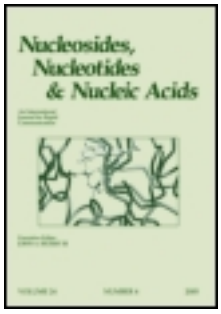

Nucleosides, Nucleotides and Nucleic Acids

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2,2′-Anhydro-4′-Thionucleosides: Precursors for 2′-Azido- and 2′-Chloro-4′-thionucleosides and for a Novel Thiolane to Thietane Rearrangement

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NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 19(9), 1475–1486 (2000)

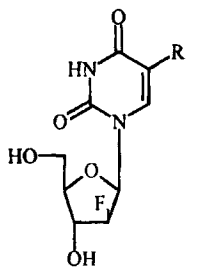
2,2'-ANHYDRO-4'-THIONUCLEOSIDES: PRECURSORS FOR 2'-AZIDO- AND 2'-CHLORO-4'-THIONUCLEOSIDES AND FOR A NOVEL THIOLANE TO THIETANE REARRANGEMENT

J. Allen Miller,* Ashley W. Pugh and G. Mustafa Ullah

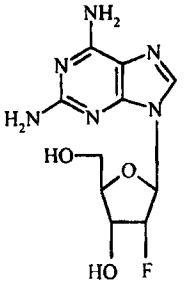
Department of Medicinal Chemistry, Wellcome Research Laboratories, Beckenham, Kent, BR3 3BS, U.K.

ABSTRACT 2,2'-Anhydro-4'-thio-β- and α-nucleosides **9** and **10** have been prepared by an *in situ* 4-thio-1,2-glycal addition route. They undergo ring-opening by azide or chloride ion to give, after deprotection, the 2'-substituted-4'-thionucleosides **13** and **14**, whereas reactions with cyanide or fluoride sources lead to the unsaturated nucleosides **17** or **18**, depending upon conditions. An unexpected and clean rearrangement to the thietane **23** occurs on treatment of uracil derivative **20** with DAST.

Interest in 2'-substituted nucleosides as potential therapeutic agents was stimulated over a decade ago following the discovery, by Watanabe and Fox and their collaborators,[1] of antiviral properties against DNA viruses in a series of 2'-β-fluoronucleosides of general structure **1**. This was heightened by the promise held by the anti-influenza properties of the 2'-α-fluororibosides e.g. **2**,[2] and by the search for 2'-azido relatives of



(1) R=H, Me, Et, I



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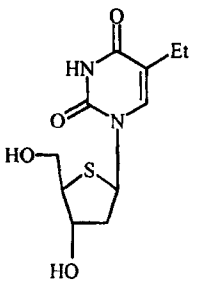

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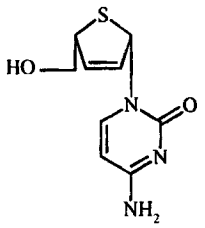

(4)

STRUCTURES (1) – (4)

