.85 (4 H, m, OCH_2Me), 3.90 (3 H, s, CO_2Me), 4.50—4.80 (3 H, m, 4′-, 5′-, and 5″-H), 5.60 (1 H, m, 3′-H), 6.35 [1 H, s, $CH(OEt)_2$], 6.70 (1 H, t, 1′-H), 7.10—7.30 (4 H, m, C_6H_4Me), and 7.75—8.05 (5 H, m, C_6H_4Me and 2-H).

Methyl 1-(2-*Deoxy*-3,5-*di*-O-p-*toluoyl*-β-D-erythro-*pentofuranosyl*)-5-*formylimidazole*-4-*carboxylate* (**19**).—Similar reaction conditions as described for the preparation of (**5**), (**6**), and (**7**) were used for the synthesis of (**19**) with one exception; the reaction was allowed to stir for 24 h. From (**18**) (2.2 g, 3.8 mmol) there was obtained, after work-up and purification by flash chromatography [dichloromethane–methanol (99:1)] (**19**), (1.8 g, 94%), m.p. 146—147 °C (Found: C, 64.2; H, 5.25; N, 5.45. $C_{27}H_{26}N_2O_8$ requires C, 64.02; H, 5.17; N, 5.53%); $\delta_H(CDCl_3)$ 2.38 and 2.39 (6 H, 2s, C_6H_4Me), 3.93 (3 H, s, CO_2Me), 6.66 (1 H, t, 1′-H), 7.05—7.30 (5 H, m, C_6H_4Me and 2-H), 7.7—7.85 (4 H, m, C_6H_4Me), and 8.17 (1 H, s, CHO).

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