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An alternative strategy for the synthesis of 3′-azido-2′,3′-dideoxy-4′-thionucleosides starting from D-xylose [1,2]

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Abstract

Methyl 5-*O*-acetyl-3-azido-2,3-dideoxy-4-thio-α,β-D-*erythro*-pentofuranoside and 1,5-*O*-diacetyl-3-azido-2,3-dideoxy-4-thio-α,β-D-*erythro*-pentofuranose were prepared in twelve and thirteen steps, respectively, by an efficient route starting from D-xylose. Both compounds were easily converted into an anomeric mixture of pyrimidine nucleosides by reaction with the 2,4-bi(trimethylsilyloxy) derivative in the presence of a Lewis acid. The anomeric mixtures were separated by chromatography. The 4′-thio analogue of AZT and related uridine nucleosides have been prepared by a novel and more efficient approach.

Keywords: Double inversion; 4,5-Epithiopentose; 4′-Thiouridine nucleosides; ThioAZT

1. Introduction

There has been increasing interest in recent years in the synthesis of nucleosides from sugar precursors in which the furanose ring oxygen atom is replaced by a sulfur atom [2–8]. Such a structural modification results in an increased resistance to phosphorylytic cleavage [9], and, consequently, 4′-thionucleosides could be an advantageous stabilizing factor when integrated into a DNA matrix [5]. Some work on analogous oligoribonucleotides has been reported by Imbach and co-workers [10]. An area of particular interest

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[1] This paper is dedicated to the memory of Professor Guy Ville who initiated this study at the Université de Picardie.

[2] For a preliminary report, see [1].

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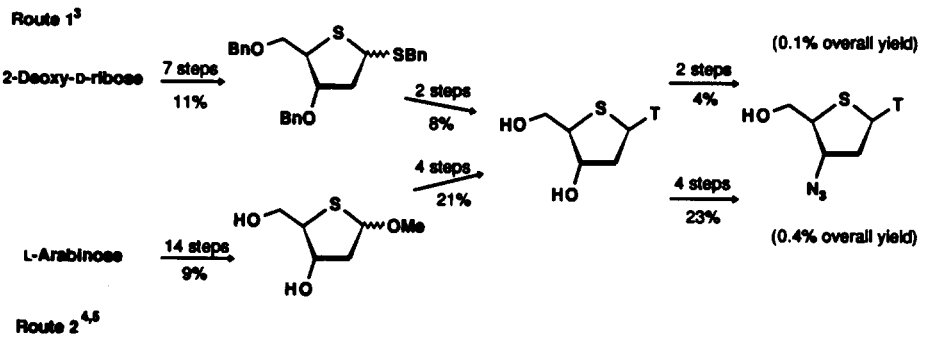


Scheme 1.

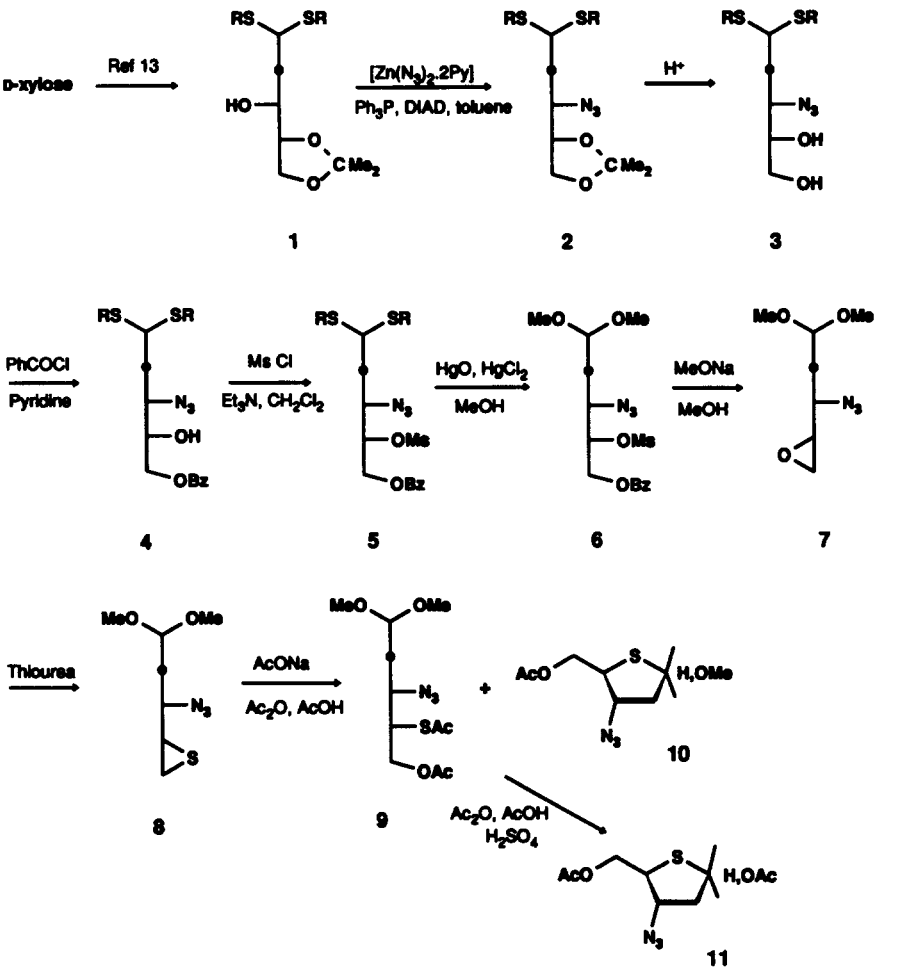
to us is the use of 4-thio sugars in the synthesis of nucleosides with potential anti-viral activity [11,12].

The synthesis of the 4′-thio analogue of AZT, i.e., 3′-azido-3′-deoxy-4′-thiothymidine, has been reported previously [4–6] using two different routes (Scheme 1). Both are based on a conventional approach to 3′-substituted nucleosides. Thus, a 2-deoxy-4-thioriboside derivative is synthesized first and then converted to a nucleoside by standard methods. The azido group is introduced at C-3′ via a 2,3′-anhydronucleoside at the ultimate or penultimate step. Apart from the large number of steps and the low overall yield, the strategies shown in Scheme 1 are of limited application. The method of introducing the azido group requires the formation of a 2,3′-anhydronucleoside, thus restricting the procedure to pyrimidine bases, and to β-nucleosides. In an attempt to find a more general method for the formation of 4′-thiothymidine and other thioAZT analogues we have developed a methodology which introduces the azido group early in the sequence of steps, thus generating a 3-azido-4-thioribofuranose derivative, which is then readily converted to a nucleoside by standard procedures.

2. Results

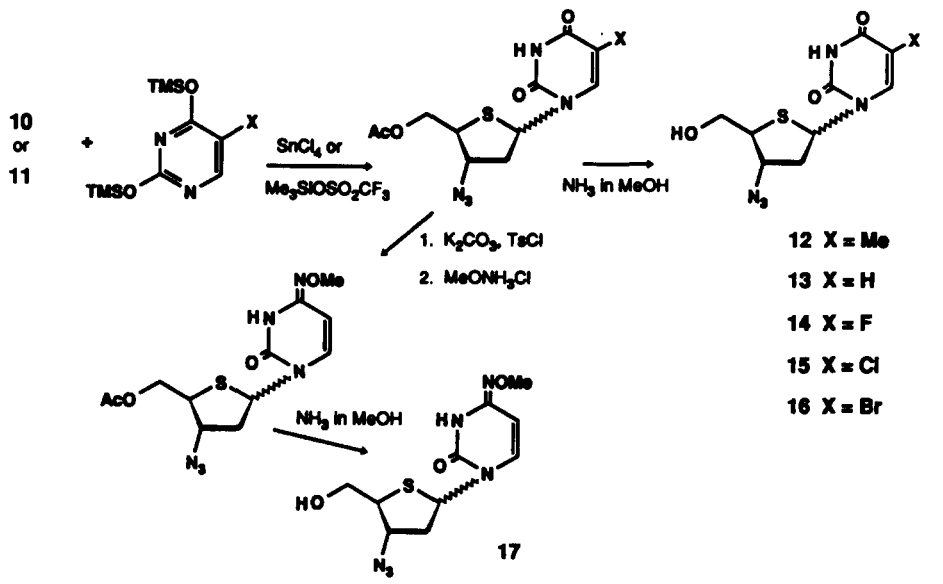
The starting material for this methodology (Scheme 2) is 2-deoxy-4,5-*O*-isopropylidene-D-*threo*-pentose diisobutyl dithioacetal (**1**), prepared from D-xylose according to a procedure developed by Wong and Gray [13]. We found that the diisobutyl dithioacetal protecting group was more convenient in terms of extractability into organic solvent than the diethyl analogue used in [13].

