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Synthesis and Biological Evaluation of Novel 2′-Deoxy-4′-thio-imidazole Nucleosides

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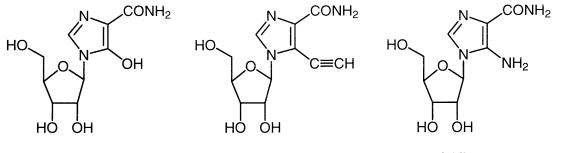
Abstract—A study on the use of 3′-directing groups for the synthesis of imidazole 2′-deoxy-4′-thionucleosides led to varying α:β ratios in the glycosylation reaction. The *para*-nitrobenzoyl group gave the optimum result in the glycosylation step; therefore, this protected thiosugar **10b** was used for the synthesis of a series of novel 2′-deoxy-4′-thio-imidazole nucleosides which have been evaluated for antiviral activity in vitro.

Introduction

The interest in thionucleosides as chemotherapeutic agents has increased considerably over the last five years owing to their demonstrated resistance towards degradative phosphorylase enzymes,[1] which results in increased stability. Synthesis of 2′-deoxy-4′-thionucleosides has concentrated almost entirely on pyrimidine analogues with anomeric ratios as high as 1:4.2 (α:β) reported[2] in the glycosylation step, the β-anomer being the required anomer for biological evaluation.

Our research involves the preparation of novel 2′-deoxy-4′-thionucleosides with a five-ring heterocycle as the base moiety. Our interest in imidazole based thionucleosides stems from the broad range of biological activity exhibited by imidazole based 4′-oxo-nucleosides, e.g. bredinin[3] and EICAR.[4] These compounds mimic the structure of 5-amino-1-β-D-ribofuranosyl-4-carboxamide[5] (AICAR) which is a key intermediate in purine biosynthesis. The biological activity exhibited by these AICAR mimics renders 4′-thio-imidazole nucleosides highly desirable synthetic targets.



This report describes the synthesis of imidazole 2′-deoxy-4′-thionucleosides, which is, to our knowledge, the first example of the preparation of this class of compound. During the course of the research, we have studied several coupling procedures to determine the optimum glycosylation method.

Chemistry

A well established method described for the synthesis of 2′-deoxy-4′-oxo-nucleosides, which circumvents the problem of anomeric ratios, is the use of a halo sugar in the coupling reaction, the sugar most frequently used being 2-deoxy-3,5-di-*O*-*para*-toluoyl-ribofuranosyl chloride.[6] The corresponding thiosugar **2** has been reported in the literature,[7] however, no experimental data was given and the word unstable was used to describe the compound. Preparation of **2** from the acetyl thiosugar **1a** (R = *p*Tol) by reaction with acetic acid and gaseous hydrochloric acid, resulted in the formation of the product in only 12% yield owing to poor crystallinity of the chlorosugar. However, preparation of the 2-deoxy-3,5-di-*O*-*para*-nitrobenzoyl-4-thio-chlorosugar **3** from the corresponding acetyl thiosugar **1b** (R = *p*NBz) gave only the required crystalline α-anomer (Scheme 1) in 78% yield.[8]

Reaction of the α-chloro-thiosugar **3** with the sodium salt of 4,5-dicyano-imidazole was expected to result in a SN2 displacement and produce solely the β-nucleoside, however the reaction gave the α-nucleoside **4**, with retention of configuration suggesting a dissociative mechanism with predominant α-face attack, in only

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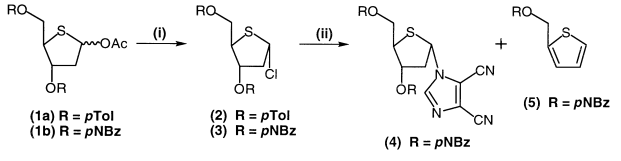
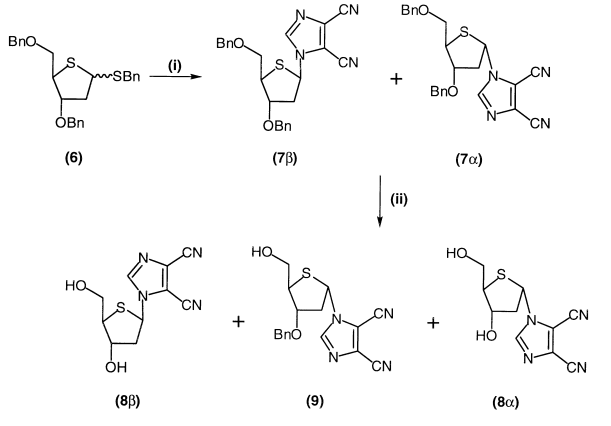
32% yield. The major product, isolated in 65% yield, was the thiophene **5**[9] which presumably resulted from α,β-elimination of the chloride **3** (Scheme 1). Further studies showed the chlorosugar **3** to be very unstable with elimination occurring readily at room temperature in a range of solvents. Possibly the greater aromaticity of thiophene compared with furan, combined with the leaving group capacity of the *para*-nitrobenzoyl group, results in the tendency of 4-thio-halosugars to eliminate.

Owing to the problems associated with the use of a chlorosugar intermediate, the Vorbruggen method was employed. The 4,5-dicyano-imidazole thionucleoside **7** was prepared in a moderate yield by direct coupling of 3,5-di-*O*-benzyl-2-deoxy-1,4-dithio-D-erythropentofuranoside **6**[10] with 4,5-dicyano-imidazole in the presence of *N*-iodosuccinimide.[11] Compound **7** was obtained as an anomeric mixture (**7**α:**7**β, 3.75:1), separation at this stage was not possible with only small quantities of each anomer obtained pure by column chromatography for characterization. Removal of the benzyl groups by treatment with boron trichloride gave a mixture of products, deprotection of the β-anomer occurred more rapidly than deprotection of the α-anomer, with compounds **8**β and **9** as the major products. Further reaction with boron trichloride produced **8**α (Scheme 2). X-ray crystallographic analysis of **8**β and **9** allowed absolute confirmation of anomeric configuration (Fig. 1).

