Synthesis of 2'-Deoxy-β-D-ribofuranosyl Imidazole and Thiazole *C*-Nucleosides[1]

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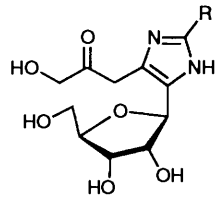
A synthetic route to 2-carbamoyl-4-(2'-deoxy-β-D-ribofuranosyl)imidazole **3**, starting from 2-deoxy-3,5-di-*O*-toluoyl-β-D-ribofuranosyl cyanide **4**, was developed. The key steps are reduction of the cyano group of compound **4** to a formyl and subsequent condensation with tosylmethyl isocyanide to yield the formamido derivative **7**, which was dehydrated to an isocyanide and ring closed with either ammonia or a primary amine to yield protected C-4 linked imidazolyl deoxyribosyl derivatives **9a–c**. Ring closure with H_2S followed by removal of the toluoyl protecting groups with ammonia gave 5-(2'-deoxy-β-D-ribofuranosyl)thiazole **11**. A cyano group can be introduced at C-2 of the imidazole nucleosides by way of the reagent *N*-cyano-4-(dimethylamino)pyridinium bromide. Subsequent hydrolysis of the cyano functional group with alkaline hydrogen peroxide yields a carboxamide substituent. All of the transformations were able to be carried out without affecting the β-configuration at the anomeric carbon. A *p*-nitrophenylethyl protecting group was introduced at N-3 of the imidazole during ring closure in order to obtain a protected derivative that could be selectively modified at the deoxyribosyl (*erythro*-pentofuranosyl) hydroxy groups.

There are only a few examples of *C*-nucleosides derived from C-4-linked imidazole. Maeba, Osaka and Ito reported the synthesis of 1-hydroxy-3-[5-(β-D-ribofuranosyl)-2-phenyl-1*H*-imidazol-4-yl]propan-2-one (**1**, R = Ph) by way of a reaction between a sugar-linked 2,6-dihydropyran-3-one and an amidine.[2] Attempts to prepare other derivatives of compounds **1** (R = OMe or Me) were unsuccessful. The protected



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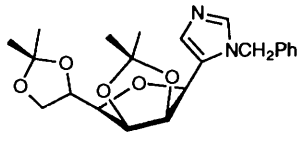

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nucleoside analogue **2** was reported as a minor product (12% yield) from the reaction of the lithio derivative of 1-benzylimidazole with 2,3:5,6-di-*O*-isopropylidene-L-gulono-1,4-lactone.[3] Neither analogue resembles naturally occurring imidazole nucleosides.

Considering the central role played by imidazole nucleotides in purine biosynthesis, there is significant potential utility for antimetabolites based on C-4 linkage rather than N-1 linkage to the sugar moiety. It is unlikely that C-4-linked imidazole analogues would participate in biochemical reactions which involve glycosidic bond cleavage (*e.g.*, nucleoside phosphorylase). Yet, because structural differences from the natural intermediates could otherwise be minimized, they may be substrates for many of the enzymes (*e.g.*, nucleoside kinases) that operate on the nucleoside at other sites. This is certainly the case with a number of N-linked and C-2 five-membered ring heterocyclic-linked nucleosides that have been found to occur naturally[4] or which have been synthetically derived and have significant activity as antitumour or antiviral agents.[5,6] It is equally likely that appropriately substituted C-4-linked imidazole nucleoside analogues will have similar biologically significant properties.

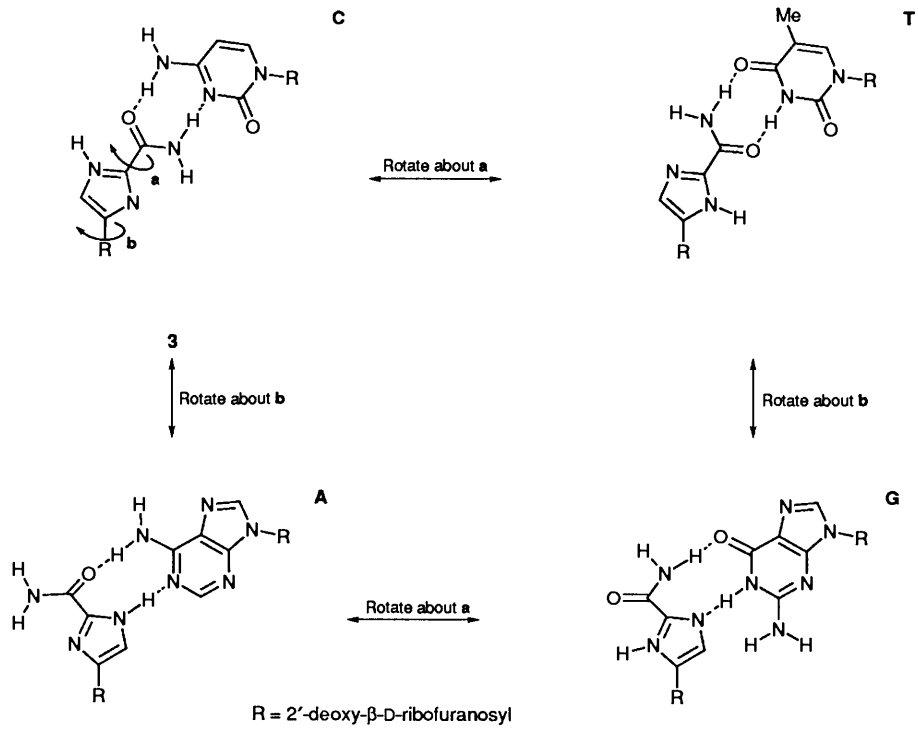
In our initial synthetic studies we decided to concentrate on deoxyribonucleosides rather than ribonucleosides because we envisaged an entirely different use for the C-4-linked imidazole nucleosides. One of the compounds reported here, 2-carbamoyl-4-(2'-deoxy-β-D-ribofuranosyl)imidazole **3**, was designed to function as a universal nucleoside. As part of a DNA molecule this nucleoside could conceivably base-pair with each of the nucleic acid bases without significantly altering local duplex structure, as illustrated in Scheme 1. Rotation about bonds **a** and **b** would appear to allow the molecule to assume approximate natural hydrogen-bonding positions without significantly perturbing the duplex backbone.