Using the modified Mitsunobu reaction developed by Viaud and Rollin [14], **1** was converted to the 3-azido-2,3-dideoxy-D-*erythro*-pentose derivative (**2**), with inversion at the C-3 site. Hydrolysis of the 4,5-*O*-isopropylidene group and benzoylation at C-5 gave **7**, which has only the C-4 hydroxyl group unprotected. The next objective was the introduction of the sulfur atom at the 4-position while keeping the same configuration at C-4 as in D-xylose. Several possible methods were examined. Use of the Lawesson reagent [15] would be an attractive method for the replacement of the 4-OH group by SH, with retention of configuration. However, we found that this reagent gave mostly a disulfide and this method was not pursued, particularly in view of the fact that a free SH group could interfere with the ultimate removal of the dithioacetal group.



Scheme 2.

Direct cyclization to a 4-thio sugar via the 4-iodo derivative has been described using triphenylphosphine and triiodoimidazole [16], but this method was avoided because it does not have the required degree of stereoselectivity, since epimerization at C-4 may occur. To circumvent these problems, we have developed a double inversion strategy in which the 4,5-oxirane dimethylacetal derivative **7** is formed first. Treatment of compound **7** with thiourea gave the corresponding 4,5-epithio derivative **8** with inversion at C-4. Opening of the episulfide ring under conditions designed to afford the acyclic acetal **9** gave the desired product in 48% yield, but some cyclization also occurred to give 33% of an anomeric mixture of methyl 5-*O*-acetyl-3-azido-2,3-dideoxy-4-thio-D-*erythro*-pentofuranosides (**10**). The dimethylacetal was cyclized by reaction with acetic anhydride in acetic acid to give 1,5-*O*-diacetyl-3-azido-2,3-dideoxy-4-thio-D-*erythro*-pentofuranose (**11**). Compounds **10** and **11** were obtained in ca. 2 and 5% overall yield, respectively, from D-xylose. Potentially, either of these derivatives of 3-azido-4-thio-de-



Scheme 3.

oxyribose can be used to form nucleosides and other novel derivatives of thio sugars. Both compounds were anomeric mixtures (ca. 1:1) which could be separated by extensive chromatography although the anomeric configurations were difficult to assign unequivocally. In every case, the nucleosides were prepared by standard reactions from the unresolved anomeric mixtures.

Because the methodology we have described above affords a protected 4-thio-D-ribose derivative with the azido group in place, the conversion of the 4-thiodeoxyribose derivative to a nucleoside is achieved with a smaller number of steps than was previously used in the routes shown in Scheme 1. Thus, the methyl glycoside **10** or the 1-*O*-acetyl derivative **11** was treated with a silylated base and the nucleoside then deprotected directly (Scheme 3). In this way, a series of pyrimidine thionucleosides were obtained as anomeric mixtures with the β anomer predominating. Purification and separation by silica gel column chromatography gave 3′-azido-3′-deoxy-4′-thiothymidine and related nucleosides in 20–30% yield (based on the protected sugar). The analogous compounds with the α configuration of the 4′-thio sugar were also obtained in impure form in 8–26% yield. These α-nucleosides were characterized spectroscopically but were not further purified.

The anomeric configuration of the nucleosides was assigned in the first instance by detailed examination of the NMR spectra. Some spectroscopic data were reported for the thymidine analogue (**12**β) by Secrist [6] but only partial chemical shift data were given. The present data for **12**β agree with the published data.

The ^{1}H spectra of the set of six nucleosides did not show all the diagnostic features which have commonly been used to determine the anomeric configuration in 2′-deoxyribonucleosides, and have also been used for 4′-thionucleosides [5]. There was no significant difference for the α and β anomers in the H-1 chemical shift, nor in the sum

of the couplings to this proton ($J_{1',2'} + J_{1',2''}$). However, the following features were found consistently: hydrogens H-2′ and H-2″ have a chemical shift separation which was in the range 0.07–0.21 for the β anomers and in the range 0.34–0.48 for the α anomers; H-3′ appears at δ 4.45–4.51 in the β anomers and at δ 4.15–4.25 in the α anomers; H-4′ appears at δ 3.30–3.42 in the β anomers and at δ 3.67–3.79 in the α anomers; H-5′ and H-5″ have essentially coincident chemical shifts in the β anomers but with a separation of 0.1–0.2 in the the α anomers. The ^{13}C NMR data were of little value for the assignment of anomeric configuration, both anomers having quite similar chemical shifts for all carbon atoms. However, using the set of diagnostic features evident in the proton spectra, the anomers were readily identified.

For unequivocal confirmation of the anomeric configuration supported by the above diagnostic criteria, NOE difference spectra were obtained for the pair of anomers of 3′-azido-5-bromo-2′,3′-dideoxy-4′-thiouridine (**16**). For the β anomer, irradiation of H-1′ established the position of H-2″, since this was the only site showing a substantial positive enhancement (H-2″ is on the *exo* face of the 4′-thioribose ring, *trans* to the C-5 group; H-2′ is on the *endo* face and appears to higher frequency in both anomers of all nucleosides investigated). Irradiation of H-6 resulted in approximately equal positive enhancements for the H-1′ and H-2′ signals and an enhancement at H-3′ which was ca. 25% smaller. No effect was detected at H-4′. A similar experiment with the α anomer showed a substantial and approximately equal enhancement for H-1′ and H-2″ with a smaller positive effect for H-4′ and no effect at H-3′. These results convincingly support the anomeric assignment.

None of the compounds **13–17** were found to possess appreciable activity against HIV-1 or HIV-2 viruses; however, all of these compounds showed minimal cytotoxicity.

3. Experimental

General Procedures.—Melting points were determined using an Electrothermal capillary apparatus with a digital thermometer and values are uncorrected. Optical rotations were obtained at room temperature on a Jasco model DIP-370 digital polarimeter. IR spectra were measured as thin films with a Perkin–Elmer 983G spectrometer. NMR spectra were recorded with a Jeol GX270 or Bruker 300WB spectrometer using standard conditions with a data point resolution of ca. 0.1 Hz. ^1H NMR chemical shifts were measured relative to Me_4Si and ^{13}C NMR chemical shifts relative to $CDCl_3$ (77.05 ppm) or $(CD_3)_2SO$ (39.5 ppm). Aryl ^1H and ^{13}C NMR chemical shifts are generally not reported. Standard heteronuclear correlation techniques were used where required for assignment. Thin layer chromatography was carried out using Kieselgel $60F_{254}$ plates (E. Merck), with detection by UV light or phosphomolybic acid spray. Silica Gel 60 was used for column chromatography. In the case of some of the azido β-nucleosides, satisfactory elemental analysis data were not obtained particularly for nitrogen and this may be attributed to thermal decomposition of the azide group. The corresponding α-nucleosides were obtained only as impure byproducts, which were characterized spectroscopically but were not purified further since these compounds were not targeted for biological screening. The specific rotations which are given should not then be regarded as necessarily definitive.