The anomeric assignment can be determined by ^{1}H NMR alone since the anomers show characteristic signals, especially for H-2′. The H-2′ of the α-anomer is one multiplet whereas the H-2′ signal of the β-anomer



Scheme 1. Reagents and conditions: (i) AcOH, HCl, 30 min. (ii) 4,5-dicyanoimidazole, NaH, THF, 16 h: *p*Tol = *para*-toluoyl, *p*NBz = *para*-nitrobenzoyl.



Scheme 2. Reagents and conditions: (i) 4,5-dicyanoimidazole, *N,O*-bis(trimethylsily)acetamide, CH_3CN,4Å sieves, NIS, rt, 5 h; (ii) BCl_3, heptane, CH_2Cl_2, −80 °C, 2 h.

generally shows a distinct signal for H-2′a (ddd or dt) and H-2′b (ddd or dt) with a separation of approximately 0.2 ppm.

Further modification of the 4,5-dicyano-imidazole thionucleoside **8**β was problematic owing to the instability of the deprotected compound. The instability of **8**β coupled with the difficulties in removing the benzyl group, resulted in a study to determine the most suitable protecting group for the synthesis of imidazole 2′-deoxy-4′-thionucleosides.

It has been demonstrated in the literature,[2,12] that stereocontrolled glycosylation is possible in the synthesis of 2′-deoxy-4′-oxo-pyrimidine nucleosides by the use of a suitable 3′-directing group. A study was therefore undertaken to determine whether this approach could be applied to the synthesis of 2′-deoxy-4′-thio-imidazole nucleosides, and to determine whether the proposed mechanism[12] of participation also occurs in the thionucleosides (Scheme 3).

If the intramolecular cation intermediate forms after treatment with either a Lewis acid (LA) or *N*-iodosuccinimide (NIS), stabilization of this cation, through the employment of suitable **X** groups should lead to an increase in the percentage of β-anomer formed on reaction with the nucleobase (B). Following this proposed mechanism, it would be expected that if **X** is an electron-releasing group, e.g. *para*-methoxybenzoyl, or $CONR^1R^2$, the electron-donating capacity of these groups should result in stabilization of the intermediate cation. Substitution at the 5′-position (R group, Scheme 3) may also affect the anomeric ratio of the resulting nucleoside by interaction of the anomeric carbon from the top face, this would be expected to contribute, though to a lesser extent than the 3′-substituent, to the overall mechanism of participation. A series of thiosugars with differing protecting groups at the 3- and 5-positions **6**, **10a–g** were prepared (Table 1); coupling of these thiobenzyl-thiosugars with the 4,5-dicyano-imidazole was performed using NIS to give the nucleosides as anomeric mixtures.[13]

From Table 1, it can be seen that the worst ratio (3.75:1) was obtained with the benzyl protecting group (**7**). Coupling with the di-*para*-methoxybenzoyl or di-*para*-nitrobenzoyl thiosugars resulted in almost identical anomeric ratios, 2.3:1 (**11**) and 2.2:1 (**4**), respectively, indicating no benefit from using either an electron releasing or electron withdrawing group in the *para* position of the benzene ring. Improved anomeric ratios were obtained with the 3′-*O*-carbamates ($CONR_2$), with the percentage of β increasing with increasing size of R (Et→^{i}Pr→Ph, **13**/**14**→**15**→**16**). However, the yield decreased simultaneously with increasing steric bulk. The anomeric ratios were determined by ^{1}H NMR, with assignment based on characteristic signals corresponding to the H-1′ protons. As a general rule the H-1′β signal (t or ψt) occurs further downfield than H-1′α (d or dd) (with the exception of **14**/**15**). Further information on the anomeric ratio was obtained from the H-2 signal of the imidazole ring (Table 2).

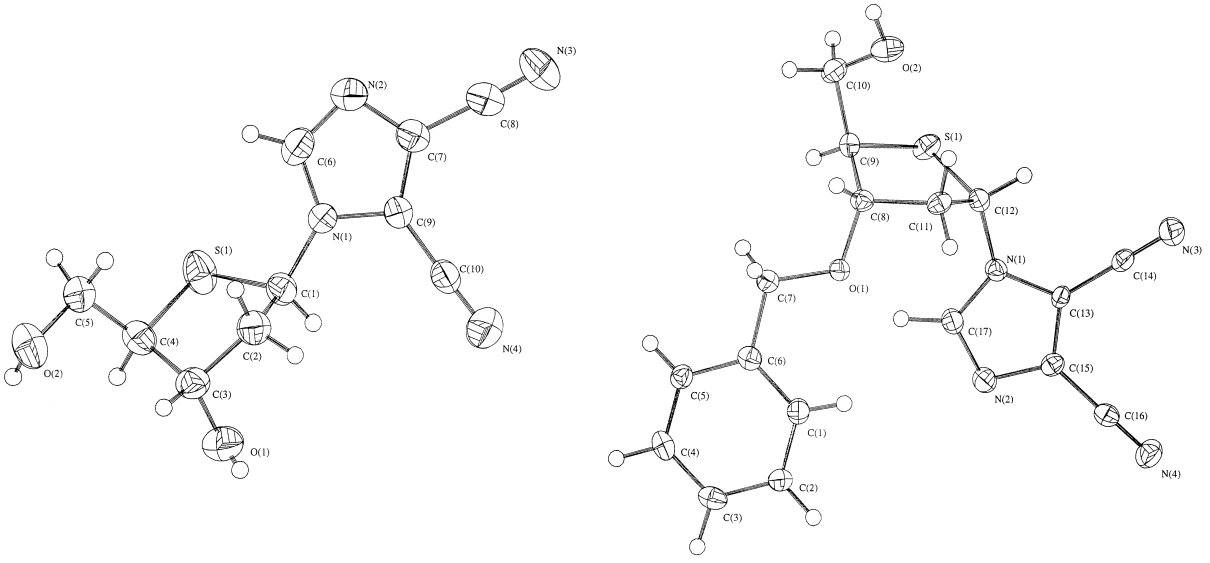
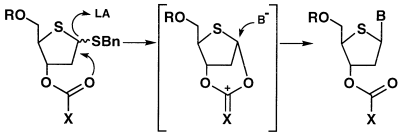


Figure 1. X-ray structure of 8β and 9.