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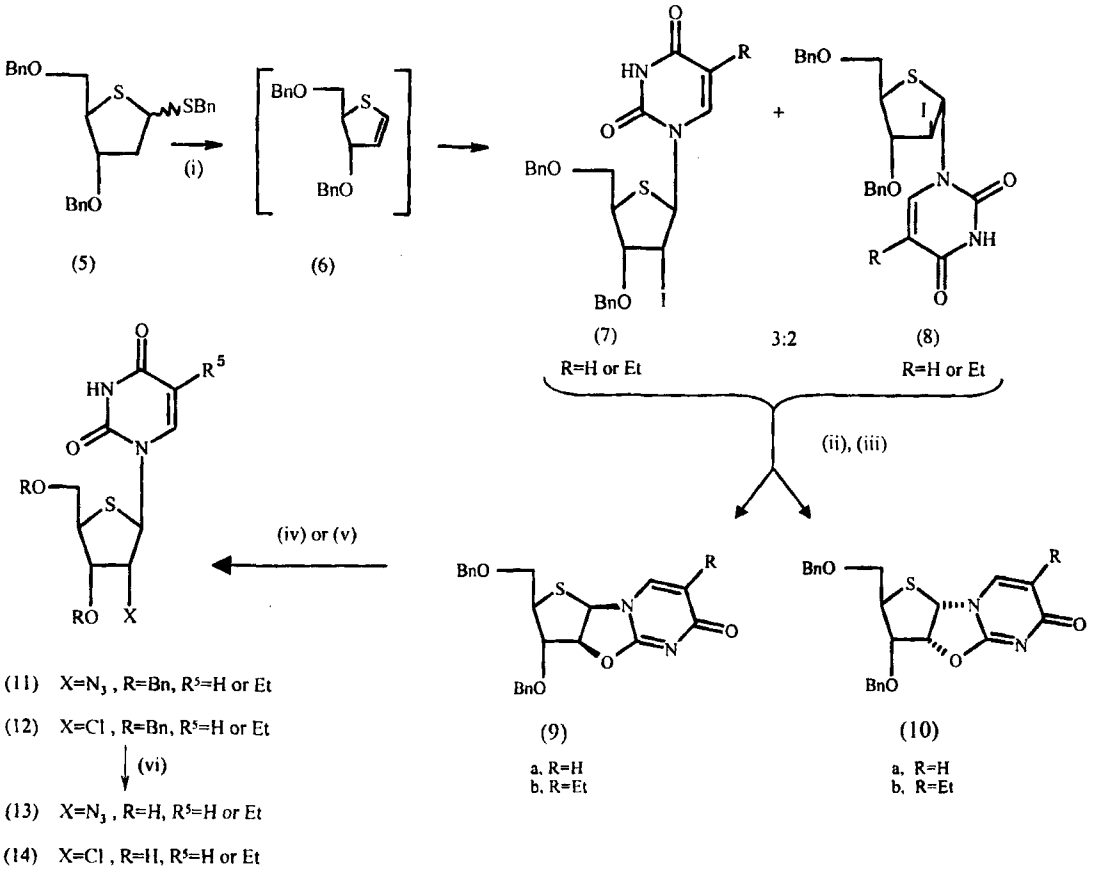
AZT.[3] Like others in the antiviral area, we shared a rekindled interest in 4'-thionucleosides[4] partly on account of the spectacular in vitro and in vivo properties of 4'-thio-β-D-nucleoside **3** against herpes viruses,[5] and of the 4'-thio-β-L-nucleoside **4** against HIV and hepatitis B,[6] and therefore sought a general synthetic access to the corresponding 2'-substituted derivatives of 4'-thionucleosides.

Based on our one-pot synthesis of 4-thio-1,2-glycals and their conversion to 2'-iodo-4'-thionucleosides,[7] it was envisaged that the 2'-iodo compounds could be cyclised to 2,2'-anhydro derivatives, as, for example, achieved by Kim and Misco for furanose nucleosides,[8] and that, in turn, the 2,2'-anhydro-4'-thionucleosides would ring-open under nucleophilic conditions[9] to give 2'-substituted-4'-thionucleosides, our target



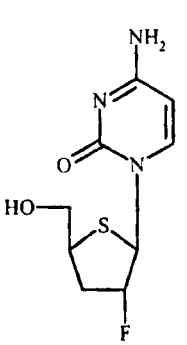
Reagents: (i) ICl, 2,6-di-t-butyl-4-methyl pyridine; ICl, $(TMS)_2$ base (60-70%); (ii) DBU/MeCN, 80°C (100%); (iii) flash chromatography; (iv) NaN_3/DMF, 120°C (for X=N_3); (v) LiCl, $KHSO_4$/DMF, 120°C (for X=Cl); (vi) BBr_3/CH_2Cl_2, -30°C.

SCHEME 1

structures. We report here that this sequence has been achieved with azide or chloride ion as nucleophile, but that with the more basic cyanide or fluoride ion elimination was the dominant reaction.