Numerous nucleoside analogues have been designed for the purpose of achieving non-discriminatory base-pairing.[7] The most extensively studied example is 2'-deoxyinosine which has been used as a putative 'universal nucleoside' in oligonucleotide probes and primers since its introduction in 1985.[8] Structural studies on deoxyinosine-modified oligonucleotides show that dI can base-pair to dC,[9] dA,[10] and T[11] and dG,[12] but the base-pairs dI–dX (X = dA, dC, dG, T) differ in stability by as much as 2 to 3 kcal mol^{-1}.†[13,14] Pairing to T or G requires substantial dislocation of the bases and consequent distortion of a double helix. On the basis of modelling studies (QUANTA, CHARMm) very little distortion would be necessary to accomodate nucleoside **3** opposite each of the four natural nucleic acid bases.

Results and Discussion

Synthetic approaches to 2'-deoxyribo-*C*-nucleosides can be classified into four main types: (1) Construction of the heterocycle on C-1 of deoxyribose; (2) construction of deoxyribose on an appropriately substituted heterocycle; (3) a hybrid approach involving construction of both subunits simultaneously; and (4) direct displacement of a leaving group from a suitably C-1-functionalized sugar derivative by a metal-derived heterocycle. Two of these approaches were investigated for the synthesis of C-4-linked imidazole nucleosides. We initially attempted to prepare C-4 imidazole sugar linkages by direct displacement of a suitably protected 1-halogeno-substituted sugar by a C-4 lithio N-1, C-2-protected imidazole.[15] When this failed we explored a second alternative in which the heterocyclic moiety

† 1 cal = 4.184 J.



Scheme 1 Potential hydrogen bonding between the 2-carbamoylimidazole moiety and **A**, **C**, **G** and **T**

was constructed on the sugar at C-1. This approach ultimately worked for the syntheses of 5-(2′-deoxy-β-D-ribofuranosyl)-imidazole and related nucleosides from 2-deoxy-3,5-di-*O*-toluoyl-β-D-ribofuranosyl cyanide **4**,[16] which is readily available from 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-D-ribofuranosyl chloride.[17] The cyanodeoxyribose **4** was converted into the aldehyde **6** in 64% yield *via* imidazolidine **5** following the procedure developed by Moffatt and co-workers for the preparation of derivatives of 2,5-anhydro-D-allose[18] (Scheme 2). In the presence of an excess of *N*,*N*′-diphenylethylenediamine the reaction of cyanide **4** with sodium hypophosphite and Raney nickel in aq. pyridine–acetic acid gave 2-(2′-deoxy-3′,5′-di-*O*-toluoyl-β-D-ribofuranosyl)-1,3-diphenylimidazolidine **5**. Compound **5** was used without purification for the preparation of aldehyde **6** by treatment with toluene-*p*-sulfonic acid (PTSA).

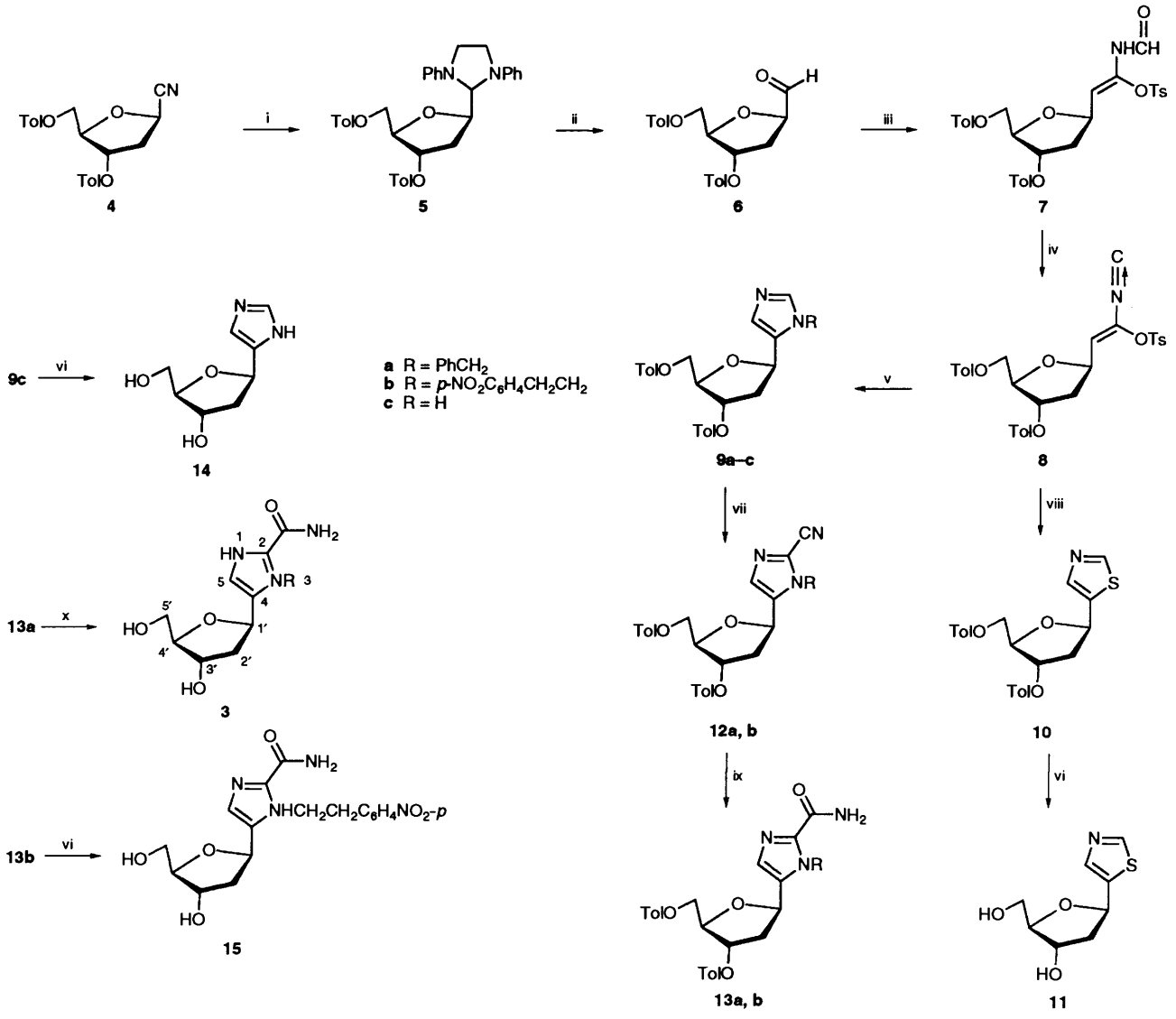
Transformation of aldehydes into C-4-substituted imidazoles by way of reaction with 1-isocyano-1-tosylalk-1-enes has been described by van Leusen and co-workers.[19] Nucleophiles react with this synthon in a two-step process culminating in the β-elimination of the tosyl group to yield aromatic heterocyclic compounds. We have found this to be a useful method for constructing both *C*-linked imidazole and thiazole nucleosides.