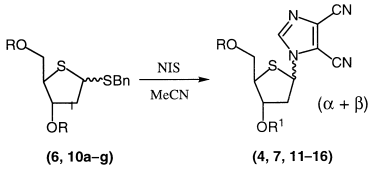


Scheme 3.

The results obtained from these studies suggest that in the case of 2′-deoxy-4′-thio-imidazole nucleosides, the directing effect of a 3′-substituent is predominantly a steric effect rather than an electronic one.

The best protecting group in terms of ease of synthesis, optimum anomeric ratios and ease of removal was the *para*-nitrobenzoyl (*p*NB) protecting group. To circumvent the problem of instability of the 4,5-dicyanoimidazole and to allow for the preparation of a series of novel compounds, 4,5-bis[(methyloxy)carbonyl]imidazole **18** was prepared from 4,5-imidazoledicarboxylic acid by reaction with concentrated sulfuric acid and methanol.

Table 1. Anomeric ratios obtained on coupling with 4,5-dicyanoimidazole



(6, 10a–g) **(4, 7, 11–16)**

Sugar	Compound	R	R^1	Yield (%)[a]	α:β
6	**7**	Bn	Bn	63	3.75:1
10a	**11**	*p*MBz	*p*MBz	44	2.3:1
10b	**4**	*p*NBz	*p*NBz	71	2.2:1
10c	**12**	*p*NBz	CONHPh	71	2.2:1
10d	**13**	*p*NBz	$CONEt_2$	54	2:1
10e	**14**	*p*MBz	$CONEt_2$	94	1.6:1
10f	**15**	*p*MBz	CON^iPr_2	64	1:1.5
10g	**16**	*p*MBz	$CONPh_2$	19[b]	1:15

[a]Unoptimized yields.
[b]Mainly starting material recovered.

Coupling of **18** with 3,5-di-*O*-*para*-nitrobenzoyl-2-deoxy-1,4-dithio-D-erythro-pentofuranoside **10b** [2] in the presence of *N*-iodosuccinimide gave the imidazole thionucleoside **19** as an anomeric mixture (**19**α:**19**β, 3:1) in 60% yield. Separation of the anomers was achieved by column chromatography with confirmation of the anomeric configuration of **19**β obtained by X-ray analysis (Fig. 2). Removal of the *p*NB group of **19**β by treatment with sodium methoxide gave the deprotected β-anomer **20** in 78% yield (Scheme 4).

Treatment of **20** with a large excess of ammonia, methylamine, ethylamine, propylamine, cyclopropylamine, and butylamine in methanol produced a library of novel imidazole 2′-deoxy-4′-thionucleosides **21a–f**, respectively, all of which were obtained in high yields (Table 3). The choice of amines was restricted to ammonia and primary amines, reactions with secondary amines, e.g. dimethylamine, were unsuccessful presumably owing to steric limitations.

Table 2. Chemical shifts and coupling constants

Compound	H-1′ (ppm)	$J_{1',2'}$	H-2
7α	5.93, dd	1.63, 6.12	8.41
7β	6.01, t	6.59	8.27
11α	6.13, dd	1.16, 6.27	8.40
11β	6.16, t	6.80	8.26
4α	6.24, dd	1.65, 6.51	8.42
4β	6.31, ψt	6.83, 7.53	8.23
12α	6.10, d	6.71	[a]
12β	6.16, ψt	6.91, 7.19	[a]
13α	6.04, dd	1.29, 6.93	[a]
13β	6.15, ψt	6.51, 7.62	[a]
14α	6.00, dd	1.67, 6.53	8.27
14β	5.96, t	6.60	8.21
15α	6.03, m	—	8.28
15β	6.03, m	—	8.26
16β	5.67, ψt	6.84, 7.20	8.14

[a]Signals obscured by aromatic peaks.

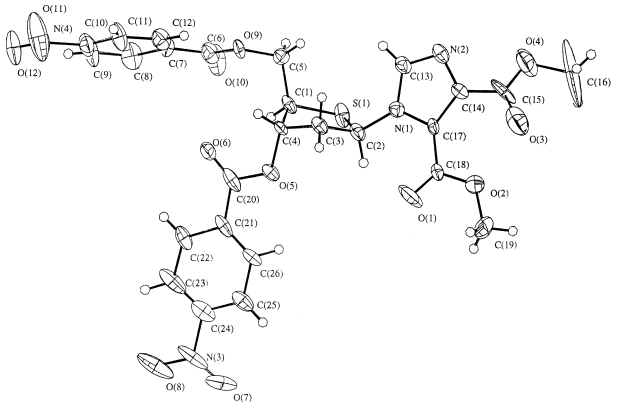
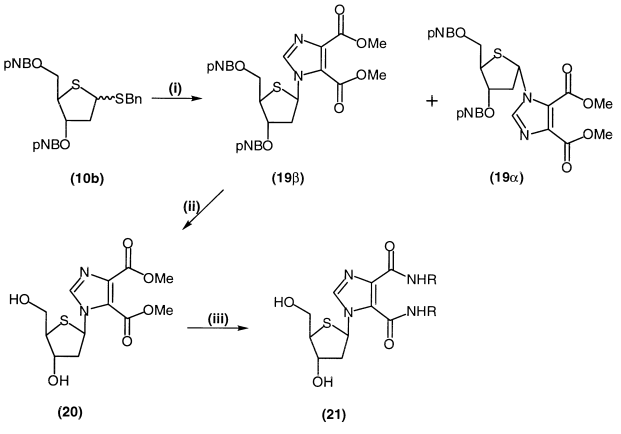


Figure 2. X-ray structure of **19**β.

Table 3. Reagents and yields for step (iii) Scheme 4

Compound	Reagent	R	Yield (%)
21a	Ammonia	H	74
21b	Methylamine	CH_3	85
21c	Ethylamine	CH_2CH_3	65
21d	Propylamine	$CH_2CH_2CH_3$	87
21e	Cyclopropylamine	Cyclopropyl	60
21f	Butylamine	$CH_2CH_2CH_2CH_3$	92



Scheme 4. Reagents and conditions: (i) 4,5-bis(methyloxy)carbonyl]-imidazole, *N,O*-bis(trimethylsilyl) acetamide, CH_3CN, 4 Å sieves, NIS, rt, 16 h; (ii) NaOMe, MeOH, rt, 16 h; (iii) Reagent (Table 3), MeOH, rt, 3–16 h.