Scheme 1 depicts the successful sequence leading to the 4'-thionucleosides **13** and **14** from the readily available thioglycoside **5** via the glycal **6** generated *in situ.*[7] Addition of bis-trimethylsilylated uracils and iodine monochloride (ICl) to **6** gives about a 3:2 ratio of 2'-iodo-β-ribonucleosides **7** and 2'-iodo-α-arabinonucleosides **8**,[7] each of which can be cyclised quantitatively, under basic conditions, to the corresponding β- and α-2,2'-anhydro derivatives **9** and **10**, respectively. Fortunately, these anhydronucleosides are readily separable by flash chromatography, allowing their individual characterisation. Largely because 2,2'-anhydro-4'-thionucleosides are relatively novel compounds (the only examples[10] of which we are aware of are all β-), ^{1}H-NMR data[11] on the α- and β-isomers does not allow conclusive distinction between them (e.g. H-1' in the two isomers have similar shifts and the same ^3J values). We therefore used nOe difference spectroscopy[12] to assign **9b** and **10b** in full detail. Thus the 2,2'-anhydro-β-nucleoside **9b** shows strong enhancement of H-2' (12%) when H-1' is saturated, and of H-1' (15%) with very low enhancement at H-3', in the converse study. When H-2' in the α-isomer **10b** is saturated, there is strong enhancement of both H-1' (14%) and H-3' (10%), and correspondingly there is enhancement at H-2' (12%) only, when H-3' is irradiated.

The 2,2'-anhydro-β-nucleosides **9a** and **9b** were then both subjected to ring-opening reactions, initially with azide or chloride ion. The 4'-thionucleosides behaved exactly as predicted from the oxygen analogues[9] and the protected β-nucleosides **11** and **12** were



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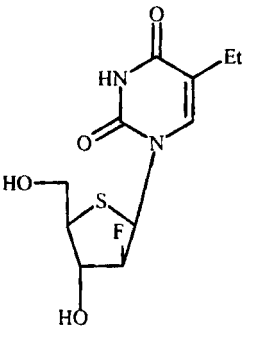
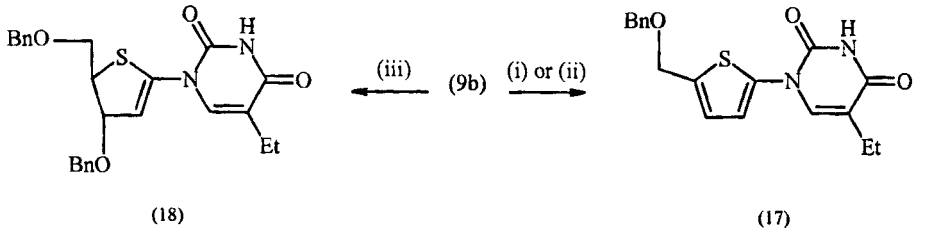


(16)

STRUCTURES (15) & (16)

formed in moderate to good yields. Subsequent debenzylation gave **13** and **14** respectively. Once again nOe studies confirmed the 4'-thio-β-ribonucleoside assignments, and the ribo configuration e.g. with (13, R^5=H).

While this study was in progress, the 3'-deoxy-2'-fluoro-4'-thio-β-ribonucleoside derivative **15** was shown to have weak HIV activity,[13] and then the 2'-fluoro-4'-thio-β-arabinonucleoside **16** was found to be highly active against HSV-1[14]. This encouraged us to try to extend our 2'-substituted series to the corresponding 2'-fluoro or 2'-cyano derivatives. However, our attempts to use 2,2'-anhydro ring-opening for this purpose failed, as shown in Scheme 2. Elimination reactions leading to **17** or **18** were the dominant outcome, a tendancy noted elsewhere for both fluoride[15] and cyanide[16] ion. The formation of ketene acetal **18** has literature precedent.[17]