*2-Deoxy-4,5-O-isopropylidene-*D-threo-*pentose diisobutyl dithioacetal* (**1**).—D-Xylose was converted to D-xylose diisobutyl dithioacetal (92%) by the method of Zinner et al. [17]; $[\alpha]_D^{27}$ +16.6° (*c* 2.5, MeOH) (lit. [17] +14.7°, *c* 3, MeOH); ^{13}C NMR ($CDCl_3$): δ 22.05, 22.2 (Me_2CHCH_2), 28.4 (Me_2CHCH_2), 38.5, 40.2 (Me_2CHCH_2), 56.2 (C-4), 64.1 (C-5), 70.5 (C-3), 73.5 (C-2), 73.7 (C-1). The isopropylidene derivative of this diisobutyl dithioacetal was prepared by the procedure of Wong and Gray [13]. 2,3:4,5-Di-*O*-isopropylidene-D-xylose diisobutyl dithioacetal was obtained as a pale yellow oil (69%); R_f 0.90 (1:1 hexanes–ether); $[\alpha]_D^{27}$ −23° (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.01 (2 d, Δ 0.005, 12 H, Me_2CHCH_2), 1.38, 1.43, 1.47 (3 s, 12 H, Me_2CH), 1.83 (m, 2 H, Me_2CHCH_2), 2.57 (2 m, Δ 0.003, 2 H, Me_2CHCH_2), 2.66 (2 m, Δ 0.013, 2 H, Me_2CHCH_2), 3.84 (d, 1 H, $J_{1,2}$ 5.4 Hz, H-1), 3.94 (t, 1 H, $J_{4,5a}$ 5.4 Hz, H-5a), 4.05 (dd, 1 H, $J_{4,5b}$ 6.6 Hz, $J_{5a,5b}$ 8.1 Hz, H-5b), 4.14 (dd, 1 H, $J_{2,3}$ 7.4 Hz, $J_{3,4}$ 3.2 Hz, H-3), 4.32 (dd, 1 H, H-2), 4.34 (ddd, 1 H, H-4); ^{13}C NMR ($CDCl_3$): δ 22.2, 22.3 (Me_2CHCH_2), 28.5, 28.6 (Me_2CHCH_2), 39.8, 40.3 (Me_2CHCH_2), 25.7, 26.2, 27.2, 27.4, 109.5, 110.1 (2 × isopropylidene), 54.4 (C-1), 66.0 (C-5), 75.4 (C-4), 78.8 (C-3), 80.1 (C-2). This xylose derivative was converted to 2-deoxy-4,5-*O*-isopropylidene-D-*threo*-pent-1-enose diisobutyl dithioacetal by the method of Wong and Gray [13]. The syrup (65%) had R_f 0.60 (1:1 hexanes–ether); $[\alpha]_D^{27}$ −6.3°(*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.6 (dd, 1 H, $J_{5a,5b}$ 8.35 Hz, H-5a), 3.8 (dd, 1 H, $J_{4,5b}$ 6.6 Hz, H-5b), 3.9 (dd, 1 H, $J_{4,5a}$ 6.6 Hz, H-4), 4.7 (dd, 1 H, $J_{3,4}$ 6.6 Hz, H-3), 5.7 (d, 1 H, $J_{2,3}$ 8.7 Hz, H-2); ^{13}C NMR ($CDCl_3$): δ 21.8, 22.0, 22.2 (Me_2CHCH_2), 28.2, 29.0 (Me_2CHCH_2), 41.8, 42.4 (Me_2CHCH_2), 25.5, 26.8, 109.1 (isopropylidene), 65.9 (C-5), 70.9 (C-3), 79.0 (C-4), 131.8 (C-2), 138.1 (C-1).

This unstable compound was reduced by the method of Wong and Gray [13] to give **1** (90%); R_f 0.5 (1:1 hexanes–ether); $[\alpha]_D^{25}$ +14.2° (*c* 1.3, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.00 (d, 12 H, Me_2CHCH_2), 1.37, 1.45 (2 s, 6 H, Me_2CH), 1.72 (m, 1 H, $J_{1,2a}$ 10.2, $J_{2a,3}$ 2.6, $J_{2a,2b}$ 14.3 Hz, H-2a), 1.81 (m, 2 H, Me_2CHCH_2), 2.01 (m, 1 H, $J_{1,2b}$ 10.0, $J_{2b,3}$ 4.4 Hz, H-2b), 2.45 (2 m, Δ 0.025, 2 H, Me_2CHCH_2), 2.59 (2 m, Δ 0.002, 2 H, Me_2CHCH_2), 3.78 (m, 1 H, H-5a), 3.90 (m, 1 H, H-3), 4.03 (m, 3 H, H-1,4,5b); ^{13}C NMR ($CDCl_3$): δ 22.15, 22.3 (Me_2CHCH_2), 28.4, 28.5 (Me_2CHCH_2), 38.9, 39.3 (Me_2CHCH_2), 25.2, 26.5, 109.3 (isopropylidene), 40.0 (C-2), 49.1 (C-1), 66.0 (C-5), 69.7 (C-3), 78.6 (C-4). Anal. Calcd for $C_{16}H_{32}O_3S_2$: C, 57.10; H, 9.58; S, 19.05. Found: C, 57.25; H, 10.01; S, 18.98.

*3-Azido-2,3-dideoxy-4,5-*O*-isopropylidene-*D-erythro-*pentose diisobutyl dithioacetal* (**2**).—To a solution of PPh_3 (30.4 g, 116 mmol) and **1** (19.5 g, 58 mmol) in anhyd toluene (250 mL), $Zn(N_3)_2 \cdot (C_5H_5N)_2$ [14] (13.3 g, 43.5 mmol) was added. Diisopropyl azodicarboxylate (23.2 mL, 116 mmol) was then added dropwise to the stirred solution. After 3 h, the solution was filtered through Celite and concentrated to a syrup. Trituration with 1:1 hexanes–ether precipitated triphenylphosphine oxide which was removed by filtration. The filtrate was concentrated and the residue chromatographed on a silica gel column (hexanes–ether gradient) to give **2** as an oil (15.7 g, 75%); R_f 0.6 (1:1 hexanes–ether); $[\alpha]_D^{27}$ −9.5° (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.00 (2 d, Δ 0.01, 12 H, Me_2CHCH_2), 1.36, 1.47, (2 s, 6 H, Me_2CH), 1.73 (m, 1 H, H-2a), 1.81 (2 m, Δ 0.01, 2 H, Me_2CHCH_2), 1.86 (m, 1 H, H-2b), 2.43 (2 m, Δ 0.044, 2 H, Me_2CHCH_2), 2.58 (2 m, Δ 0.025, 2 H, Me_2CHCH_2), 3.9 (m, 2 H, H-1,5a), 3.97 (m, 1 H, H-3), 4.05 (m, 2 H,

H-4,5b); ^{13}C NMR ($CDCl_3$): δ 22.2, 22.3, 22.4 (Me_2CHCH_2), 28.5 (Me_2CHCH_2), 37.5, 38.5 (Me_2CHCH_2), 26.3, 109.8 (isopropylidene), 39.5 (C-2), 49.4 (C-1), 61.4 (C-3), 65.9 (C-5), 78.0 (C-4). Anal. Calcd for $C_{16}H_{31}O_2N_3S_2$: C, 53.14; H, 8.64; N, 11.62; S, 17.73. Found: C, 53.44; H, 8.96; N, 12.03; S, 17.15.

3-Azido-2,3-dideoxy-D-erythro-*pentose diisobutyl dithioacetal* (**3**).—A solution of **2** (26.0 g, 72 mmol) in 19:1 EtOH–water (60 mL) was passed through a thermostatically jacketted column set at 50°C and filled with Amberlite 15 (H^+ form) resin (140 g) suspended in 19:1 EtOH–water (180 mL). The column was further eluted with 19:1 EtOH–water (200 mL). The eluants were pooled and concentrated to give **3** as an oil (20.0 g, 87%); R_f 0.30 (1:1 hexanes–ether); $[\alpha]_D^{27}$ +2.5° (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.00 (2 d, Δ 0.005, 12 H, Me_2CHCH_2), 1.82 (2 m, Δ 0.005, 2 H, Me_2CHCH_2), 1.94 (m, 1 H, H-2a), 1.98 (m, 1 H, H-2b), 2.35 (br s, 1 H, OH), 2.45 (2 m, Δ 0.045, 2 H, Me_2CHCH_2), 2.58 (2 m, Δ 0.025, 2 H, Me_2CHCH_2), 2.95 (br s, 1 H, OH), 3.75 (m, 3 H, H-4,5b,5a), 3.9 (m, 2 H, H-1,3); ^{13}C NMR ($CDCl_3$): δ 22.1, 22.2, 22.25, 22.3 (Me_2CHCH_2), 28.4 (Me_2CHCH_2), 38.7, 39.4 (Me_2CHCH_2), 37.2 (C-2), 49.4 (C-1), 62.1 (C-3), 63.2 (C-5), 73.7 (C-4).