As illustrated in Scheme 2, aldehyde **6** reacted with the anion of tosylmethyl isocyanide to yield the formamide **7** in 62% yield, as a mixture of *Z* and *E* isomers. The dehydration of the formamide **7** with phosphoryl trichloride gave the α,β-unsaturated sulfonyl isocyanide **8**. Compound **8** is relatively unstable, but can be separated in small amounts by rapid chromatography on silica gel. The protected imidazole nucleoside **9c** was obtained in 86% yield by treatment of isocyanide **8** with ammonia in methanol, while nucleoside **9a** was obtained in 56% yield from benzylamine. For relatively-large-scale reactions, isocyanide **8** was not purified, but was allowed to react with amines immediately following its preparation from intermediate **7**. Compound **9b** was obtained in 44% yield in this way from 2-(*p*-nitrophenyl)ethylamine. The *p*-nitrophenylethyl protecting group was chosen to enable eventual conversion of the imidazole nucleoside into a phosphoramidite that could be used in oligonucleotide synthesis. Compound **8** could also be used as an intermediate for the preparation of thiazole nucleosides. 5-(2′-Deoxy-3′,5′-di-*O*-toluoyl-β-D-ribofuranosyl)thiazole **10** was obtained in 60% yield when H_2S was bubbled into a solution of compound **8** in DME.

The cyano group was introduced into the 2-position of N-protected imidazoles **9a** and **9b** by treatment with 1-cyano-4-(dimethylamino)pyridinium bromide CAP.[20] An eight-fold excess of CAP gave the best yield. CAP was produced *in situ* by combining equivalent amounts of cyanogen bromide and 4-(dimethylamino)pyridine in dimethyl formamide (DMF) at 0 °C. In addition to the desired 2-cyano derivative, bromination occurred in variable amounts at C-2 in a side-reaction. Hydrolysis of the cyano group of compound **12a** with basic hydrogen peroxide in aq. MeOH solution furnished amide **13a** in good yield. An essentially quantitative yield of nucleoside **13b** was obtained from nitrile **12b** with hydrogen peroxide in MeOH–1,4-dioxane solution.

Nucleoside **3** was obtained by removal of the benzyl and *p*-toluoyl protecting groups of amide **13a** with sodium in liquid ammonia. Compounds **14**, **15** and **11** were obtained from their toluoyl-protected precursors by treatment with ammonia in methanol at 55 °C. The *p*-nitrophenylethyl protecting group is stable under these conditions but can be removed by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

One criterion of a useful *C*-nucleoside synthesis is that a readily available stereochemically pure starting material can be transformed into the final *C*-nucleoside without anomerization at C-1′. The ^{1}H NMR spectrum indicated that the configuration at C-1′ remained unchanged from the starting material to final products. The pattern of the methylene protons (2′-H_2) of the deprotected product **3** was consistent with the assignment.[21] The signals for the two C-2′-protons were centred at δ_H 2.1 and 2.2 and spanned a total region of 0.2 ppm, which is typical of a β anomer. The 2′-H_2 protons of an α anomer would be expected to span a region of 1.0 ppm or greater. Furthermore



Scheme 2 *Reagents and conditions:* i, Raney nickel, NaH_2PO_2, *N,N'*-diphenylethylenediamine, HOAC–Py–water (1:2:1); ii, PTSA monohydrate, methylene dichloride–acetone; iii, tosylmethyl isocyanide, Bu^{t}OH, DME, −35 to −30 °C; iv, Et_3N, $POCl_3$, DME, −5 °C; v, RNH_2, MeOH; vi, conc. NH_3 in methanol, 55 °C; vii, DMAP, cyanogen bromide, DMF; viii, H_2S, DME; ix, H_2O_2, methanol–water, pH 10; x, sodium, liquid ammonia (2 mol equiv. in MeOH)

the peak widths for the anomeric proton 1'-H all fell in the range 13.0 ± 1.0 Hz, which is also characteristic of β anomers.

Nucleosides **3** and **14** were screened for activity against a broad spectrum of DNA and RNA viruses but were found to be completely devoid of activity.*

In summary, a route to C-4-linked imidazole deoxyribonucleosides, which allows subsequent placement of substituents at C-2, has been developed. Studies to explore the potential of one of these derivatives (**3**) as a universal nucleoside are in progress.