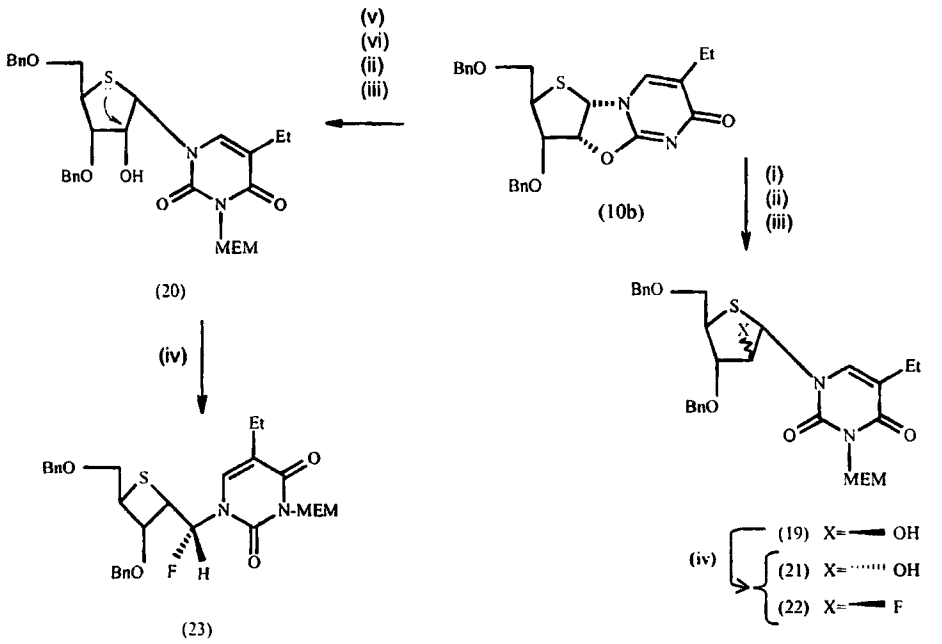


(18) (17)

Reagents: (i) CsF, 18-crown-6/DMF, 120°C; (ii) KCN, 18-crown-6/DMF, 120°C; (iii) TBAF/THF, 120°C (sealed tube) or TBAF, silica/DMF, 22°C.

SCHEME 2

This led us to turn to methodology based on diethylaminosulphur trifluoride (DAST), which, as expected,[18] failed to react with the β-anhydronucleoside **9b**. We then used the α-anhydro series, starting with **10b**, to probe the feasibility of introducing fluorine via 2'-hydroxy compounds derived from anhydro precursors. Standard methodology was used to make the diastereomeric alcohols **19** and **20**, in each of which the 5-ethyluracil N-3 is blocked by a methoxyethoxymethyl (MEM) group – a device recently used by Marquez et al. to avoid participation by the uracil and reformation of the α-anhydro structure.[19] When the β-arabinonucleoside **19** was treated with DAST, in the presence of potassium fluoride, a mixture of the 2'-inverted α-ribonucleoside **21** and the 2'-fluoro-α-arabinonucleoside **22** was obtained in very low yields. Both of these may well have been formed via the 2,2'-anhydro-α-nucleoside **10b**, a likely intermediate given that the "up"



Reagents: (i) NaOAc/DMF, 120°C; (ii) MEM-chloride, Et_3N/THF, reflux; (iii) NaOMe/MeOH, 22°C; (iv) DAST, KF/CH_2Cl_2, 0→20°C; (v) NaOH/EtOH, 80°C; (vi) AcCl/Py, 20°C. (Bn = -CH_2Ph ; MEM = -$CH_2OCH_2CH_2OMe$)

SCHEME 3

2'-OH group in **19** is *anti-* to the base. Others have observed a similar inversion-retention pattern in normal ribonucleosides.[20]

By contrast, the α-ribonucleoside **20** gave only one product under the same conditions. The proton NMR of this compound showed that the protected base was intact, but that there was no characteristic low coupling multiplet in the region (around 6.0–6.3 ppm) associated with the anomeric proton of a 4'-thionucleoside.[11] Instead, there was a double-doublet at δ 6.92 ppm, for which the coupling constants were 48Hz and 5Hz. The larger coupling clearly belongs to a geminal -CHF group, typical values for which lie in the range 45-80Hz. However, the chemical shift of the proton of the -CHF group is far removed from the range of 5.0 to 5.4 ppm consistently observed in 2'-fluoronucleosides, e.g. H-2' in **22** appears at 5.08 ppm ($^2J_{HF}$ 54Hz).