Biological Results

The antiviral activity of compounds **8**β, **20**, and **21a–f** were evaluated against HSV-1 and HSV-2, HCMV, VZV, and HIV-1. All of the compounds were inactive at 100 μM with the exception of **21f**, which had poor activity against HCMV ($IC_{50} = 67$ μM). None of the compounds displayed toxicity up to a concentration of 100 μM.

Conclusion

Synthetically NIS coupling is favored for the preparation of the imidazole nucleosides, however, this still results in rather poor anomeric ratios. The recently published work of Tanaka et al.,[14] which employs a 4-thio-furanoid glycol in the glycosylation step, could be applied to the synthesis of 4′-thio-imidazole nucleosides and may result in a higher percentage of the β-anomer being obtained. The biological data illustrates the limitations in modification of the AICAR/Ribavirin based structures, and the lack of activity displayed by the imidazole nucleosides would suggest that phosphorylation to the triphosphates is not occurring.

The poor biological data may also be owing to the presence of the 3′-hydroxy group; we are currently investigating the synthesis of the 2′,3′-dideoxy (DD) and 2′,3′-didehydro (D_4) analogues for further biological evaluation.

Experimental

^1H and ^{13}C NMR spectra were recorded with a Brucker Avance DPX300 spectrometer operating at 300 and 75 MHz, respectively, with Me_4Si as an internal standard. Mass spectra and accurate mass FAB were determined by the EPSRC mass spectrometry centre, Swansea, UK. Microanalyses were determined at the Department of Chemistry, Cardiff University. Flash column chromatography was performed with silica gel 60 (230–400 mesh) (Merck) and TLC were carried out on precoated silica plates (Kiesel gel 60 F_{254}, BDH). Melting points were determined on an electrothermal instrument and are uncorrected.

1-(2-Deoxy-3,5-di-*O*-benzyl-4-thio-)-α/β-D-ribofuranosyl) -4,5-dicyano imidazole (7α, 7β). To a suspension of 4,5-dicyanoimidazole (4.0 g, 33.87 mmol) in dry acetonitrile (50 mL) was added *N,O*-bis(trimethylsilyl)acetamide (8.4 mL, 33.87 mmol) and the reaction stirred at rt under nitrogen for 1.5 h. Crushed activated 4 Å sieves (3.0 g) were then added followed by a solution of 3,5-di-*O*-benzyl-2-deoxy-1,4-dithio-D-erythropentofuranoside **6** (12.32 g, 28.22 mmol) in dry acetonitrile (50 mL). After stirring for 10 min, a solution of *N*-iodosuccinimide (6.99 g, 31.05 mmol) in acetonitrile (25 mL) was added and the resulting dark brown mixture stirred under nitrogen at rt for 5 h. The reaction was concentrated under reduced pressure and the resulting residue dissolved in dichloromethane (300 mL), washed with aqueous sodium thiosulphate (150 mL), dried ($MgSO_4$) and concentrated to give the crude product. Purification by flash column chromatography (petroleum ether:ethyl acetate, 3:1 v/v) gave the required product as a light-brown syrup: Yield 7.67 g (63%); α:β ratio, 3.75:1.

7α: ^1H NMR ($CDCl_3$) δ 8.40 (s, 1, H-2), 7.39 (m, 8, Ph), 7.21 (m, 2, Ph), 5.94 (dd, *J* 1.7, 6.2 Hz, 1, H-1′), 4.59 (m, 3, H-3′ and CH_2Ph), 4.44 (m, 2, CH_2Ph), 4.16 (m, 1, H-4′), 3.58 (dd, *J* 5.2, 10.0 Hz, 1, H-5′), 3.42 (dd, *J* 8.5, 10.0 Hz, 1, H-5′), 2.60 (m, 2, H-2′); ^{13}C NMR ($CDCl_3$) δ 142.94 (CH, C-2), 137.80 (C, Ph), 137.01 (C, Ph), 129.10, 129.01, 128.70, 128.49, 128.33, and 128.15 (6×CH, Ph), 123.56 (C, C4/C5), 112.12 and 111.71 (2×CN), 108.51 (C, C4/C5), 83.77 (CH, C-1′), 73.85

(CH_2, C-5′), 71.98 and 71.79 (2×CH_2, *C*H_2Ph), 65.89 (CH, C-3′), 55.61 (CH, C-4′) 43.21 (CH_2, C-2′).

7β: ^{1}H NMR ($CDCl_3$) δ 8.30 (s, 1, H-2), 7.41 (m, 10, 2×Ph), 6.02 (t, *J* 6.6 Hz, 1, H-1′), 4.77 (d, *J* 3.3 Hz, 1, H-3′), 4.63 (m, 4, 2×C*H*$_2$Ph), 4.38 (dd, *J* 4.2, 8.1 Hz, 1, H-4′), 3.81 (m, 2, H-5′), 2.75 (dt, *J* 6.1, 11.1 Hz, 1, H-2′), 2.50 (ddd, *J* 4.3, 6.9 Hz, 1, H-2′); ^{13}C NMR ($CDCl_3$) δ 142.82 (CH, C-2), 138.81 (C, Ph), 138.76 (C, Ph), 130.36, 130.27, 130.16, 129.94, 129.66, 129.55, 129.35, and 128.69 (8×CH, Ph), 125.52 (C, C4/C5), 113.12 and 113.09 (2×CN), 109.49 (C, C4/C5), 83.27 (CH, C-1′), 75.25 and 73.66 (2×CH_2, *C*H_2Ph), 71.90 (CH_2, C-5′), 65.52 (CH, C-3′), 55.56 (CH, C-4′) 44.57 (CH_2, C-2′).

7α/β Anal. $C_{24}H_{22}N_4O_2S$ requires C, 66.96; H, 5.15; N, 13.01. Found: C, 67.02; H, 4.99; N, 13.09%.