Experimental

General Information.—NMR spectra were obtained on a Varian VXR-500S spectrometer. ^1H and ^{13}C spectra were referenced to $SiMe_4$; *J*-values are given in Hz. FAB mass spectra were recorded by the Mass Spectroscopy Laboratory, Department of Medicinal Chemistry and Pharmacognosy, Purdue University. 2'-Deoxyribose was purchased from Crystal Chem. All other reagents and anhydrous solvents were purchased from Aldrich. TLC plates (Kieselgel 60F-254) and silica gel 60 PF254 containing gypsum for chromatotron purifications were products of Merck. All the reagents were used as received.

2-(2'-Deoxy-3',5'-*di*-O-*toluoyl*-β-D-*ribofuranosyl*)-1,3-*diphenylimidazolidine* **5**.—Raney nickel (24.0 g) was suspended in a mixed solvent of pyridine (160 cm^3), acetic acid (80 cm^3), and water (80 cm^3). To the stirred suspension were added sequentially *N,N'*-diphenylethylenediamine (7.36 g, 34.67 mmol), sodium hypophosphite hydrate (19.40 g), and cyanodeoxyribose **4**[16] (6.50 g, 17.13 mmol). The mixture was stirred for 1.5 h at room temperature, then was filtered, and the solid was washed thoroughly with chloroform. The filtrate was extracted three times with 100 cm^3 portions of chloroform. The combined chloroform solution was washed with water, dried

* Antiviral screening was carried out in the laboratory of Professor E. De Clercq at the Katholieke Universiteit Leuven.

over Na_2SO_4, filtered, and evaporated under reduced pressure to give a syrup. An analytical sample of compound **5** was obtained by chromatography on a silica gel column (hexane and acetone) as a foam: TLC analysis, R_f 0.41 [hexane–acetone (3:1)]; $\delta_H(CDCl_3)$ 7.79–7.88 (4 H, q), 7.26–6.68 (14 H, m), 5.65 (4 H, d, *J* 2.0, 1-H), 5.40 (1 H, br d, 3'-H), 4.76–4.70 (1 H, m, 1'-H), 4.39–4.33 (2 H, m, 5'-H_2), 4.31–4.26 (1 H, m, 4'-H), 3.78–3.54 (4 H, m, PhCH_2), 2.41 (3 H, s, Me), 2.39 (3 H, s, Me), 2.54–2.27 (1 H, m, 2'-H^a) and 2.18–2.12 (1 H, m, 2'-H^b); FAB *m/z* 577.0 (MH^+).

2,5-*Anhydro*-3-*deoxy*-4,6-*di*-O-*toluoyl*-D-*ribohexose* **6**.—The imidazolidine **5** was dissolved in methylene dichloride (300 cm^3). PTSA monohydrate (6.5 g, 34.0 mmol) was added in acetone (30 cm^3) to the stirred solution in a flask placed in an ice–water-bath. The mixture was allowed to warm to room temperature over a period of 30 min. Further small portions of PTSA monohydrate were added as necessary until the starting material completely disappeared by TLC analysis. The mixture was filtered and the precipitate was washed with methylene dichloride. The combined filtrate was evaporated under reduced pressure without heating. The residue was re-dissolved in methylene dichloride, and the solution was washed with water, dried over Na_2SO_4, filtered, and evaporated. Compound **6** was separated on a silica gel column (yield 4.11 g, 62%, based on 2-deoxy-3,5-di-*O*-toluoyl-β-D-ribofuranosyl cyanide) as a foam: R_f 0.33 [hexane–acetone (3:1)]; $\delta_H(CDCl_3)$ 9.86 [< 1 H, br s, C*H*$(OH)_2$], 9.72 (< 1 H, d, *J* 2.0, CHO), 7.98–7.86 (4 H, m), 7.29–7.20 (4 H, m), 5.58–5.46 (1 H, m, 3'-H), 4.73–4.37 (3 H, m, 4'-H and 5'-H_2), 3.51–3.44 (1 H, m, 1'-H) and 2.56–2.20 (8 H, m, 2'-H_2 and Me); FAB *m/z* 383 (MH^+).

N-[2-(2'-*Deoxy*-3',5'-*di*-O-*toluoyl*-β-D-*ribofuranosyl*)-1-*tosylvinyl*]*formamide* **7**.—A solution of tosylmethyl isocyanide (2.12 g, 10.81 mmol) in 1,2-dimethoxyethane (DME) (14 cm^3) was added to a stirred suspension of potassium *tert*-butoxide (1.61 g, 14.35 mmol) in DME (10 cm^3) at −35 °C under nitrogen. A solution of aldehyde **6** (4.11 g, 10.75 mmol) in DME (19 cm^3) was added dropwise to the mixture at the same temperature. After 30 min the mixture was poured into ice–water acidified by acetic acid (200 cm^3; pH 3). The products were extracted with methylene dichloride, and the extract was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue was separated by chromatography on a silica gel column and compound **7** was obtained as a foam (4.0 g, 64%): R_f 0.24 [hexane–acetone (3:1)]; $\delta_H(CDCl_3)$ 8.095 (s, NH), 7.98–7.87 (6 H, m), 7.72 (0.5 H, s, CHO), 7.70 (0.5 H, s, CHO), 7.35–7.18 (6 H, m), 6.94 (0.5 H, d, *J* 2.5, HC=), 6.77 (0.5 H, d, *J* 8.0, HC=), 5.57–5.49 (1 H, m, 3-H), 4.89–4.83 (1 H, m, 1'-H), 4.58–4.51 (2 H, m, 5'-H_2), 4.46–4.40 (1 H, m, 4'-H) and 2.54–2.20 (11 H, m, 2'-H_2 and Me); FAB *m/z* 578 (MH^+).