3-Azido-5-O-*benzoyl-2,3-dideoxy*-D-erythro-*pentose diisobutyl dithioacetal* (**4**).—A solution of benzoyl chloride (8.8 g, 68.9 mmol) in $CHCl_3$ (10 mL) was added to a solution of **3** (20.0 g, 62.3 mmol) in pyridine (125 mL) at −10°C. The mixture was stirred for 4 h at 0°C, for a further 16 h at room temperature, then diluted with iced water, and extracted with CH_2Cl_2. The organic phase was washed sequentially with HCl (0.1 M) and water, then dried ($MgSO_4$) and concentrated to a gum. Chromatographic purification on silica gel (hexanes–ether gradient) gave the product as a colourless syrup (20.4 g, 77%); R_f 0.4 (1:1 hexanes–ether); $[\alpha]_D^{27}$ +7.8° (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.99 (3 d, Δ 0.005, 0.028, 12 H, Me_2CHCH_2), 1.82 (2 m, Δ 0.009, 2 H, Me_2CHCH_2), 2.04 (m, 2 H, H-2a,2b), 2.45 (2 m, Δ 0.045, 2 H, Me_2CHCH_2), 2.58 (2 m, Δ 0.013, 2 H, Me_2CHCH_2), 3.94 (m, 1 H, $J_{1,2a}$ 6.0, $J_{1,2b}$ 9.0 Hz, H-1), 4.01 (m, 2 H, H-3,4), 4.45 (m, 1 H, $J_{4,5a}$ 6.0, $J_{5a,5b}$ 12.0 Hz, H-5a), 4.54 (m, 1 H, $J_{4,5b}$ 3.0 Hz, H-5b); ^{13}C NMR ($CDCl_3$): δ 22.1, 22.2, 22.3, 22.35 (Me_2CHCH_2), 28.5 (Me_2CHCH_2), 38.6, 39.5 (Me_2CHCH_2), 128.2, 129.4, 129.7, 133.3 (phenyl), 166.9 (carbonyl), 37.1 (C-2), 49.5 (C-1), 62.2 (C-3), 66.3 (C-5), 72.6 (C-4).

3-Azido-5-O-*benzoyl-2,3-dideoxy-4*-O-*mesyl*-D-erythro-*pentose diisobutyl dithioacetal* (**5**).— Methanesulfonyl chloride (18.8 g, 165 mmol) was added dropwise to a stirred solution of **4**, (47.0 g, 110 mmol) in CH_2Cl_2 (100 mL) and Et_3N (20 mL) at 0°C. The mixture was maintained at 0°C for 30 min, at room temperature for 2 h, then washed sucessively with HCl (0.1 M, 400 mL) and satd aq $NaHCO_3$ (400 mL). The organic phase was dried ($MgSO_4$) and concentrated to give **8** as a syrup (50.0 g, 90%); R_f 0.45 (1:1 hexanes–ether); $[\alpha]_D^{27}$ +25.0° (*c* 1.3; $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.00 (m, 12 H, Me_2CHCH_2), 1.82 (2 m, Δ 0.003, 2 H, Me_2CHCH_2), 1.99 (m, 1 H, $J_{1.2a}$ 9.8, $J_{2a,3}$ 4.0 Hz, H-2a), 2.04 (m, 1 H, $J_{1,2b}$ 5.1, $J_{2b,3}$ 9.4 Hz, H-2b), 2.45 (2 m, Δ 0.04, 2 H, Me_2CHCH_2), 2.61 (2 m, Δ 0.013, 2 H, Me_2CHCH_2), 3.93 (dd, 1 H, H-1), 4.33 (m, 1 H, $J_{3,4}$ 4.0 Hz, H-3), 4.52 (m, 1 H, $J_{4,5a}$ 7.1, $J_{5a,5b}$ 12.5 Hz, H-5a) 4.65 (m, 1 H, $J_{4,5b}$ 3.3 Hz, H-5b), 5.15 (m, 1 H, H-4); ^{13}C NMR ($CDCl_3$): δ 21.8, 22.1, 22.3 (Me_2CHCH_2), 28.4 (Me_2CHCH_2), 38.5, 39.4 (Me_2CHCH_2), 36.8 (C-2), 49.2 (C-1), 61.2 (C-3), 62.6 (C-5), 80.1 (C-4), 128.5, 129.8, 130.2, 133.7 (phenyl), 165.9 (CO).

*3-Azido-5-*O*-benzoyl-2,3-dideoxy-4-*O*-mesyl-*D-erythro*-pentose dimethyl acetal* (**6**).—Mercuric oxide (24.4 g, 112.6 mmol) and mercuric chloride (24.4 g, 90 mmol) were added to a solution of **5** (17.0 g, 34.8 mmol) in MeOH (100 mL). The mixture was stirred for 2 h at 60°C and filtered through Celite. The residue was washed well with MeOH, and the filtrates were combined and concentrated. The residue was taken up in $CHCl_3$, washed with KI (1 M), dried ($MgSO_4$), and concentrated to a syrup, which was chromatographed on a silica gel column (hexanes–EtOAc gradient) to give **6** as a syrup (9.5 g, 70%); R_f 0.15 (1:1 hexanes–ether); $[\alpha]_D^{27}$ +21° *c* 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.76 (m, 1 H, $J_{1,2a}$ 3.6, $J_{2a,3}$ 9.7, $J_{2a,2b}$ 14.5 Hz, H-2a), 1.84 (m, 1 H, $J_{1,2b}$ 6.9, $J_{2b,3}$ 3.7 Hz, H-2b), 3.91 (m, 1 H, H-3), 4.5 (dd, 1 H, H-1), 4.41 (m, 1 H, $J_{4,5a}$ 7.3, $J_{5a,5b}$ 12.6 Hz, H-5a), 4.5 (m, 1 H, $J_{4,5b}$ 3.3 Hz, H-5b), 4.93 (m, 1 H, H-4), 3.0, 3.26, 3.28 (3 s, 9 H, OMe); ^{13}C NMR ($CDCl_3$): δ 38.7 (SO_2Me), 53.5, 53.7 (OMe), 32.8 (C-2), 58.9 (C-3), 61.4 (C-5), 79.2 (C-4), 100.8 (C-1), 127.5, 128.3, 128.6, 132.4 (C_6H_5), 164.8 (CO).

*4,5-Anhydro-3-azido-2,3-dideoxy-*L*-threo-pentose dimethyl acetal* (**7**).—Sodium methoxide (1.6 g, 29.6 mmol) in MeOH (25 mL) was added to a solution of **6** (10.0 g, 25.84 mmol) in $CHCl_3$ (90 mL). The mixture was stirred for 24 h at 0°C, then washed successively with water, satd aq NaCl, and water. The organic phase was dried ($MgSO_4$) and concentrated to a syrup, which was chromatographed on a silica gel column (hexanes–ether gradient) to give **7** as an oil (3.7 g, 76%); R_f 0.3 (1:1 hexanes–ether); $[\alpha]_D^{27}$ −1.5° (*c* 1.6; $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.87 (m, 2 H, H-2a,2b), 2.68 (dd, 1 H, $J_{4,5a}$ 2.5, $J_{5a,5b}$ 4.9 Hz, H-5a), 2.84 (dd, 1 H, $J_{4,5b}$ 4.0 Hz, H-5b), 3.08 (m, 1 H, $J_{3,4}$ 7.6 Hz, H-4), 3.30 (q, 1 H, $J_{3,4}$ 6.7 Hz, H-3), 4.54 (t, 1 H, $J_{1,2}$ 5.8 Hz, H-1), 3.35, 3.37 (2 s, 6 H, OMe); ^{13}C NMR ($CDCl_3$): δ: 34.3 (C-2), 44.7 (C-5), 53.0, 53.5 (OMe), 54.1 (C-3), 60.5 (C-4), 101.5 (C-1). Anal. Calcd for $C_7H_{13}N_3O_2$: C, 44.91; H, 6.99; N, 22.44. Found: C, 45.12; H, 7.16; N, 21.83.

