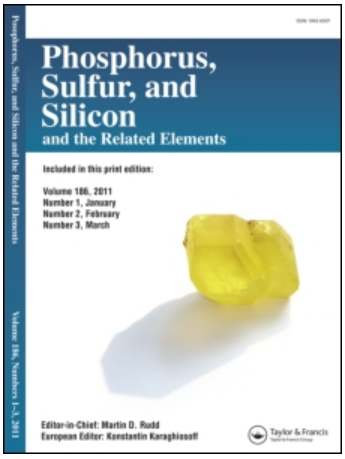

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SYNTHESIS AND REACTIONS OF NEW 3′-DEOXY-5′-THIOALKYL-β-D-*ERYTHRO*-PENTOFURANOSYLTHYMINES AND RELATED ANALOGUES

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5′-Thioalkyl derivatives ***4–6*** *were prepared from direct displacement of the 5′-*O*-tosylate analogue* ***3*** *in moderate yields. Oxidation of* ***4*** *and* ***5*** *with 1.0 aq. MMMP gave the sulfones* ***7*** *and* ***8****, respectively, while similar treatment with 0.5 eq. MMPP or soudium periodate,* ***4*** *afforded the sulfoxide* ***9****. Treatment of* ***4*** *and* ***5*** *with diphenyl sulphite furnished the 2,2′ anhydro analogues* ***10*** *and* ***11****, which gave the 2′-ethylsulfanyl derivetives* ***12*** *and* ***13*** *on treatment with sodium ethanethiolate, respectively. Similarly,* ***10*** *gave the 2′-azido derivative* ***14****. Compound* ***17*** *might obtained from* ***13****, via the episulphonium ion* ***16****. Basic hydrolysis of* ***10*** *furnished the arabino analogue* ***15****.*

Keywords: 3′-Deoxythymines; antitumor agents; sulfones and sulfoxide; sulfur participation; thioalkylation

Nucleosides antimetabolites play an important role in the field of chemotherapy for cancer and viral diseases[1] because of their ability to interefere with DNA synthesis by inhibiting DNA polymerase.[2] Chemical modification of the sugar moiety in such nucleosides recently have received considerable attention.[3–8] Since the discovery of Cordycepin,[9] a naturally-occuring nucleoside antibiotic with antibactrial and antitumor activity,[10] its identification as 3′-deoxyadenosine[11] has increased in recent years along with interest in the chemistry and biology of 3′-deoxynucleosides in general. A number of related nuleoside analogues have been prepared.[12–14] Breslow et al.[15] have investigated the propreties of 2′,5″ linked oligomers as well as the synthesis of protected

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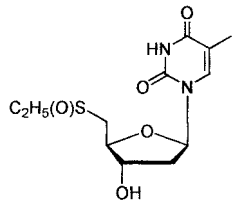
phosphoramidites of 3′-deoxyadenosine and 3′-deoxy-5-methyluridine for use in solid phase oligonucleotide synthesis. On the other hand, it has been reported that among several 5′-thioalkyl nucleosides, 5′-*S*-ethyl-5′-thiothymidine **1** was found to be a noncompetitive inhibitor for



1

the human tumor cell lines,[16,17] the metachondrial, and cytoplasmic isozymes (% inhibition of rat M-TK and C-TK = 7.0 μM and 4.0 μM, respectively, in comparison to the thymidine itself 7.2 μM and 2.25 μM, respectively).[16] Recently some 5′-thioalkyl nucleosides were found to exhibite activity as antitumor or antiviral agents.[18–20] Agrofoglio et al.[21] have reported the anticancer activity of 5′-*S*-ethyl 3′-deoxy-5′-thiothymidine with a moderate activity (IC_{50} = 90.2′ μM). As a part of our program[22–30] on exploring the syntheses and biological evaluation of new thiosugars and their nucleosides, we report here the synthesis of 3′-deoxynucleosides carrying modified sugar moieties bearing different thioalkyl groups and their chemical behavior toward some nucleophiles as promising anticancer or antiviral candidates.