2-(2'-*Deoxy*-3',5'-*di*-O-*toluoyl*-β-D-*ribofuranosyl*)-1-*isocyano*-1-*tosylethylene* **8**.—To a stirred solution of the formamide **7** (300 mg, 0.52 mmol) in DME (7.0 cm^3) was added triethylamine (0.42 cm^3, 3.0 mmol), followed by phosphoryl trichloride (0.06 cm^3, 0.64 mmol) at −5 °C under nitrogen. The mixture was stirred at the same temperature for 1 h, then was quenched by ice–water (50 cm^3). The products were extracted with methylene dichloride, and the extracts were washed with cold water, dried over Na_2SO_4, and evaporated to dryness. The residue was separated by chromatography on silica gel and compound **8** was obtained as a foam (120 mg, 42%): R_f 0.53 [hexane–acetone (3:1)]; $\delta_H([^2H_6]$acetone) 7.95–7.99 (4 H, q, Tol 2- and 6-H), 7.87 (2 H, d, *J* 8.5, Tos 2- and 6-H), 7.55 (2 H, d, *J* 8.5, Tos 3- and 5-H), 7.36–7.33 (4 H, t, Tol 3- and 5-H), 5.67 (1 H, br d, 3'-H), 5.23–5.19 (1 H, m, 1'-H), 4.60–4.54 (3 H, m, 4'-H and 5'-H), 2.69–2.65 (1 H, m, 2'-H), 2.50 (3 H, s, TosMe), 2.48–2.45 (1 H, m, 2'-H), 2.43 (3 H, s, TolMe) and 2.41 (3 H, s, TolMe).

5-(2'-*Deoxy*-3',5'-*di*-O-*toluoyl*-β-D-*ribofuranosyl*)-1H-*imidazole* **9c**.—A 2.0 mol dm^{-3} solution of ammonia in methanol (0.16 cm^3) was added to a solution of isocyanide **8** (88 mg, 0.16 mmol) in methyl alcohol (6.0 cm^3) at room temperature. The solution was diluted with water (50 cm^3) after being stirred for 5 h and the mixture was extracted three times with ethyl acetate. The combined organic phase was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue was separated on silica gel with a mixed eluent hexane–acetone (2:1) and *compound* **9c** was obtained as a solid (57 mg, 86%): ν_{max}(KBr)/cm^{-1} 3271, 3128, 1713, 1605, 1267, 1103 and 749; $\delta_H([^2H_6]$acetone) 7.98 (4 H, d, *J* 8.0), 7.64 (1 H, d, *J* 1.0, 2-H), 7.32 (4 H, m), 7.13 (1 H, d, *J* 1.0, 5-H), 5.65 (1 H, dt, *J* 6.0, 3'-H), 5.31 (1 H, dd, *J* 10.5 and 5.5, 1'-H), 4.53 (2 H, m, 5'-H_2), 4.44 (1 H, dt, *J* 6.0 and 2.0, 4'-H), 2.70 (1 H, m, 2'-H), 2.45 (1 H, m, 2'-H), 2.41 (3 H, s, Me) and 2.39 (3 H, s, Me); $\delta_C([^2H_6]$acetone) 166.48 and 166.30 (C=O), 144.66, 144.40, 130.33, 130.28, 129.91 and 129.48 (arom C), 136.01 (C-2), 128.22 and 128.20 (C-4 and -5), 83.08 (C-5'), 78.03 and 75.87 (C-1' and -4'), 65.59 (C-3'), 38.96 (C-2'), 21.56 and 21.54 (Me); high-resolution FAB–MS (Found: MH^+, 421.1768. $C_{24}H_{25}N_2O_5$ requires MH, 421.1763).

1-*Benzyl*-5-(2'-*deoxy*-3',5'-*di*-O-*toluoyl*-β-D-*ribofuranosyl*-1H-*imidazole* **9a**.—Benzylamine (69 mg, 0.64 mmol) was added to a solution of isocyanide **8** (181 mg, 0.32 mmol) in methanol (18 cm^3). The solvent was removed after 30 min. *Compound* **9a** was obtained by chromatography on silica gel, with mixed eluent acetone–hexane (1:4→1:2), as a solid (93 mg, 56%): $\delta_H(CD_3OD)$ 7.87 (4 H, t, *J* 8.0, Tol-H), 7.68 (1 H, s, 2-H), 7.31–7.25 (7 H, m), 7.17 (2 H, dd, *J* 2.5 and 7.3), 6.98 (1 H, s, 4-H), 5.50 (1 H, dt, *J* 1.5 and 6.5, 3'-H), 5.34 (1 H, d, J_{AB} 15.5, PhCH_2), 5.28 (1 H, d, J_{AB} 15.5, PhCH_2), 5.08 (1 H, dd, *J* 5.0 and 10.5, 1'-H), 4.54 (1 H, dd, *J* 4.0 and 11.75, 5'-H^a), 4.44–4.54 (1 H, dd, *J* 4.0 and 11.75, 5'-H^b), 4.40–4.37 (1 H, m, 4'-H), 2.55–2.45 (1 H, m, 2'-H^a), 2.41 (3 H, s, Me), 2.39 (3 H, s, Me) and 2.35–2.30 (1 H, m, 2'-H^b); FAB–MS, *m/z* 511.0 (MH^+) (Found: C, 72.6; H, 6.0; N, 5.4. $C_{31}H_{30}N_2O_5$ requires C, 72.93; H, 5.92; N, 5.49%).