The low-field double-doublet (δ 6.92) is suggestive[21] of a part structure in which N-1 of the uracil is now attached to the newly formed -CHF group. Again nOe difference spectroscopy was highly informative and led to thietane **23** as the structure of the

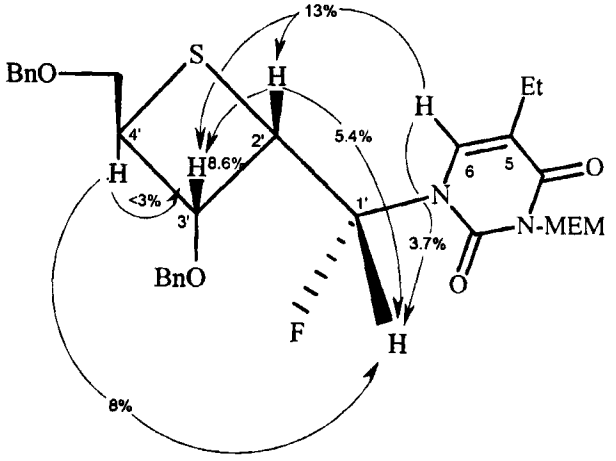
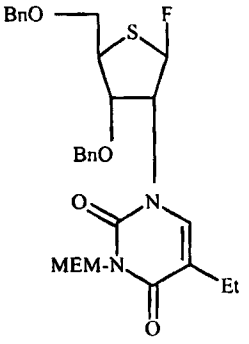


FIGURE: nOe enhancements (⇀) in thietane (23)



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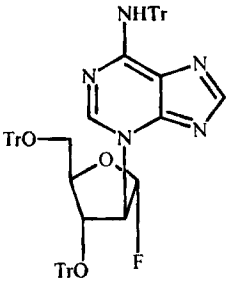
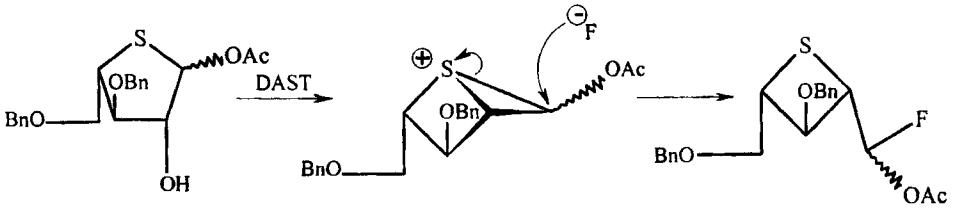


(25)

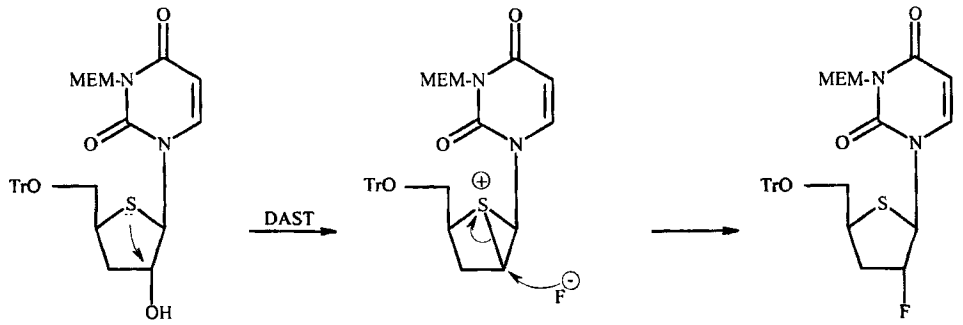
STRUCTURES 24 & 25

rearrangement product – see Figure for full details of the observed nOe enhancements. From these data (see Figure for labelling of atoms), it is clear that H-2' and H-3' lie on the same "up"-face of the thietane, and this is confirmed by the large coupling (^3J 13Hz) between these protons. Moreover, the geminal (^2J 48Hz to H-1') and vicinal (^3J 22Hz to H-2') proton-fluorine coupling constants, together with the lack of fluorine coupling to H-3', confirms the connectivity. This connectivity could also be accommodated in a glycosyl fluoride structure **24**, akin to **25** obtained by Pankiewicz et al.,[25] from a DAST reaction in the adenine series, but neither the ^{1}H-shifts nor the nOe data are compatible with this.