1-(2-Deoxy-4-thio-α/β-D-ribofuranosyl)-4,5-dicyanoimidazole (8α, 8β) and 1(2-deoxy-3-*O*-benzyl-4-thio-α-D-ribofuranosyl)-4,5-dicyano imidazole (9). To a stirred 1 M solution of BCl_3 in heptane (29.6 mL, 29.6 mmol) and dry dichloromethane (100 mL) at −80 °C was added a solution of **7**α/β (5.1 g, 11.85 mmol) in dry dichloromethane (100 mL) dropwise over a period of 15 min while maintaining the temperature at −80 °C. The reaction was then stirred at −80 °C under nitrogen for 2 h, after this time the reaction was quenched by the slow addition of a 1:1 v/v solution of methanol and concentrated ammonium hydroxide (60 mL) while maintaining the temperature at −80 °C. The reaction was then allowed to warm to rt and the aqueous and organic layers separated. The aqueous layer was washed with chloroform (3×50 mL), then the organic layer and chloroform washes combined, dried ($MgSO_4$) and concentrated under reduced pressure. Initial purification by flash column chromatography (petroleum ether:ethyl acetate, 3:1 v/v) enabled recovery of unreacted starting material (2.21 g), then changing the eluent to chloroform:methanol 9:1 v/v gave first the monodeprotected α-anomer **9** (1.06 g, 46% based on recovered starting material) as an off-white solid, followed by the deprotected β-anomer **8**β (0.31 g, 18% based on recovered starting material) as a white crystalline solid. Treatment of **9** with BCl_3 again as described resulted in a small amount of fully deprotected α-anomer **8**α as a pale-yellow syrup. Mp: **8**β, 110–112 °C; **9**, 108–109 °C.

8α: ^{1}H NMR (CD_3OD) δ 8.53 (s, 1, H-2), 6.12 (dd, *J* 2.2, 7.1 Hz, 1, H-1′), 4.57 (ddd, *J* 2.7, 4.2, 5.1 Hz, 1, H-3′), 3.81 (m, 1, H-4′), 3.60 (dd, *J* 1.8, 6.6 Hz, 2, H-5′), 2.72 (ddd, *J* 4.2, 7.1, 11.4 Hz, 1, H-2′), 2.50 (dt, *J* 2.6, 5.1 Hz, 1, H-2′); ^{31}C NMR (CD_3OD) δ 143.17 (CH, C-2), 126.27 (C, C4/C5), 112.05 and 111.82 (2×CN), 108.18 (C, C4/C5), 75.73 (CH, C-1′), 65.28 (CH, C-3′) 64.16 (CH_2, C-5′), 60.82 (CH, C-4′) 44.02 (CH_2, C-2′); anal. $C_{10}H_{10}N_4O_2S$ requires C, 47.99; H, 4.03; N, 22.39. Found: C, 47.86; H, 4.04; N, 22.44%.

8β: ^{1}H NMR (CD_3OD) δ 8.56 (s, 1, H-2), 6.13 (t, *J* 6.2 Hz, 1, H-1′), 4.53 (dd, *J* 4.7, 9.8 Hz, 1, H-3′), 3.81 (m, 1, H-4′), 3.46 (m, 2, H-5′), 2.64 (m, 2, H-2′); ^{13}C NMR (CD_3OD) δ 142.20 (CH, C-2), 123.23 (C, C4/C5), 112.13 and 111.67 (2×CN), 108.07 (C, C4/C5), 73.99 (CH, C-1′), 63.52 (CH, C-3′) 62.78 (CH_2, C-5′), 59.03 (CH, C-4′) 43.97 (CH_2, C-2′); Anal. $C_{10}H_{10}N_4O_2S$ requires C, 47.99; H, 4.03; N, 22.39. Found: C, 48.07; H, 3.99; N, 22.48%.

9: ^{1}H NMR ($CDCl_3$) δ 8.47 (s, 1, H-2), 7.43 (m, 3, Ph), 7.28 (m, 2, *ortho*-Ph), 6.03 (ψt, J 0.7, 5.9 Hz, 1, H-1′), 4.67 (d, *J* 11.8 Hz, 1, C*H*$_2$Ph), 4.50 (m, 2, H-4′ and C*H*$_2$Ph), 4.15 (ψt, *J* 5.8, 6.1 Hz, 1, H-3′), 3.80 (dd, *J* 4.9, 11.4 Hz, 1, H-5′), 3.67 (dd, *J* 6.9, 11.4 Hz, 1, H-5′), 2.76 (ddd, *J* 4.3, 6.9, 11.0 Hz, 1, H-2′) overlapping (br s, 1, OH), 2.66 (d, *J* 14.8 Hz, 1, H-2′); ^{13}C NMR ($CDCl_3$) δ 141.38 (CH, C-2), 135.43 (C, Ph), 127.52, 127.11, 126.62 and 126.32 (4(CH, Ph), 121.77 (C, C4/C5), 110.55 and 110.24 (2(CN), 106.88 (C, C4/C5), 82.56 (CH, C-1′), 70.49 (CH_2, *C*H_2Ph) 65.01 (CH, C-3′), 64.45 (CH_2, C-5′), 59.37 (CH, C-4′) 44.68 (CH_2, C-2′); anal. $C_{17}H_{16}N_4O_2S$ requires C, 59.98; H, 4.74; N, 16.46. Found: C, 60.25; H, 4.62; N, 16.36%.

1-(2-Deoxy-3,5-di-*O*-*para*-nitrobenzoyl-4-thio-α/β-D-ribofuranosyl)-4,5-bis(methyloxycarbonyl)imidazole (19α, 19β). To a suspension of 4,5-bis(methyloxycarbonyl)imidazole **18** (0.2 g, 1.08 mmol) in dry acetonitrile (10 mL) was added *N,O*-bis(trimethylsilyl)acetamide (0.26 mL, 1.08 mmol) and the reaction stirred at rt under nitrogen for 1.5 h. Crushed activated 4 Å sieves (2.0 g) were then added followed by a solution of 3,5-di-*O*-*para*-nitrobenzoyl-2-deoxy-1,4-dithio-D-erythropentofuranoside **10b** (0.5 g, 0.91 mmol) in dry acetonitrile (10 mL). After stirring for 10 min, a solution of *N*-iodosuccinimide (0.24 g, 1.08 mmol) in acetonitrile (5 mL) was added and the resulting dark-brown mixture stirred under nitrogen at rt for 16 h. The reaction was concentrated under reduced pressure and the resulting residue dissolved in dichloromethane (50 mL), washed with aqueous sodium thiosulphate (25 mL), dried ($MgSO_4$) and concentrated to give the crude product. Purification by flash column chromatography (petroleum ether:ethyl acetate, 3:1 v/v) eluted the β-anomer **19**β first followed by the α-anomer **19**α. The required products were obtained as yellow solids: mp **19**α 64–66 °C, **19**β 86–88 °C; Total yield 0.33 g (60%); α:β ratio 3:1.