1-*Benzyl*-5-(2'-*deoxy*-3',5'-*di*-O-*toluoyl*-β-D-*ribosuranosyl*)-1H-*imidazole*-2-*carbonitrile* **12a**.—To a solution of cyanogen bromide (1.23 g, 11.6 mmol) in DMF (30 cm^3) at 0 °C was added 4-(dimethylamino)pyridine (DMAP) (1.42 g, 11.6 mmol). A yellow precipitate appeared in a few minutes and the mixture was allowed to warm to room temperature, and then was recooled to 0 °C after 20 min. A solution of compound **9a** (495 mg, 0.97 mmol) in DMF (15 cm^3) was added, and the mixture was warmed to room temperature, and then was heated at 45 °C for 10 h. The precipitate disappeared within 2 h. After cooling, the solution was poured into 0.2 mol dm^{-3} aq. $NaHCO_3$ and extracted three times with ethyl acetate. The combined organic phase was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue was separated by chromatography on silica gel with a mixed eluent of hexane–ethyl acetate (3:1). Compound **12a** was obtained as a solid (412 mg, 79%): FAB–MS, *m/z* 536.0 (MH^+); $\delta_H([^2H_6]$acetone) 7.93–7.88 (4 H, q, Tol-H), 7.37–7.22 (10 H, m), 5.64 (1 H, br d, 3'-H), 5.58 (2 H, s, PhCH_2), 5.31 (1 H, dd, *J* 5.5 and 10.8, 1'-H), 4.58–4.49 (3 H, m, 4'-H and 5'-H_2), 2.64–2.58 (1 H, m, 2'-H^a) 2.53–2.49 (1 H, m, 2'-H^b), 2.41 (3 H, s, Me) and 2.40 (3 H, s, Me).

1-*Benzyl*-5-(2'-*deoxy*-3',5'-*di*-O-*toluoyl*-β-D-*ribofuranosyl*)-1H-*imidazole*-2-*carboxamide* **13a**.—The solution of nitrile **12a** (833 mg, 1.56 mmol) in methanol (63 cm^3)–water (25 cm^3) was adjusted to pH 10 with aq. ammonium hydroxide, and hydrogen peroxide (0.48 cm^3) was added. A precipitate

appeared within 1 h. The mixture was stirred at room temperature for 6 h, concentrated, and filtered, to yield compound **13a** (734 mg), which was used directly in the following reaction without further purification. An analytical sample was obtained by chromatography on silica gel [hexane–ethyl acetate (4:1→1:2)]: $\delta_H[(CD_3)_2SO]$ 7.89–7.83 (4 H, q, Tol-H), 7.50 (2 H, s, NH_2), 7.39–7.03 (10 H, m, Tol-H, Ph, and 4-H), 6.08 (1 H, d, 3'-H), 5.65–5.51 (2 H, q, PhCH_2), 5.11 (1 H, q, 1'-H), 4.55–4.35 (3 H, m, 4'-H and 5'-H_2), 2.50–2.15 (8 H, m, 2 × Me and 2'-H_2); high-resolution FAB–MS [Found: (MH^+), 554.2288. $C_{32}H_{31}N_3O_6$ requires MH, 554.2291].

5-(2'-*Deoxy*-β-D-*ribofuranosyl*)-1H-*imidazole*-2-*carboxamide* **3**.—Compound **13a** (734 mg) was suspended in liquid ammonia (150 cm^3) at −40 °C. Small pieces of sodium metal were gradually added until the solution remained blue for *ca.* 5 min. A small amount of ammonium chloride was added and the blue colour immediately disappeared. The liquid ammonia was allowed to evaporate off at room temperature. The residue was dissolved in methanol (50 cm^3), and the solution was filtered, and evaporated to dryness. The products were separated by chromatography on silica gel with acetone and then methanol as eluent (1:0, 1:1, 0:1). *Compound* **3** was further purified on a column of Bio-gel P-2, and dried by lyophilization, to give a solid (96 mg, 32%): ν_{max}(KBr)/cm^{-1} 1673; $\delta_H(CD_3OD)$ 7.20 (1 H, s, 5-H), 5.16 (1 H, dd, *J* 5.5 and 10.0, 1'-H), 4.37–4.34 (1 H, m, 4'-H), 3.92–3.88 (1 H, m, 3'-H), 3.68 (1 H, dd, *J* 4.3 and 11.8, 5'-H), 3.63 (1 H, dd, *J* 4.8 and 11.8, 5'-H), 2.23 (1 H, ddd, *J* 5.8, 10 and 13.3, 2'-H) and 2.15 (1 H, ddd, *J* 2.0, 5.5 and 13.3, 2'-H); $\delta_C(CD_3OD)$ 162.08 (C=O), 141.90 (C-2), 130.28 (C-4), 129.25 (C-5), 89.06 (C-5'), 75.10 (C-1'), 74.14 (C-4'), 63.86 (C-3') and 42.62 (C-2'); high-resolution FAB–MS [Found: (MH^+), 228.0985. $C_9H_{13}N_3O_4$ requires (MH), 228.0984].

5-(2'-*Deoxy*-β-D-*ribofuranosyl*)-1H-*imidazole* **14**.—Compound **9c** (100 mg) was dissolved in conc. methanolic ammonia (30 cm^3). The solution was heated at 55 °C overnight, and evaporated to dryness. The residue was dissolved in water and the mixture was filtered. The water was removed by lyophilization and compound **14** was isolated by chromatography on a preparative TLC plate with acetone–methanol (5:1) as developer. Further purification was accomplished on a Bio-Gel P-2 column with water as eluent. A solid was obtained after the eluate was lyophilized (28 mg, 64%): $\delta_H(CD_3OD)$ 7.65 (1 H, d, *J* 1.0, 5-H), 7.06 (1 H, d, *J* 1.0, 2-H), 5.15 (1 H, dd, *J* 5.5 and 10.5, 1'-H), 4.35 (1 H, m, 3'-H), 3.89 (1 H, m, 4'-H), 3.67 (1 H, dd, *J* 4.5 and 12, 5'-H^a), 3.61 (1 H, dd, *J* 4.5 and 12, 5'-H^b), 2.22 (1 H, ddd, *J* 6.0, 10.5 and 13, 2'-H^a) and 2.09 (1 H, ddd, *J* 1.5, 5.5 and 13, 2'-H^b); $\delta_C(CD_3OD)$ 139.27 (C-2), 136.69 (C-4), 117.65 (C-5), 89.08 (C-5'), 75.09 (C-1'), 74.16 (C-4'), 63.98 (C-3') and 42.64 (C-2'); high-resolution FAB–MS [Found: (MH^+), 185.0903. $C_8H_{12}N_2O_3$ requires (MH), 185.0926].