*3-Azido-2,3,4,5-tetradeoxy-4,5-epithio-*D*-erythro-pentose dimethyl acetal* (**8**).—A solution of **7** (7.0 g, 37.4 mmol) and thiourea (4.0 g, 52 mmol) in MeOH (150 mL) was stirred at room temperature for 12 h. The solvent was evaporated and the residue taken up in CH_2Cl_2. This solution was washed several times with ice-cold water, and then dried ($MgSO_4$) and concentrated to a syrup, which was chromatographed on a silica gel column (hexanes–ether gradient) to give **8** as an oil (6.0 g, 80%); R_f 0.60 (1:1 hexanes–ether); $[\alpha]_D^{27}$ +11.3° (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.87 (m, 1 H, $J_{1,2a}$ 4.0, $J_{2a,3}$ 9.7, $J_{2a,2b}$ 14.2 Hz, H-2a), 2.04 (m, 1 H, $J_{1,2b}$ 7.5, $J_{2b,3}$ 3.8, H-2b), 2.41 (dd, 1 H, $J_{4,5a}$ 5.0, $J_{5a,5b}$ 1.5 Hz, H-5a), 2.59 (dd, 1 H, $J_{4,5b}$ 6.0 Hz, H-5b), 2.99 (m, 1 H, $J_{3,4}$ 8.1 Hz, H-4), 3.12 (m, 1 H, H-3), 4.58 (dd, 1 H, H-1), 3.32, 3.34 (2 s, 6 H, OMe); ^{13}C NMR ($CDCl_3$): δ 23.7 (C-5), 36.1 (C-4), 37.2 (C-2), 52.6, 53.2 (OMe), 64.2 (C-3), 101.4 (C-1). Anal. Calcd for $C_7H_{13}O_2N_3S$: C, 41.36; H, 6.44; N, 20.67; S, 15.77. Found: C, 41.30; H, 6.59; N, 20.09, S, 15.44.

*5-*O*-Acetyl-4-*S*-acetyl-3-azido-2,3-dideoxy-4-thio-*D*-erythro-pentose dimethyl acetal* (**9**) *and methyl 5-*O*-acetyl-3-azido-2,3-dideoxy-4-thio-α,β-*D*-erythro-pentofuranoside* (**10**).—A solution of **8** (9.0 g, 44.3 mmol) and AcONa (7.2 g, 8.8 mmol) in a mixture of AcOH (16.5 mL) and Ac_2O (84 mL) was refluxed for 16 h. The mixture was diluted with ice–water (500 mL) and stirred for 2 h, then extracted with CH_2Cl_2. The extract was dried ($MgSO_4$), concentrated and separated on a silica gel column (hexanes–ether

gradient) into two components. The species with R_f 0.38 (3:2 hexanes-ether), identified as **9**, was obtained as an oil (5.6 g, 48%); $[\alpha]_D^{26}$ −6.6° (*c* 1.7, $CHCl_3$); IR, ν 2100 cm^{-1} (N_3); CIMS: *m/z* 323 $[M + NH_4]^+$; ^1H NMR ($CDCl_3$): δ 1.78 (m, 1 H, $J_{1,2a}$ 4.0, $J_{2a,2b}$ 14.3, $J_{2a,3}$ 10.2 Hz, H-2a), 2.01 (m, 1 H, $J_{1,2b}$ 7.6, $J_{2b,3}$ 3.4 Hz, H-2b), 2.08 (s, 3 H, OCOMe), 2.38 (s, 3 H, SCOMe), 3.36, 3.37 (2 s, 6 H, OMe), 3.77 (m, 1 H, $J_{3,4}$ 6.0 Hz, H-3), 3.89 (q, 1 H, H-4), 4.28 (d, 2 H, $J_{4,5}$ 5.2 Hz, H-5a,5b); ^{13}C NMR ($CDCl_3$): δ 20.7 (OCO*Me*), 30.6 (SCO*Me*), 53.2, 53.6 (OMe), 35.4 (C-2), 46.5 (C-4), 63.2 (C-3), 60.4 (C-5), 102.0 (C-1), 170.4 (OC = O), 193.5 (SC = O). Anal. Calcd for $C_{11}H_{19}N_3O_5S$: C, 43.26; H, 6.27; N, 13.76; S, 10.50. Found: C, 43.18; H,6.28; N, 13.80, S, 10.66.

The second component was a mixture of the α and β anomers of **10**, obtained as an oil (2.8g, 33%); IR, ν 2100 (N_3) cm^{-1}; CIMS: *m/z* 249 $[M + NH4]^+$. Anal. Calcd for $C_8H_{13}O_3N_3S$: C, 41.54; H, 5.66; N, 18.17; S, 13.86. Found: C, 41.90; H, 5.70; N, 17.72; S, 13.53. This anomeric mixture was further chromatographed on a silica gel column (hexanes–ether gradient) to effect the quantitative separation of the anomers. The species with R_f 0.40 (1:1 hexanes–ether), assigned as the α anomer (**10**α), was obtained as an oil (1.4g, 16.5%); $[\alpha]_D^{24}$ +251° (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.10 (s, 3 H, COMe), 2.39 (m, 1 H, $J_{1,2a}$ 2.4, $J_{2a,3}$ 4.4, $J_{2a,4}$ 0.44, $J_{2a,2b}$ 14.4 Hz, H-2a), 2.49 (m, 1 H, $J_{1,2b}$ 5.6, $J_{2b,3}$ 5.8 Hz, H-2b), 3.65 (m, 1 H, $J_{3,4}$ 3.9, $J_{4,5a}$ 7.8, $J_{4,5b}$ 5.9 Hz, H-4), 3.34 (s, 3 H, OMe), 4.07 (m, 1 H, $J_{5a,5b}$ 11.5 Hz, H-5a), 4.085 (m, 1 H, H-3), 4.12 (m, 1 H, H-5b), 5.17 (dd, 1 H, H-1); ^{13}C NMR ($CDCl_3$): δ 20.8 (COMe), 41.2 (C-2), 50.9 (C-4), 57.2 (OMe), 64.8 (C-3), 65.1 (C-5), 89.7 (C-1), 170.5 (C = O).

The species with R_f 0.55 (1:1 hexanes–ether) was assigned as the β anomer (**10**β), also obtained as an oil (1.4 g, 16.5%); $[\alpha]_D^{24}$ −188° (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.04 (s, 3 H, COMe), 2.15 (m, 1 H, $J_{1,2a}$ 4.7, $J_{2a,3}$ 10.4, $J_{2a,2b}$ 13.1 Hz, H-2a), 2.48 (m, 1 H, $J_{1,2b}$ 1.6, $J_{2b,3}$ 5.9, $J_{2b,4}$ 0.50 Hz, H-2b), 3.22 (s, 3 H, OMe), 3.45 (m, 1 H, $J_{3,4}$ 7.0, $J_{4,5a}$ 7.5, $J_{4,5b}$ 6.0 Hz, H-4), 4.08 (m, 1 H, H-3), 4.12 (m, 1 H, $J_{5a,5b}$ 11.2 Hz, H-5a), 4.16 (m, 1 H, H-5b), 4.91 (dd, 1 H, $J_{1,3}$ 0.45 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ 20.7 (COMe), 43.6 (C-2), 49.7 (C-4), 56.2 (OMe), 65.9 (C-3), 66.3 (C-5), 88.0 (C-1), 170.4 (C = O).

*1,5-Di-O-acetyl-3-azido-2,3-dideoxy-4-thio-β-*D-erythro-*pentofuranose* (**11**β) *and the corresponding* α *anomer* (**11**α).—Concd H_2SO_4 (0.24 mL) was added to a solution of **9** (1.25 g, 4.1 mmol) in Ac_2O (8 mL) and AcOH (8 mL) at −10°C, and the mixture was stirred at this temperature for 1 h. After addition of NaOAc (3.2 g), the mixture was stirred for 1.5 h at room temperature, then diluted with ice-cold water (150 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined extracts were washed with satd aq $NaHCO_3$, dried, and concentrated to a gum. This material was chromatographed on a silica gel column (hexanes–EtOAc gradient) to give **11** (70%, α:β ratio 1:1); CIMS: *m/z* 277 $[M + NH_4]^+$. Anal. Calcd for $C_9H_{13}N_3O_4S$: C, 41.70; H, 5.02; N, 16.22; S, 12.36. Found: C, 41.50; H, 5.50; N, 15.84; S, 12.01.