(26) (27)

SCHEME 4

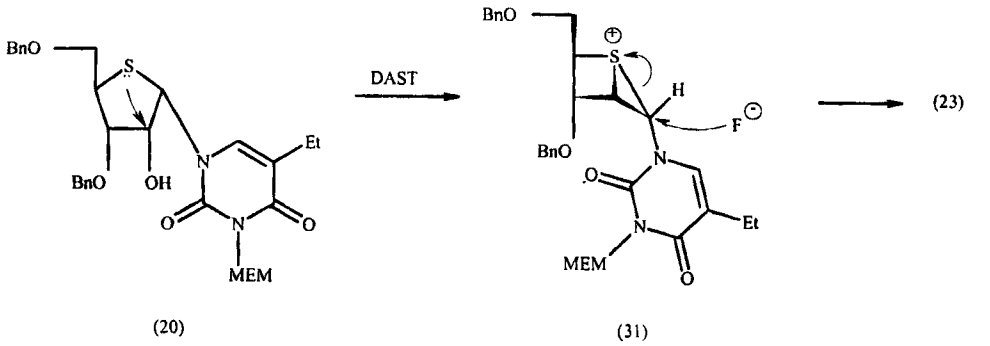


(28) (30) (29)

SCHEME 5

Although apparently novel in the nucleoside field, this kind of ring-contraction of a thiosugar has been described by Jeong et al.[26] These authors reported the DAST-mediated conversion of the acetoxythiolane **26** into the thietane **27** (see Scheme 4), but no supporting structural evidence for the latter was provided. A plausible mechanism for these ring-contractions arises from the work of Marquez et al.,[19] on DAST-mediated fluorinations in which the -OH to -F substitution was achieved with retention of configuration, e.g. **28** to **29**, and not with the anticipated inversion (see Scheme 5).[20,27] The authors postulated the involvement of a bicyclo[2.1.0]episulphonium intermediate **30**,[19] in which the adjacent thietane -CH_2- is unsubstituted, and hence regiospecific bridgehead attack by fluoride is unhindered, and leads to the 'thermodynamic' product **29**, with retention of configuration at C-2'. In the present case (see Scheme 6), and that reported by Jeong et al.,[26] the adjacent thietane position is substituted by a benzyloxy group, which obstructs bridgehead attack by fluoride and therefore attack at the thiirane -CH- now competes, and leads to the 'kinetic' products **23**, or **27**, respectively. The stereochemistry of our bicyclic intermediate **31** is determined by the "down" orientation

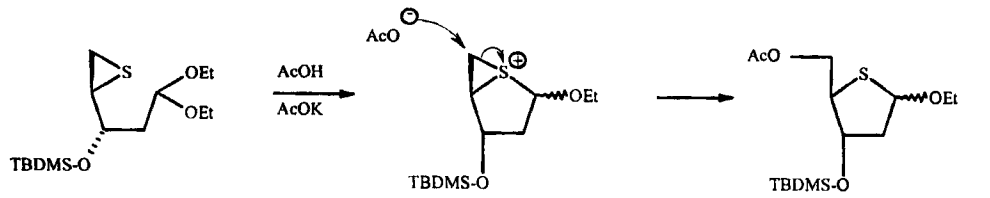
of the free 2'-OH group in **20**, and thereafter the new stereogenic centre at C-1' in **23** would be expected to have a single configuration – as is observed, and is depicted in Scheme 6.



(20) (31)

SCHEME 6

A related situation has been described by Uenishi et al.,[28] in which attack by acetate at the thiirane -CH_2- in the bicyclo[3.1.0]episulphonium ion **32** is preferred to bridgehead attack (shielded by the TBDMS group) and explains the formation of the 2'-deoxy-4'-thioribose derivative **33**, as in Scheme 7.



(32) (33)

(TBDMS = ^{t}BuMe$_2$Si-)

SCHEME 7

When tested in standard in vitro screens against HSV-1, HSV-2 and HCMV, none of the deprotected nucleosides **13** or **14** showed any anti-viral activity.