5-(2'-*Deoxy*-3',5'-*di*-O-*toluoyl*-β-D-*ribofuranosyl*)-1-[2-(4-*nitrophenyl*)*ethyl*]-1H-*imidazole* **9b**.—To a stirred solution of the formamide **7** (1.0 g, 1.73 mmol) in DME (20 cm^3) was added triethylamine (1.4 cm^3, 10.0 mmol), followed by phosphoryl trichloride (0.2 cm^3, 2.15 mmol) at −5 °C under nitrogen. The mixture was stirred at the same temperature for 1 h. A solution of 2-(4-nitrophenyl)ethylamine hydrochloride (0.70 g, 3.45 mmol) and sodium methoxide (187 mg, 3.46 mmol) in methanol (30 cm^3) was added. After 30 min the solvent was removed and the residue was purified by chromatography on silica gel with hexane–acetone as eluent (4:1→2:1). Compound **9b** was obtained as a solid (433 mg, 44%): δ_H([$^2H_6$]acetone) 8.04 (2 H, d, *J* 8.5), 7.97 (2 H, d, *J* 8.0), 7.88 (2 H, d, *J* 8.0), 7.41 (2 H, d, *J* 8.5, ArH), 7.38 (1 H, s, 4-H), 7.35 (2 H, d, *J* 8.0, Tol-H), 7.25 (2 H, d, *J* 8.0, Tol-H), 6.96 (1 H, s, 2-H), 5.64–5.62 (1 H, m, 3'-H), 5.32 (1 H, dd, *J* 5.0 and 11.0, 1'-H), 4.63–4.50 (3 H, m, 4'-H and 5'-H_2), 4.42 (2 H, t, *J* 7.5, CH_2N), 3.33–3.30 (2 H, m, $ArCH_2$), 2.75–2.69 (1 H, m, 2'-H^a), 2.55–2.51 (1 H, m, 2'-H^b), 2.41 (3 H, s, Me) and 2.36 (3 H, s, Me); high-resolution FAB–MS [Found: (MH^+), 570.2217. $C_{32}H_{31}N_3O_7$ requires (MH), 570.2240].

5-(2'-*Deoxy*-3',5'-*di*-O-*toluoyl*-β-D-*ribofuranosyl*)-1-[2-(4-*nitrophenyl*)*ethyl*]-1H-*imidazole*-2-*carbonitrile* **12b**.—To a solution of cyanogen bromide (0.4468 g, 4.22 mmol) in DMF (10 cm^3) at 0 °C was added DMAP (0.5153 g, 4.22 mmol). A yellow precipitate appeared in a few minutes and the mixture was allowed to warm to room temperature, and was then recooled to 0 °C after 20 min. A solution of compound **9b** (200 mg, 0.35 mmol) in DMF (5 cm^3) was added and the mixture was warmed to room temperature and then was heated at 45 °C for 10 h. The precipitate disappeared within 2 h. After cooling, the solution was poured into 0.2 mol dm^{-3} aq. $NaHCO_3$ and extracted three times with ethyl acetate. The combined organic phase was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue was separated by chromatography on silica gel with a mixed eluent of hexane–ethyl acetate (4:1, 3:1). Compound **12b** was obtained as a solid (90 mg, 43%): δ_H([$^2H_6$]acetone) 8.10 (2 H, d, *J* 9.0, ArH), 7.97 (2 H, d, *J* 8.0, Tol-H), 7.87 (2 H, d, *J* 8.0, Tol-H), 7.41 (2 H, d, *J* 9.0, ArH), 7.36 (2 H, d, *J* 8.0, Tol-H), 7.26 (2 H, d, *J* 8.0, Tol-H), 7.22 (1 H, s, 4-H), 5.67 (1 H, dt, *J* 1.5 and 6.5, 3'-H), 5.39 (1 H, dd, *J* 5.5 and 10.75, 1'-H), 4.68–4.52 (5 H, m, 4'-H, 5'-H_2 and NCH_2), 3.45–3.36 (2 H, m, PhCH_2), 2.80–2.74 (1 H, m, 2'-H^a), 2.66–2.62 (1 H, m, 2'-H^b), 2.42 (3 H, s, Me) and 2.37 (3 H, s, Me); FAB–MS 595.3 (MH^+).

5-(2'-*Deoxy*-3',5'-*di*-O-*toluoyl*-β-D-*ribofuranosyl*)-1-[2-(4-*nitrophenyl*)*ethyl*]-1H-*imidazole*-2-*carboxamide* **13b**.—To a solution of nitrile **12b** (140 mg, 0.24 mmol) in methanol (20 cm^3) containing 1,4-dioxane (2 cm^3), adjusted to pH 9.0 with aq. ammonium hydroxide, was added 30% hydrogen peroxide (0.22 cm^3). TLC indicated that the reaction was complete quantitatively within 30 min. The product was used directly in the next reaction. An analytical sample was obtained by chromatography on silica gel [hexane–ethyl acetate (2:1, 1:1)]: δ_H([$^2H_6$]acetone) 8.07 (2 H, d, *J* 9.0), 7.97 (2 H, d, *J* 8.0, Tol-H), 7.86 (2 H, d, *J* 8.0, Tol-H), 7.49 (2 H, d, *J* 9), 7.36 (2 H, d, *J* 8.0, Tol-H), 7.24 (2 H, d, *J* 8.0, Tol-H), 7.09 (1 H, s, 4-H), 5.65–5.62 (1 H, m, 3'-H), 5.30 (1 H, dd, *J* 5.0 and 10.5, 1'-H), 4.94–4.84 (1 H, m, NCH_2), 4.68–4.59 (1 H, m, PhCH_2), 4.55–4.50 (1 H, m, NCH_2), 3.67–3.57 (1 H, m, 4'-H), 3.31–3.25 (2 H, m, 5'-H_2), 2.76 (1 H, ddd, *J* 6.5, 10.5 and 13.5, 2'-H^a), 2.56 (1 H, ddd, *J* 1.5, 5.0 and 13.5, 2'-H^b), 2.42 (3 H, s, Me) and 2.36 (3 H, s, Me); FAB–MS, 613.3 (MH^+).