19α: ^{1}H NMR ($CDCl_3$) δ 8.30 (m, 8, H-2 and Ar), 7.81 (d, *J* 8.7 Hz, 2, Ar), 6.55 (d, *J* 5.7 Hz, 1, H-1′), 5.84 (d, *J* 4.2 Hz, 1, H-3′), 4.57 (dd, *J* 5.8, 11.5 Hz, 1, H-5′), 4.47 (dd, *J* 8.6, 11.4 Hz, 1, H-5′), 4.33 (m, 1, H-4′), 3.96 (s, 3, CH_3), 3.94 (s, 3, CH_3), 2.97 (dt, *J* 5.2, 11.2 Hz, 1, H-2′), 2.82 (m, 1, H-2′); ^{13}C NMR ($CDCl_3$) δ 164.72 and 164.18 (2×C=O), 160.94 (C, C4/C5), 151.28 (C, C4/C5), 139.99, 139.75, 135.07 and 134.16 (4×C, Ar), 131.40, 131.28, 124.25, 124.18, and 123.98 (CH, Ar and C-2), 79.60 (CH, C-1′), 65.88 (CH_2, C-5′), 65.25 (CH, C-3′), 54.63 (CH, C-4′), 53.27 and 53.09 (2×CH3), 44.21 (CH_2, C-2′); anal. $C_{26}H_{22}N_4O_{12}S$ requires C, 50.82; H, 3.61; N, 9.12. Found: C, 50.81; H, 3.68; N, 9.18%.

19β: ^{1}H NMR ($CDCl_3$) δ 8.31 (m, 9, H-2 and Ar), 6.65 (t, *J* 6.2 Hz, 1, H-1′), 5.88 (d, *J* 3.8 Hz, 1, H-3′), 4.70 (d, *J* 6.6 Hz, 2, H-5′), 4.17 (m, 1, H-4′), 4.00 (s, 6, 2×CH_3), 3.09 (m, 1, H-2′), 2.85 (m, 1, H-2′); Anal. $C_{26}H_{22}N_4O_{12}S$

requires C, 50.82; H, 3.61; N, 9.12. Found: C, 50.97; H, 3.69; N, 9.36%.

1-(2-Deoxy-4-thio-β-D-ribofuranosyl)-4,5-bis(methyloxycarbonyl) imidazole (20). To a solution of **19**β (1.45 g, 2.36 mmol) in dry methanol (30 mL) was added sodium methoxide (0.13 g, 2.36 mmol) and the reaction stirred at rt under nitrogen for 16 h. The reaction was then concentrated under reduced pressure and the crude residue purified by flash column chromatography (petroleum ether:ethyl acetate, 3:1 v/v) to give the product **20** as an off-white waxy solid in a yield of 0.58 g (78%): ^{1}H NMR (CD_3OD) δ 8.53 (s, 1, H-2), 6.27 (t, *J* 5.9 Hz, 1, H-1′), 4.50 (dd, *J* 4.9, 11.0 Hz, 1, H-3′), 3.95 (s, 3, CH_3), 3.89 (s, 3, CH_3), 3.82 (d, *J* 5.2 Hz, 2, H-5′), 3.48 (dd, *J* 5.2, 10.3 Hz, 1, H-4′), 2.57 (m, 2, H-2′); ^{13}C NMR (CD_3OD) δ 161.22 and 159.03 (2×C=O), 137.41 (CH, C-2), 134.04 (C, C4/C5), 124.52 (C, C4/C5), 72.19 (CH, C-1′), 61.04 (CH_2, C-5′), 60.08 (CH, C-3′), 56.68 (CH, C-4′), 50.59 and 49.94 (2×CH_3), 43.04 (CH_2, C-2′); MS (FAB), *m*/*z* 317 $(M+H)^+$, 339 $(M+Na)^+$, 633 $(2M+H)^+$, 655 $(2M+Na)^+$; anal. $C_{12}H_{16}N_2O_6S$ requires C, 45.56; H, 5.10; N, 9.12. Found: C, 45.47; H, 4.91; N, 9.06%.

1-(2-Deoxy-4-thio-β-D-ribofuranosyl)-4,5-bis(carbamoyl)-imidazole (21a). Compound **20** (42 mg, 0.13 mmol) was treated with saturated methanolic ammonia (10 mL) at rt for 16 h. The reaction was then concentrated under reduced pressure and purified by flash column chromatography (petroleum ether:ethyl acetate, 4:1 v/v increasing to ethyl acetate:methanol, 95:5 v/v) to give 28 mg (74%) of **21a** as a white solid: mp 120 °C dec; ^{1}H NMR (CD_3OD) δ 8.59 (s, 1, H-2), 6.95 (dd, *J* 4.7, 6.2 Hz, 1, H-1′), 4.43 (ddd, *J* 5.3, 7.4, 10.6 Hz, 1, H-3′), 3.83 (m, 2, H-5′), 3.44 (dd, *J* 5.3, 10.8 Hz, 1, H-4′), 2.61 (ddd, *J* 6.7, 7.4, 13.8 Hz, 1, H-2′), 2.45 (ddd, *J* 4.7, 9.3, 13.5 Hz, 1, H-2′); ^{13}C NMR (CD_3OD) δ 166.69 and 162.33 (2×C=O), 139.00 (CH, C-2), 136.45 (C, C4/C5), 127.00 (C, C4/C5), 73.58 (CH, C-1′), 62.71 (CH_2, C-5′), 61.71 (CH, C-3′), 57.90 (CH, C-4′), 45.43 (CH_2, C-2′); anal. $C_{10}H_{14}N_4O_4S$ requires C, 41.95; H, 4.93; N, 19.57. Found: C, 41.81; H, 5.05; N, 19.37%.