EXPERIMENTAL

Preparation of 2,2'-anhydro-4'-thio-α-and β-nucleosides 9b and 10b

A solution of a mixture of the β- and α-2,2'-iodonucleosides **7b** and **8b** (6.34g, 10.96 mmol) in dry dichloromethane (700 ml) was treated with DBU (3.34g, 21.94 mmol)

under nitrogen, at 40°C. The reaction mixture was heated at reflux (~6 hours). After the reaction mixture cooled, water (500 ml) was added, the organic layer was separated and the water layer was reextracted with dichloromethane (2x50 ml). The combined organic extracts were washed with brine solution and dried ($MgSO_4$) and, after removing the solvent, crude product was purified by flash column chromatography, eluting with ethyl acetate. The first component, 2,2'-anhydro-4'-thio-β-nucleoside **9b** (2.4g, 48.6%), was a white solid, m.p 194.5-195.5°C; (Found: C, 66.52; H, 5.81; N, 6.15%; M^+, 450; $C_{25}H_{26}N_2O_4S$ requires C, 66.64; H, 5.82; N, 6.22%; M^+, 450.53); ^{1}H-NMR ($CDCl_3$) 1.15 (t, 3H, $C\underline{H}_3CH_2$), 2.45 (q,2H, $C\underline{H}_2CH_3$), 3.3 and 3.45 (2xdd, 2H, CH_2O), 3.78 (dd, appears as t, 1H, H-4'), 4.4 (dd, 2H, $OC\underline{H}_2Ph$), 4.6 (br s, 1H, H-3'), 4.65 (s, 2H, $OC\underline{H}_2Ph$), 5.45 (d, 1H, H-2'), 6.0 (d, 1H, H-1'), 7.0 (tight t, 1H, H-6), 7.2-7.4 (m, 10H, 2x Ph) ppm. The second eluate was 2,2'-anhydro-4'-thio-α-nucleoside **10b** (2.1g 42.5%), a white solid, m.p 179-180°C; (Found: C, 66.35; H, 5.82; N, 6.15%; M^+, 450); ^{1}H-NMR ($CDCl_3$) 1.15 (t, 3H, $C\underline{H}_3CH_2$), 2.4 (q, 2H, $C\underline{H}_2CH_3$), 3.6-3.85 (m, 5H, 2x CH_2O and H-3'), 4.05 (dd, 1H, H-4'), 4.55 (dd, 2H, $OC\underline{H}_2Ph$), 4.65 (dd, 2H, $OC\underline{H}_2Ph$), 5.45 (dd, 1H, H-2'), 5.8 (d, 1H, H-1'), 7.0 (tight t, 1H, H-6), 7.3 (m, 10H, 2x Ph) ppm.

General procedure for ring opening of 2,2'anhydro-4'-thionucleosides by nucleophiles : Compound (11, R^5=Et)

In a typical reaction, a solution of 2,2'-anhydro-4'-thio-β-nucleoside **9b** (450mg, 1.0 mmol) in dry DMF (15 ml) was treated with sodium azide (324mg, 4.98 mmol) under nitrogen, at 120-140°C. The reaction mixture was stirred and heated until reaction was complete (~48 hours), and, after cooling to room temperature, water (50 ml) was added and the reaction mixture was extracted with ethyl acetate (4x50 ml). The combined organic extracts were washed with brine solution and dried ($MgSO_4$). After removal of the solvent, the crude product was purified by flash column chromatography, eluting with ethyl acetate-light petroleum (b.p. 40-60°C) (1:1), and 2'-azido-4'-thionucleoside (11, R^5=Et) (211mg, 42.8%) was isolated as a syrup. (Found: $(M+1)^+$, 494; $C_{25}H_{27}N_5O_4S$ requires M, 493.56); IR, (neat) 2106 (s, N_3); ^{1}H-NMR ($CDCl_3$) 0.95 (t, 3H, $C\underline{H}_3CH_2$), 2.15 (q, 2H, $C\underline{H}_2CH_3$), 3.65 (m, 3H, OCH_2 and H'-4), 3.98 (dd, 1H, H-2'), 4.2 (dd, appears as t, 1H, H'-3), 4.55 (s, 2H, $OC\underline{H}_2Ph$), 4.6 (dd, 2H, $OC\underline{H}_2Ph$), 6.22 (d, 1H, H-1'), 7.3 (m, 10H, 2x Ph), 7.78 (s, 1H, H-6) and 9.6 (br s, 1H, NH) ppm.