Further chromatography on silica gel (hexanes–ethyl ether gradient) gave two components. The fraction with R_f 0.15 (1:1 hexanes–ethyl ether), assigned as the α anomer (**11**α), was obtained as a syrup (35%); $[\alpha]_D^{24}$ +30° (*c* 2.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.08, 2.09 (2 s, 6 H, 2 COMe), 2.48 (m, 1 H, $J_{2a,2b}$ 13.5 Hz, H-2a), 2.49 (m, 1 H, H-2b), 3.65 (m, 1 H, $J_{3,4}$ 3.0 Hz, H-4), 4.18 (m, 1 H, $J_{2a,3}$ 4.0, $J_{2b,3}$ 4.8 Hz, H-3), 4.01 (m, 1 H, $J_{4,5a}$ 8.2, $J_{5a,5b}$ 11.7 Hz, H-5a), 4.06 (m, 1 H, $J_{4.5b}$ 6.1 Hz, H-5b), 6.15 (dd, 1

H, $J_{1,2a}$ 5.1, $J_{1,2b}$ 3.0 Hz, H-1); ^{13}C NMR ($CDCl_3$): δ 20.8, 21.1 (COMe), 39.1 (C-2), 51.7 (C-4), 64.6 (C-3), 64.7 (C-5), 80.1 (C-1), 170.4 (C = O). Anal. Found: C, 42.38; H, 5.16; N, 15.27; S, 11.90. The species with R_f 0.20, assigned as the β anomer (**11**β), was obtained as a syrup (35%); $[\alpha]_D^{24}$ −50° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.05, 2.08 (2 s, 6 H, 2 COMe), 2.28 (m, 1 H, $J_{1,2a}$ 5.2, $J_{2a,3}$ 10.5, $J_{2a,2b}$ 13.5 Hz, H-2a), 2.53 (m, 1 H, $J_{1,2b}$ 1.9, $J_{2b,3}$ 5.6 Hz, H-2b), 3.49 (m, 1 H, H-4), 4.11 (m, 1 H, $J_{3,4}$ 7.0 Hz, H-3), 4.21 (m, 1 H, $J_{4,5a}$ 6.4, $J_{5a,5b}$ 11.2 Hz, H-5a), 4.26 (m, 1 H, $J_{4,5b}$ 7.4 Hz, H-5b), 6.00 (dd, 1 H, H-1); ^{13}C NMR ($CDCl_3$): δ 20.8, 21.1 (COMe), 41.6 (C-2), 50.0 (C-4), 65.2 (C-3), 65.8 (C-5), 78.4 (C-1), 170.0, 170.5 (C = O). Anal. Found: C, 42.77; H, 5.25; N, 15.54; S, 12.05.

3′-Azido-3′-deoxy-4′-thiothymidine (**12**β) *and the corresponding* α *anomer* (**12**α). —$SnCl_4$ (500 μL, 4 mmol) in dichloroethane (10 mL) was added dropwise to a suspension of **11** (0.5 g, 3.86 mmol) and 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine [prepared by refluxing thymine (0.5 g, 4 mmol) and hexamethyldisilazane (HMDS, 15 mL) for 5 h and concentrating the mixture to a gum] in dry dichloroethane (50 mL). The mixture was stirred at room temperature for 5 h, then diluted with CH_2Cl_2 (100 mL), and stirred with satd aq $NaHCO_3$ (50 mL) for 30 min at room temperature. The organic phase was separated, washed several times with water (50 mL), dried ($MgSO_4$), and concentrated to a gum. This gum was taken up in MeOH saturated with NH_3 (50 mL), the mixture was stirred at room temperature for 12 h, then concentrated to give the mixture of anomers (**12**α) and (**12**β), which were separated by column chromatography (99.5:0.5 Et_2O–Me_2CO). The fraction with R_f 0.22 (7:3 $CHCl_3$–Me_2CO), which was isolated as a brown gum by precipitation from EtOAc with hexanes, was identified as the α anomer **12**α (77 mg, 14%); $[\alpha]_D^{25}$ +100° (*c* 0.65, MeOH); ^{1}H NMR (Me_2SO-d_6): δ 2.23 (m, 1 H, $J_{1',2''}$ 7.2, $J_{2'',3'}$ 8.0, $J_{2',2''}$ 13.3 Hz, H-2″), 2.67 (m, 1 H, $J_{1',2'}$ 7.2, $J_{2',3'}$ 5.7 Hz, H-2′), 3.74 (q, 1 H, H-4′), 3.48 (m, 1 H, $J_{4',5'}$ 6.5, $J_{5',5''}$ 11.3 Hz, H-5′), 3.63 (m, 1 H, $J_{4',5''}$ 5.7 Hz, H-5″), 4.15 (q, 1 H, $J_{3',4'}$ 6.4 Hz, H-3′), 6.15 (t, 1 H, H-1′), 7.91 (s, 1 H, H-6), 11.6 (br s, 1 H, NH); ^{13}C NMR (Me_2SO-d_6): δ 12.2 (Me), 38.6 (C-2″), 55.2 (C-3′), 58.0 (C-4′), 62.6 (C-5′), 63.5 (C-1′), 109.9 (C-5), 137.2 (C-6), 150.7 (C-2), 163.6 (C-4). Anal. Calcd for $C_{10}H_{13}N_5O_3S$: C, 42.39; H, 4.62; N, 24.72. Found: C, 42.51; H, 4.93; N, 22.85.

The fraction with R_f 0.28 (7:3 $CHCl_3$–Me_2CO), identified as the β anomer (**12**β), was obtained as a white solid by precipitation from EtOAc with hexanes (76.5 mg, 14%); mp 122–123°C (lit. [5] 120–121°C); $[\alpha]_D^{25}$ −62.4° (*c* 0.5, MeOH); ^{1}H NMR (Me_2SO-d_6): δ 1.80 (s, 3 H, Me), 2.32 (m, 1 H, $J_{1',2''}$ 7.0, $J_{2'',3'}$ 5.0, $J_{2',2''}$ 13.6 Hz, H-2″), 2.46 (m, 1 H, $J_{1',2'}$ 7.5, $J_{2',3'}$ 5.0 Hz, H-2′), 3.65 (m, 2 H, H-5′,5″), 3.39 (q, 1 H, H-4′), 4.51 (q, 1 H, H-3′), 6.17 (t, 1 H, H-1′), 7.85 (s, 1 H, H-6), 11.4 (br s, 1 H, NH); ^{13}C NMR (Me_2SO-d_6): δ 12.3 (Me), 38.4 (C-2′), 55.4 (C-3′), 59.6 (C-4′), 63.0 (C-5′), 64.3 (C-1′), 110.0 (C-5), 136.7 (C-6), 150.7 (C-2), 163.5 (C-4).

3′-Azido-2′,3′-dideoxy-4′-thiouridine (**13**β) *and the corresponding* α *anomer* (**13**β). —The procedure was as described above but using $SnCl_4$ (250 μL, 2 mmol) in dichloroethane (10 mL), **11** (0.5 g, 1.93 mmol) and 2,4-bis(trimethylsilyloxy)pyrimidine [obtained by reacting uracil (0.25 g, 2.25 mmol) with HMDS (8 mL)] in dichloroethane (20 mL). Chromatographic purification of the product on a silica gel column (hexanes–EtOAc gradient) gave two components. The fraction with R_f 0.26 (1:4 hexanes–EtOAc) was identified as the β anomer (**13**β), which was obtained as a white solid by precipita-

tion from EtOAc with hexanes (100 mg, 19%); mp 129–130°C; $[\alpha]_D^{25}$ −75° (*c* 0.2, MeOH); ^{1}H NMR (Me_2SO-d_6): δ 2.36 (m, 1 H, $J_{1',2''}$ 6.8, $J_{2'',3'}$ 5.4, $J_{2',2''}$ 13.4 Hz, H-2″), 2.43 (m, 1 H, $J_{1',2'}$ 7.1, $J_{2',3'}$ 4.0 Hz, H-2′), 3.41 (q, 1 H, H-4′), 3.66 (d, 2 H, H-5′,5″), 4.46 (q, 1 H, H-3′), 5.66 (d, 1 H, $J_{5,6}$ 8.2 Hz, H-5), 6.15 (t, 1 H, H-1′), 8.01 (d, 1 H, H-6), 11.2 (br s, 1 H, NH); ^{13}C NMR (Me_2SO-d_6): δ 38.8 (C-2), 55.4 (C-3′), 60.0 (C-4′), 62.9 (C-5′), 64.3 (C-1′), 102.3 (C-5), 141.4 (C-6), 150.7 (C-2), 163.0 (C-4). Anal. Calcd for $C_9H_{11}N_5O_3S$: C, 40.14; H, 4.12; N, 26.01. Found: C, 40.42; H, 4.22; N, 23.63.