1-(2-Deoxy-4-thio-β-D-ribofuranosyl)-4,5-bis(*N*-methylcarbamoyl) imidazole (21b). Compound **20** (44 mg, 0.13 mmol) was treated with methylamine (33% wt in industrial methylated spirit, 4 mL) at rt for 16 h. The reaction was then concentrated under reduced pressure and purified by flash column chromatography (petroleum ether:ethyl acetate, 4:1 v/v increasing to ethyl acetate:methanol, 95:5 v/v) to give 37 mg (85%) of **21b** as a white solid: mp 139–140 °C; ^{1}H NMR (CD_3OD) δ 8.53 (s, 1, H-2), 6.91 (dd, *J* 4.7, 6.3 Hz, 1, H-1′), 4.43 (ddd, *J* 5.2, 7.5, 10.5 Hz, 1, H-3′), 3.83 (dd, *J* 2.7, 5.2 Hz, 2, H-5′), 3.44 (dd, *J* 5.3, 10.8 Hz, 1, H-4′), 2.92 (s, 3, CH_3), 2.91 (s, 3, CH_3), 2.60 (ddd, *J* 6.7, 7.3, 13.7 Hz, 1, H-2′), 2.45 (ddd, *J* 4.7, 9.4, 13.5 Hz, 1, H-2′); ^{13}C NMR (CD_3OD) δ 163.12 and 159.35 (2×C=O), 137.04 (CH, C-2), 134.46 (C, C4/C5), 125.39 (C, C4/C5), 72.02 (CH, C-1′), 61.16 (CH_2, C-5′), 60.04 (CH, C-3′), 56.33 (CH, C-4′), 43.79 (CH_2, C-2′), 23.68 and 23.41 (2×CH_3); anal. $C_{12}H_{18}N_4O_4S$ requires C, 45.85; H, 5.77; N, 17.82. Found: C, 45.74; H, 5.91; N, 17.74%.

1-(2-Deoxy-4-thio-β-D-ribofuranosyl)-4,5-bis(*N*-ethylcarbamoyl) imidazole (21c). Compound **20** (64 mg, 0.20 mmol) was treated with ethylamine (2 M solution in methanol, 20 mL) at rt for 16 h. The reaction was then concentrated under reduced pressure and purified by flash column chromatography (petroleum ether:ethyl acetate, 4:1 v/v increasing to ethyl acetate:methanol, 95:5 v/v) to give 45 mg (65%) of **21c** as a white solid: mp 134–135 °C; ^{1}H NMR (CD_3OD) δ 8.53 (s, 1, H-2), 6.91 (dd, *J* 4.8, 6.2 Hz, 1, H-1′), 4.43 (ddd, *J* 5.2, 7.5, 10.5 Hz, 1, H-3′), 3.83 (dd, *J* 2.8, 5.2 Hz, 2, H-5′), 3.41 (m, 5, 2×C*H*$_2$CH3 and H-4′), 2.60 (dt, *J* 6.7, 7.2, 13.7 Hz, 1, H-2′), 2.45 (ddd, *J* 4.7, 9.4, 13.5 Hz, 1, H-2′), 1.24 (dd, *J* 7.3, 14.6 Hz, 6, 2×CH_2C*H*$_3$); ^{13}C NMR (CD_3OD) δ 163.96 and 160.09 (2×C=O), 138.59 (CH, C-2), 136.05 (C, C4/C5), 127.24 (C, C4/C5), 73.61 (CH, C-1′), 62.77 (CH_2, C-5′), 61.67 (CH, C-3′), 57.92 (CH, C-4′), 45.39 (CH_2, C-2′), 34.25 (CH_2, 2×C*H*$_2$ CH_3), 13.86 and 13.54 (2×CH_3); anal. $C_{14}H_{22}N_4O_4S$ requires C, 49.11; H, 6.48; N, 16.36. Found: C, 48.96; H, 6.36; N 16.53%.

1-(2-Deoxy-4-thio-β-D-ribofuranosyl)-4,5-bis(*N*-propylcarbamoyl) imidazole (21d). Compound **20** (64 mg, 0.20 mmol) was treated with a solution of propylamine (10 mL) in dry methanol (10 mL) at rt for 16 h. The reaction was then concentrated under reduced pressure and purified by flash column chromatography (petroleum ether:ethyl acetate, 4:1 v/v increasing to ethyl acetate:methanol, 95:5 v/v) to give 44 mg (87%) of **21d** as a white solid: ^{1}H NMR ($CDCl_3$) δ 11.49 (t, *J* 5.1 Hz, 1, NH), 8.51 (s, 1, H-2), 7.85 (t, *J* 5.8 Hz, 1, NH), 7.05 (dd, *J* 4.1, 6.0 Hz, 1, H-1′), 4.43 (ddd, *J* 5.6, 7.8, 10.3 Hz, 1, H-3′), 3.88 (m, 2, H-5′), 3.59 (dd, *J* 5.2, 9.7 Hz, 1, H-4′), 3.38 (m, 4, 2×CH_2 propyl), 2.77 (m, 1, H-2′), 2.51 (dt, *J* 4.0, 7.3 Hz, 1, H-2′), 1.68 (m, 4, 2×CH_2 propyl), 1.02 (t, *J* 7.4 Hz, 6, 2×CH_3 propyl); ^{13}C NMR ($CDCl_3$) δ 161.42 and 157.59 (2×C=O), 135.89 (CH, C-2), 133.66 (C, C4/C5), 125.62 (C, C4/C5), 72.64 (CH, C-1′), 61.38 (CH_2, C-5′), 60.06 (CH, C-3′), 54.86 (CH, C-4′), 43.72 (CH_2, C-2′), 39.63 and 39.55 (2×CH_2 propyl), 20.89 and 20.74 (2×CH_2 propyl), 9.91 and 9.69 (2×CH_3 propyl); anal. $C_{16}H_{22}N_4O_4S$ requires C, 51.87; H, 7.07; N, 15.12. Found: C, 52.05; H, 7.25; N, 15.27%.