General procedure for debenzylation of 3',5'-di-*O*-benzyl protected 4'-thionucleosides.

In a typical example, 3',5'-di-*O*-benzyl-2'-azido-4'-thionucleoside (11, R^5=Et) (211mg, 0.428 mmol) was dissolved in dry dichloromethane (10 ml) and the solution stirred at -60°C, under nitrogen. Boron tribromide (1M solution in CH_2Cl_2) (2.5 ml, 2.5 mmol) was syringed into the reaction mixture through a rubber septum, and the reaction mixture was stirred for four hours over a temperature range of -60°C to -30°C. The reaction was quenched by adding methanolic ammonia at -30°C. Solvent was removed and residues were stirred in methanol (20 ml). Undissolved salt was removed by filtration and the filtrate was concentrated before purification by flash column chromatography, eluting first with ethyl acetate-light petroleum (b.p. 40-60°C) (7:3) to remove the less polar impurities, followed by ethyl acetate to elute the product, 2'-azido-4'-thionucleoside (13, R^5=Et) (73mg, 54.5%) isolated as a white solid m.p 74-75.5°C; (Found: $(M+1)^+$, 314; $C_{11}H_{15}N_5O_4S$ requires M, 313.34); ^{1}H-NMR (CD_3OD) 1.1 (t, 3H, $C\underline{H}_3CH_2$), 2.35 (q, 2H, $C\underline{H}_2CH_3$), 3.45 (dd, 1H, H-4'), 3.7 (2xdd, 2H, $C\underline{H}_2OH$), 4.1 (dd, 1H, H-2'), 4.4 (t, 1H, H-3'), 4.8 (br s, 2H, 2x OH), 6.2 (d, 1H, H-1'), 8.1 (s, 1H, H-6) ppm.

Reaction of N-MEM protected 4'-thio-α-nucleoside 20 with DAST.

4'-Thio-α-nucleoside **20** (100mg, 0.18 mmol) was dissolved in dry dichloromethane (5 ml) and the reaction mixture stirred at -78°C, under nitrogen. DAST ($118.75x10^{-3}$ mL, 0.9 mmol) was syringed into the reaction mixture at -78°C, and stirred for 1 hour. Dry potassium fluoride (5-fold excess) was added at -78°C and the reaction mixture was slowly allowed to warm-up to room temperature, and stirred for 1 hour. Sodium hydrogen carbonate solution was carefully added and the reaction mixture was extracted with chloroform (3x5 ml). After removing the solvent, crude product was purified by preparative tlc, running in ethyl acetate-light petroleum (b.b. 40-60°C) (1:1) and the thietane **23** (~80 mg) was isolated as an oil; (Found: $(M+1)^+$, 559; $C_{29}H_{35}FN_2O_6S$ requires M, 558.64); ^{1}H-NMR ($CDCl_3$) 1.15 (t, 3H, $C\underline{H}_3CH_2$), 2.35 (q, 2H, $C\underline{H}_2CH_3$), 3.30 (s, 3H, OCH_3), 3.5-3.8 (m, 6H, 5'-CH_2 and OCH_2CH_2O), 3.92 (2x dd, *J* 22.5, 13.5 and 5 Hz, 1H, H-2'), 4.2 (dd, 1H, H-4'), 4.4-4.5 (s + dd overlapping, 5H, H-3' and 2x $OC\underline{H}_2Ph$), 5.4 (dd, 2H, OCH_2N), 6.9 (dd, *J* 48 and 5 Hz, 1H, H-1'), 7.2-7.4 (m, 11H, H-6 and 2x Ph) ppm. ^{1}H-NMR (d_6-DMSO) revealed H-6 as an isolated singlet at δ 7.7 and allowed nOe studies on H-6 to be carried out.

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