5-(2'-*Deoxy*-β-D-*ribofuranosyl*)-1-[2-(4-*nitrophenyl*)*ethyl*]-1H-*imidazole*-2-*carboxamide* **15**.—Compound **13b** was poured into a solution of conc. ammonia in methanol, and the mixture was heated overnight at 55 °C in a pressure vessel. The ammonia and methanol were removed by evaporation under reduced pressure and the residue was separated by chromatography on silica gel [hexane–acetone (2:1, 1:1, 1:2)]. Compound **15** was obtained as a solid (70 mg, 79%), m.p. 78–81 °C; $\delta_H[(CD_3)_2SO]$ 8.16 (2 H, d, *J* 9.0, ArH), 7.76 (1 H, s, NH_2), 7.47 (2 H, d, *J* 9.0, ArH), 7.43 (1 H, s, NH_2), 7.00 (1 H, s, 4-H), 5.12 (1 H, d, 3'-H), 4.96 (1 H, dd, *J* 5.0 and 10.0, 1'-H), 4.74 (1 H, t, 4'-H), 4.70–4.64 (1 H, m, 5'-H), 4.60–4.55 (1 H, m, 5'-H), 4.21–4.09 (1 H, m, PhCH_2), 3.805–3.77 (1 H, m, PhCH_2), 3.22–3.12 (1 H, m, NCH_2), 2.23 (1 H, ddd, *J* 6.0, 10.0 and 12.5, 2'-H^a) and 1.98 (1 H, ddd, *J* 1.5, 5.0 and 12.5, 2'-H^b); high-resolution FAB–MS [Found: (MH^+), 377.1460. $C_{17}H_{21}N_4O_6$ requires (MH), 377.1461]; $\delta_C[(CD_3)_2SO]$ 160.68 (C=O), 146.55

(CNO_2), 146.20 (C-2), 139.23 (ArC), 135.68 (C-4), 130.04 (C-5), 125.37 (ArC), 123.48 (ArC), 88.01 (C-5'), 71.68 (C-1'), 69.68 (C-4'), 62.21 (C-3'), 55.81 (CH_2N), 45.88 (C-2') and 36.77 ($PhCH_2$).

5-(2'-Deoxy-3',5'-di-O-toluoyl-β-D-ribofuranosyl)thiazole **10**.—To a stirred solution of the formamide **7** (200 mg, 0.35 mmol) in DME (5 cm^3) was added triethylamine (0.28 cm^3, 2.0 mmol), followed by phosphoryl trichloride (0.038 cm^3, 0.40 mmol) at −5 °C under nitrogen. The mixture was stirred at the same temperature for 1 h, and then hydrogen sulfide was bubbled into the solution for 2 min. The mixture was poured into saturated aq. $NaHCO_3$ and extracted three times with ethyl acetate. The organic phase was washed with water, dried over sodium sulfate, and evaporated to dryness. The residue was purified by chromatography on silica gel with hexane–ethyl acetate (3:1) as eluent. Compound **10** was obtained as a solid (91 mg, 60%): FAB–MS (MH^+), 438.0; δ_H([$^2H_6$]acetone) 8.93 (1 H, s, 2-H), 7.983 (2 H, d, *J* 6.5, Tol-H), 7.96 (2 H, d, *J* 10.5, Tol-H), 7.91 (1 H, s, 4-H), 7.35 (2 H, d, *J* 6.5, Tol-H), 7.32 (2 H, d, *J* 10.5, Tol-H), 5.69–5.67 (1 H, m, 3'-H), 5.65 (1 H, dd, *J* 5.0 and 10.5, 1'-H), 4.63–4.52 (3 H, m, 4'-H and 5'-H_2), 2.71 (1 H, ddd, *J* 1.0, 5.0 and 13.8, 2'-H^a), 2.41 (3 H, s, Me), 2.40 (3 H, s, Me) and 2.44–2.38 (1 H, m, 2'-H^b).

5-(2'-Deoxy-β-D-ribofuranosyl)thiazole **11**.—Compound **10** (90 mg) was heated at 55 °C overnight in a solution of conc. ammonia in methanol in a pressure vessel. The ammonia and methanol were removed by evaporation under reduced pressure and the residue was separated by chromatography on silica gel eluting with hexane and acetone (gradient). Compound **11** was obtained as a solid (30 mg, 72.5%): δ_H([$^2H_4$]methanol) 8.94 (1 H, s, 2-H), 7.83 (1 H, s, 4-H), 5.44 (1 H, dd, *J* 5.5 and 10.0, 1'-H), 4.34 (1 H, dt, *J* 2.0 and 5.5, 4'-H), 3.94–3.91 (1 H, m, 3'-H), 3.65–3.57 (2 H, m, 5'-H_2), 2.29 (1 H, ddd, *J* 1.5, 5.5 and 13, 2'-H^a) and 2.09 (1 H, ddd, *J* 6.0, 10.0 and 13.0, 2'-H^b); δ_C(CD_3OD) 155.28 (C-5), 140.68 (C-2), 89.44 (C-5'), 75.00 (C-1'), 74.26 (C-4'), 63.89 (C-3') and 45.17 (C-2'); high-resolution FAB–MS MH^+ [Found: (MH^+), 202.0538. $C_8H_{11}NO_3S$ requires (MH), 202.0538].

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