1-(2-Deoxy-4-thio-β-D-ribofuranosyl)-4,5-bis(*N*-cyclopropylcarbamoyl) imidazole (21e). Compound **20** (63 mg, 0.20 mmol) was treated with a solution of cyclopropylamine (5 mL) in dry methanol (10 mL) at rt for 16 h. The reaction was then concentrated under reduced pressure and purified by flash column chromatography (petroleum ether:ethyl acetate, 4:1 v/v increasing to ethyl acetate:methanol, 95:5 v/v) to give 44 mg (60%) of **21e** as a white solid: mp 169–170 °C; ^{1}H NMR (DMSO-d_6) δ 11.20 (s, 1, NH), 8.62 (d, *J* 4.7 Hz, 1, NH), 8.47 (s, 1, H-2), 6.83 (t, *J* 5.9 Hz, 1, H-1′), 5.28 (br. s, 1, OH), 5.15 (br. s, 1, OH), 4.33 (d, *J* 5.0 Hz, 1, H-3′), 3.68 (dd, *J* 5.8, 11.2 Hz, 1, H-5′), 3.55 (m, 1, H-5′), 3.38 (m, 1, H-4′),

2.83 (m, 2, 2×CH cyclopropyl), 2.41 (t, *J* 5.7 Hz, 2, H-2′), 0.74 (m, 2, CH_2 cyclopropyl), 0.67 (m, 4, CH_2 cyclopropyl), 0.50 (m, 2, CH_2 cyclopropyl); ^{13}C NMR (DMSO-d_6) δ 164.21 and 159.77 (2×C=O), 137.61 (CH, C-2), 134.39 (C, C4/C5), 126.32 (C, C4/C5), 72.46 (CH, C-1′), 62.21 (CH_2, C-5′), 60.47 (CH, C-3′), 57.84 (CH, C-4′), 43.73 (CH_2, C-2′), 22.48 and 21.95 (2×CH cyclopropyl), 5.54 and 5.36 (4×CH_2 cyclopropyl); MS (FAB), *m*/*z* 367 $(M+H)^+$, 389 $(M+Na)^+$, 733 $(2M+H)^+$, 755 $(2M+Na)^+$; anal. $C_{16}H_{22}N_4O_4S$ (366.4402); accurate mass FAB 366.1365 (M), 367.1444 (M + H).

1-(2-Deoxy-4-thio-β-D-ribofuranosyl)-4,5-bis(*N*-butylcarbamoyl) imidazole (21f). Compound **20** (44 mg, 0.15 mmol) was treated with a solution of butylamine (10 mL) in dry methanol (10 mL) at rt for 3 h. The reaction was then concentrated under reduced pressure and purified by flash column chromatography (chloroform:methanol, 9:1 v/v to give 61 mg (92%) of **21f** as a waxy solid: ^1H NMR ($CDCl_3$) δ 8.40 (s, 1, H-2), 7.07 (ψt, *J* 4.8, 5.1 Hz, 1, H-1′), 4.57 (dd, *J* 5.4, 12.3 Hz, 1, H-3′), 3.98 (dd, *J* 4.3, 11.5 Hz, 1, H-5′), 3.85 (dd, *J* 6.2, 11.5 Hz, 1, H-5′), 3.56 (dd, *J* 5.4, 10.4 Hz, 1, H-4′), 3.40 (m, 4, 2×CH_2 butyl), 2.75 (dt, *J* 7.1, 14.0 Hz, 1, H-2′), 2.46 (dt, *J* 4.2, 8.5 Hz, 1, H-2′), 1.63 (m, 4, 2×CH_2 butyl), 1.44 (dt, *J* 7.2, 14.8 Hz, 4, 2×CH_2 butyl), 0.98 (dt, *J* 3.9, 7.2 Hz, 6, 2×CH_3 butyl); ^1C NMR ($CDCl_3$) δ 159.77 (2×C=O), 136.29 (C, C4/C5), 126.28 (C, C4/C5), 122.67 (CH, C-2), 74.80 (CH, C-1′), 63.65 (CH_2, C-5′), 62.08 (CH, C-3′), 57.08 (CH, C-4′), 45.81 (CH_2, C-2′), 39.70, 39.57, 31.81, 31.63, 20.73 and 20.53 (6×CH butyl), 14.23 and 14.16 (2×CH_3 butyl); MS (FAB), *m*/*z* 399 $(M+H)^+$, 421 $(M+Na)^+$; anal. $C_{18}H_{30}N_4O_4S$ (398.5254); accurate mass FAB 398.2019 (M), 399.2089 (M + H).

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8. Analytical data for **3** :$C_{19}H_{15}ClN_2O_8S$ MW 466.8551; mp 118 °C dec; δ_H 8.36 (m, 8, Ar), 5.96 (dd, *J* 1.1, 4.6 Hz, 1, H-1) overlapping 5.94 (dd, *J* 1.2, 5.1 Hz, 1, H-4), 4.49 (dd, *J* 5.4, 10.8 Hz, 1, H-5a), 4.39 (m, 2, H-3 and H-5b), 3.03 (m, 1, H-2), 2.96 (dt, *J* 4.6, 5.5, 10.1 Hz, 1, H-2); mass spec. (ES^+) *m*/*z* 467.98 (M + H).
9. Analytical data for **5**: $C_{12}H_9NO_4S$ MW 266.6604; mp 91–92 °C; δ_H 8.29 (ddd, *J* 2.0, 6.8, 9.1 Hz, 4, Ar), 7.41 (d, *J* 5.1 Hz, 1, H-1), 7.24 (d, *J* 3.6 Hz, 1, H-3), 7.07 (dd, *J* 3.6, 5.0 Hz, 1, H-2), 5.60 (s, 2, H-5); δ_C 164.90 (C=O), 137.44 (C, Ar), 135.72 (C, Ar), 131.31 (CH, Ar), 129.26 (CH, C-1), 127.81 and 127.43 (2×CH, C-2 and C-3), 107.50 (C, C-4), 62.24 (CH_2, C-5).
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