The fraction with R_f 0.31 (1:4 hexanes–EtOAc), identified as the α anomer (**13**α), could only be obtained as a brown gum (80 mg, 16%); $[\alpha]_D^{25}$ +43° (*c* 0.4, MeOH); ^{1}H NMR (Me_2SO-d_6): δ 2.22 (m, 1 H, $J_{1',2''}$ 6.3, $J_{2'',3'}$ 6.3, $J_{2',2''}$ 13.4 Hz, H-2″), 2.68 (m, 1 H, $J_{1',2'}$ 6.9, $J_{2',3'}$ 5.5 Hz, H-2′), 3.47 (m, 1 H, H-5′), 3.55 (m, 1 H, H-5″), 3.70 (q, 1 H, H-4′), 4.25 (q, 1 H, $J_{3',4'}$ 5.5 Hz, H-3′), 5.68 (d, 1 H, $J_{5,6}$ 8.2 Hz, H-5), 6.12 (t, 1 H, H-1′), 8.07 (d, 1 H, H-6), 11.3 (br s, 1 H, NH); ^{13}C NMR (Me_2SO-d_6): δ 39.4, (C-2″), 55.6 (C-3′), 59.4 (C-4′), 62.7 (C-5′), 63.8 (C-1′), 101.9 (C-5), 141.9 (C-6), 150.7 (C-2), 163.0 (C-4).

3′-Azido-2′,3′-dideoxy-5-fluoro-4′-thiouridine (**14**β) *and the corresponding* α *anomer* (**14**α).—The procedure was as described above but using $SnCl_4$ (900 μL, 7.2 mmol) in dichloroethane (40 mL), **11** (1.86 g, 7.2 mmol) and 5-fluoro-2,4-bis(trimethylsilyloxy)-pyrimidine [obtained by reacting 5-fluorouracil (1.6 g, 12.3 mmol) with HMDS (50 mL)] in dry dichloroethane (40 mL). Chromatographic purification of the product on a silica gel column (hexanes–EtOAc gradient), gave two components. The fraction with R_f 0.54 (1:4 hexanes–EtOAc) was identified as the α anomer (**14**α), which was obtained as a gum (412 mg, 20%); $[\alpha]_D^{25}$ + 19.2° (*c* 0.3, MeOH); ^{1}H NMR (Me_2SO-d_6): δ 2.26 (m, 1 H, $J_{1',2''}$ 6.5, $J_{2'',3'}$ 6.5, $J_{2',2''}$ 13.4 Hz, H-2″), 2.66 (m, 1 H, $J_{1',2'}$ 7.0, $J_{2',3'}$ 6.0 Hz, H-2′), 3.46 (m, 1 H, $J_{4',5'}$ 6.5, $J_{5',5''}$ 11.2 Hz, H-5′), 3.59 (m, 1 H, $J_{4',5''}$ 6.1 Hz, H-5″), 3.77 (q, 1 H, H-4′), 4.18 (q, 1 H, H-3′), 6.12 (t, 1 H, H-1′), 8.39 (d, 1 H, $J_{5,6}$ 7.5 Hz, H-6), 11.8 (br s, 1 H, NH); ^{13}C NMR (Me_2SO-d_6): δ 39.3 (C-2″), 55.4 (C-3′), 59.4 (C-4′), 62.6 (C-5′), 63.6 (C-1′), 139.8 ($J_{C,F}$ 231 Hz, C-5), 126.3 ($J_{C,F}$ 35 Hz, C-6), 149.3 (C-2), 156.9 ($J_{C,F}$ 25 Hz, C-4).

The fraction with R_f 0.68 (1:4 hexanes–EtOAc), identified as the β anomer (**14**β), was obtained as a white solid by precipitation from EtOAc with hexanes (144 mg, 7%); $[\alpha]_D^{25}$ −17.5° (*c* 0.3, MeOH); ^{1}H NMR (Me_2SO-d_6): δ 2.33 (m, 1 H, $J_{1',2''}$ 6.0, $J_{2'',3'}$ 7.0, $J_{2',2''}$ 13.4 Hz, H-2″), 2.48 (m, 1 H, $J_{1',2'}$ 7.0, $J_{2',3'}$ 5.2 Hz, H-2′), 3.67 (br t, 2 H, H-5′,5″), 3.39 (q, 1 H, H-4′), 4.48 (q, 1 H, H-3′), 6.10 (t, 1 H, H-1′), 8.41 (d, 1 H, $J_{5,6}$ 7.6 Hz, H-6), 11.9 (br s, 1 H, NH); ^{13}C NMR (Me_2SO-d_6): δ 39.0 (C-2″), 55.3 (C-3′), 60.5 (C-4′), 62.4 (C-5′), 63.9 (C-1′), 139.8 ($J_{C,F}$ 231 Hz, C-5), 125.8 ($J_{C,F}$ 34 Hz, C-6), 149.4 (C-2), 156.9 ($J_{C,F}$ 26 Hz, C-4). Anal. Calcd for $C_9H_{10}FN_5O_3S$: C, 37.63; H, 3.51; N, 24.38. Found: C, 37.57; H, 3.54; N, 23.73.

3′-Azido-5-chloro-2′,3′-dideoxy-4′-thiouridine (**15**β) *and the corresponding* α *anomer* (**15**α).—*tert*-Butyldimethylsilyl trifluoromethanesulfonate (2 mL, 8.7 mmol) was added to a suspension of **10** (2.0 g, 8.7 mmol) and 5-chloro-2,4-bis(trimethyl-silyloxy)pyrimidine [prepared as above from 5-chlorouracil (1.5 g, 10.2 mmol) and HMDS (50 mL)] in dry MeCN (30 mL). The mixture was stirred at room temperature for 1 h and then worked up and deprotected as above. The product was chromatographed on silica gel (1:1 hexanes–EtOAc, then EtOAc) to give two components. The fraction

with R_f 0.41 (EtOAc) was identified as the α anomer (**15**α), which was obtained as a gum (520 mg, 20%); $[\alpha]_D^{25}$ +7.2° (*c* 0.2, MeOH); ^{1}H NMR (Me_2SO-d_6): δ 2.30 (m, 1 H, $J_{1',2''}$ 6.8, $J_{2'',3'}$ 7.1, $J_{2',2''}$ 13.6 Hz, H-2''), 2.65 (m, 1 H, $J_{1',2'}$ 6.8, $J_{2',3'}$ 5.0 Hz, H-2'), 3.78 (q, 1 H, H-4'), 3.45 (m, 1 H, H-5'), 3.56 (m, 1 H, H-5''), 4.20 (q, 1 H, H-3'), 6.105 (t, 1 H, H-1'), 8.40 (s, 1 H, H-6); ^{13}C NMR (Me_2SO-d_6): δ 39.7 (C-2'), 55.7 (C-3'), 60.1 (C-4'), 62.7 (C-5'), 63.9 (C-1'), 107.2 (C-5), 139.3 (C-6), 150.0 (C-2), 159.0 (C-4).

The fraction with R_f 0.55 (EtOAc) was identified as the β anomer (**15**β), which was obtained as a white solid by precipitation from EtOAc with hexanes (230 mg, 9%); mp 166–167°C; $[\alpha]_D^{25}$ −43° (*c* 0.2, MeOH); ^{1}H NMR (Me_2SO-d_6): δ 2.36 (m, 1 H, $J_{1',2''}$ 6.6, $J_{2'',3'}$ 6.0, $J_{2',2''}$ 13.6 Hz, H-2''), 2.55 (m, 1 H, $J_{1',2'}$ 6.6, $J_{2',3'}$ 5.1 Hz, H-2'), 3.70 (d, 2 H, H-5',5''), 3.43 (q, 1 H, H-4'), 4.46 (q, 1 H, $J_{3',4'}$ 5.2 Hz, H-3'), 6.10 (t, 1 H, H-1'), 8.45 (s, 1 H, H-6); ^{13}C NMR (Me_2SO-d_6): δ 39.4 (C-2'), 55.3 (C-3'), 60.8 (C-4'), 62.1 (C-5'), 63.8 (C-1'), 107.2 (C-5), 138.8 (C-6), 149.9 (C-2), 158.6 (C-4). Anal. Calcd for $C_9H_{10}ClN_5O_3S$: C, 35.56; H, 3.32; N, 23.06. Found: C, 36.06; H, 3.44; N, 22.37.

3'-Azido-5-bromo-2',3'-dideoxy-4'-thiouridine (**16**β) *and the corresponding* α *anomer* (**16**α).—*tert*-Butyldimethylsilyl trifluoromethanesulfonate (1 mL, 4.35 mmol) was added to a suspension of **11** (0.8 g, 3.5 mmol) and 5-bromo-2,4-bis(trimethylsilyloxy)pyrimidine [prepared as above from 5-bromouracil (0.8 g, 4.2 mmol) and HMDS (25 mL)] in dry MeCN (20 mL). The mixture was stirred at room temperature for 1 h and then concentrated to dryness. The residue was chromatographed on silica gel (hexanes–EtOAc gradient) to give two components. The fraction with R_f 0.35 (EtOAc) was identified as the α anomer (**16**α), obtained as a gum (82 mg, 21%); $[\alpha]_D^{25}$ +63° (*c* 0.7, MeOH); ^{1}H NMR (Me_2SO-d_6): δ 2.32 (m, 1 H, $J_{1',2''}$ 6.8, $J_{2'',3'}$ 5.2, $J_{2',2''}$ 13.1 Hz, H-2''), 2.66 (m, 1 H, $J_{1',2'}$ 6.8, $J_{2',3'}$ 7.0 Hz, H-2'), 3.79 (q, 1 H, H-4'), 3.45 (m, 1 H, $J_{4',5'}$ 6.9, $J_{5',5''}$ 11.2 Hz, H-5'), 3.56 (m, 1 H, $J_{4',5''}$ 6.1 Hz, H-5''), 4.21 (q, 1 H, $J_{3',4'}$ 5.4 Hz, H-3'), 6.09 (t, 1 H, H-1'), 8.48 (s, 1 H, H-6); ^{13}C NMR (Me_2SO-d_6): δ 39.3 (C-2'), 55.6 (C-3'), 59.9 (C-4'), 62.6 (C-5'), 63.8 (C-1'), 95.6 (C-5), 141.6 (C-6), 150.1 (C-2), 159.0 (C-4).

The fraction with R_f 0.51 (EtOAc) was identified as the β anomer (**16**β), obtained as a white solid by precipitation from EtOAc with hexanes (53 mg, 14%); mp 168–169°C; $[\alpha]_D^{25}$ −52° (*c* 0.4, MeOH); ^{1}H NMR (Me_2SO-d_6): δ 2.33 (m, 1 H, $J_{1',2''}$ 6.2, $J_{2'',3'}$ 6.2, $J_{2',2''}$ 13.6 Hz, H-2''), 2.54 (m, 1 H, $J_{1',2'}$ 6.2, $J_{2',3'}$ 5.0 Hz, H-2'), 3.68 (m, 2 H, H-5', H-5''), 3.40 (q, 1 H, H-4'), 4.46 (q, 1 H, $J_{3',4'}$ 4.0 Hz, H-3'), 6.07 (t, 1 H, H-1'), 8.56 (s, 1 H, H-6); ^{13}C NMR (Me_2SO-d_6): δ 39.4 (C-2), 55.3 (C-3'), 60.8 (C-4'), 62.0 (C-5'), 63.8 (C-1'), 95.8 (C-5), 141.1 (C-6), 150.2 (C-2), 159.0 (C-4). Anal. Calcd for $C_9H_{10}BrN_5O_3S$: C, 31.04; H, 2.90; N, 20.12. Found: C, 31.11; H, 2.77; N, 18.63.

*3'-Azido-2',3'-dideoxy-4-*N*-methoxy-4'-thiocytidine* (**17**β) *and the corresponding* α *anomer* (**17**α).—Toluenesulfonyl chloride (0.4 g, 2.1 mmol), 5'-*O*-acetyl-3'-azido-2',3'-dideoxy-4'-thiouridine (0.5 g, 1.6 mmol) [prepared as above from **11** and 2,4-bis(trimethylsilyloxypyrimidine)], and K_2CO_3 (0.4 g, 2.8 mmol) were dissolved in dry MeCN (25 mL) and the solution was maintained at 90°C for 2 h. The solvent was evaporated and the residue taken up in pyridine (50 mL) and methoxylamine hydrochloride (1.3 g) was added. After 30 min at room temperature, the solution was diluted with water (100 mL) and extracted with EtOAc (100 mL). This extract was washed with dil HCl and with water until neutral, then dried and concentrated to dryness. The residue was dissolved in

MeOH saturated with NH_3, the mixture stirred at room temperature for 12 h, and then concentrated to a gum. The crude product was purified by chromatography (1:1 hexanes–ether) to give two components. The fraction with R_f 0.34 (EtOAc), identified as the β anomer (**17**β), was obtained as a white solid by precipitation from EtOAc with hexanes (90 mg, 14%); mp 86–88°C; $[\alpha]_D^{25}$ +60° (*c* 0.5, MeOH); ^{1}H NMR (Me_2SO-d_6): δ 2.26 (m, 1 H, $J_{1',2''}$ 6.8, $J_{2'',3'}$ 4.2, $J_{2',2''}$ 13.8 Hz, H-2″), 2.35 (m, 1 H, $J_{1',2'}$ 8.5, $J_{2',3'}$ 4.8 Hz, H-2′), 3.61 (m, 2 H, H-5′,5″), 3.36 (dt, 1 H, H-4′), 3.66 (s, 3 H, OMe), 4.48 (q, 1 H, $J_{3',4'}$ 3.0 Hz, H-3′), 5.62 (d, 1 H, $J_{5,6}$ 8.2 Hz, H-5), 6.18 (dd, 1 H, H-1′), 7.28 (s, 1 H, H-6); ^{13}C NMR (Me_2SO-d_6): δ 37.8 (C-2′), 55.3 (C-3′), 59.6 (OMe), 61.0 (C-4′), 63.3 (C-5′), 64.6 (C-1′), 98.2 (C-5), 131.4 (C-6), 143.6 (C-4), 149.2 (C-2).

The fraction with R_f 0.46 (EtOAc) was identified as the α anomer (**17**α), which was obtained as a gum (40 mg, 14%); $[\alpha]_D^{25}$ +6° (*c* 0.5, MeOH); ^{1}H NMR (Me_2SO-d_6): δ 2.14 (m, 1 H, $J_{1',2''}$ 7.2, $J_{2'',3'}$ 7.2, $J_{2',2''}$ 13.5 Hz, H-2″), 2.62 (m, 1 H, $J_{1',2'}$ 7.2, $J_{2',3'}$ 6.1 Hz, H-2′), 3.67 (q, 1 H, H-4′), 3.46 (m, 1 H, $J_{4',5'}$ 6.0, $J_{5',5''}$ 11.2 Hz, H-5′), 3.58 (m, 1 H, $J_{4',5''}$ 6.1 Hz, H-5″), 3.66 (s, 3 H, OMe), 4.16 (dt, 1 H, $J_{3',4'}$ 6.0 Hz, H-3′), 5.63 (d, 1 H, H-5), 6.14 (t, 1 H, H-1′), 8.48 (s, 1 H, H-6); ^{13}C NMR (Me_2SO-d_6): δ 39.0 (C-2′), 55.2 (C-3′), 58.0 (OMe), 61.0 (C-4′), 62.7 (C-5′), 63.5 (C-1′), 97.9 (C-5), 131.9 (C-6), 143.6 (C-4), 149.2 (C-2).

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