RESULTS AND DISCUSSION

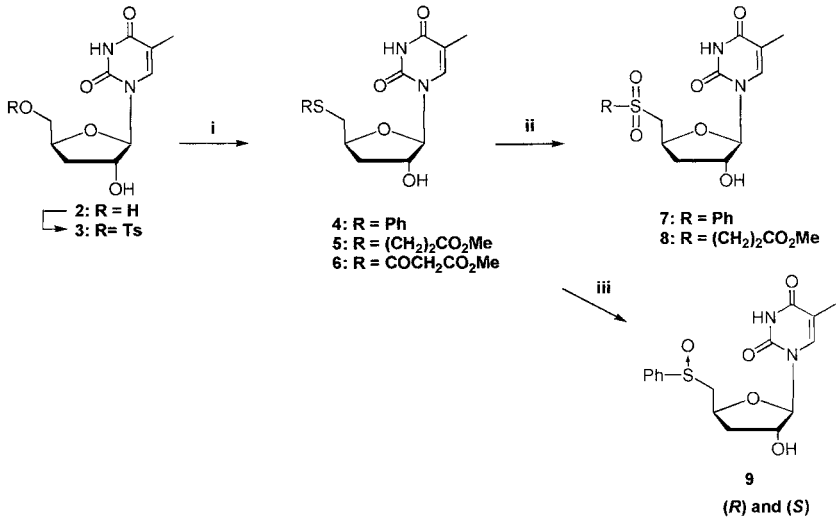
The starting material 3′-deoxy-5′-*O*-toluene-*p*-sulphonyl-β-D-*erythro*-pentofuranosylthymine (**3**)[23] was prepared in our laboratory in 45% from tosylation of the previously reported free nucleoside **2**.[15] Reaction of the tosylate **3** with sodium thiophenolate, methyl 3-mercaptopropionate, and methyl 3-mercapto-2-oxo-propionate in DMF at 70°C gave, after chromatographic separation, the 5′-alkylthiothymine derivatives **4–6** in 52, 59, 56% yield respectively. The structures of **4–6** were identified from the ^{1}H NMR spectra, which showed common pattern of spectral features. The chemical shifts of H-1′ in compounds **4–6** (δ_H 5.69, 5.66, and 5.68) with the corresponding $J_{1',2'}$ values (2.0, 2.1, and 2.4 Hz respectively) clearly indicated that these compounds have the β-configuration and are in agreement with the *N*-type conformation of the sugar moiety. The signals at δ_H 4.60, 4.57, and 4.58,

respectively, as doublet of doublets of doublets were attributed to H-2′ ($J_{2',3'(exo)} < 1.0$ Hz, $J_{2',3''(endo)}$ 4.5, 4.4, and 4.2 Hz, respectively) while the multiplets at δ_H 4.38, 4.37, and 4.39, with $J_{4',5''}$ values of 4.6, 4.5, and 4.5 Hz, respectively, were assigned to H-4′. The ^{1}H NMR spectra revealed the typical *erythro* configuration where H-3″ protons were appeared as doublets of doublets at δ_H 2.10, 2.08, and 2.11 ($J_{3'',4'}$ 4.5 Hz), and H-3′ protons were appeared as doublets of doublets of doublets at δ_H 1.67, 1.64, and 1.65 ($J_{3',4'}$ 10.2, 10.0, and 10.2 Hz, $J_{gem}\sim$13.5 Hz respectively. Furthermore, the assignments of H-3′ and H-3″ were determined from the irradiation experiments of H-2′ which revealed a clear decoupling with these protons and as a result of this irradiation, the former protons in **4–6** were enhanced to the doublet of doublets. The thioalkyl groups at C-5′ were fully analyzed.

Next, we studied the oxidation of **4** and **5** by different methods. Thus, boiling with 1.0 mmol equivalent of magnesium monoperoxyphthalate hexahydrate (MMPP) in CH_2Cl_2/MeOH, by using the procedure of Agrofoglio and coworkers,[21] resulted in the formation of the sulfone derivatives **7** (75%), and **8** (69%), respectively. Similarly, oxidation of **4** with 0.50 mmol equivalent under the same condition furnished, after chromatography, the diastereomeric mixture (*R*:*S*) of sulfoxide **9** (70%). Altenatively, **9** was obtained in 65% yield, by following Walker et al.[31] procedure, from treatment of **4** with sodium periodate in aqueous MeOH between 0–23°C for 18 h. The structures of **7–9** was secured by the ^{1}H NMR and mass spectra [FABMS m/z: 367, 399, 383 $(MNa)^+$ respectively] (Scheme 1).

When the 5′-thioalkyl derivatives **4** and **5** were heated with a fourfold excess of diphenyl sulphite, by applying Reese et al.[32] procedure, at 156°C ±1 in dimethylacetamide solution and catalytic amount of 1-methylimidazole then the products treated with triethylamine, it resulted in the formation of the oily 2,2′-anhydro analogues **10** and **11** respectively. The formation of such anhydro derivatives of thymidine and uridine and their yield percentages were discussed extensively by many laboratories using different reagents (references cited by Walker et al.[31]). The structures of **10** and **11** were characterized by their spectral analysis. The H-1′ in the ^{1}H NMR spectra of **10** and **11** were appeared as doublets at δ_H 5.97 and 5.96 with $J_{1',2'}$ 5.5 Hz and 5.7 Hz, respectively, indicating for the *arabino* configuration. These data are in consistent with those of the 2,2′-anhydro-1-[3-deoxy-5-*O*-(4-methoxytrityl)-β-D-*threo*pentofuranosyl] thymine, prepared by Lin et al.[33]

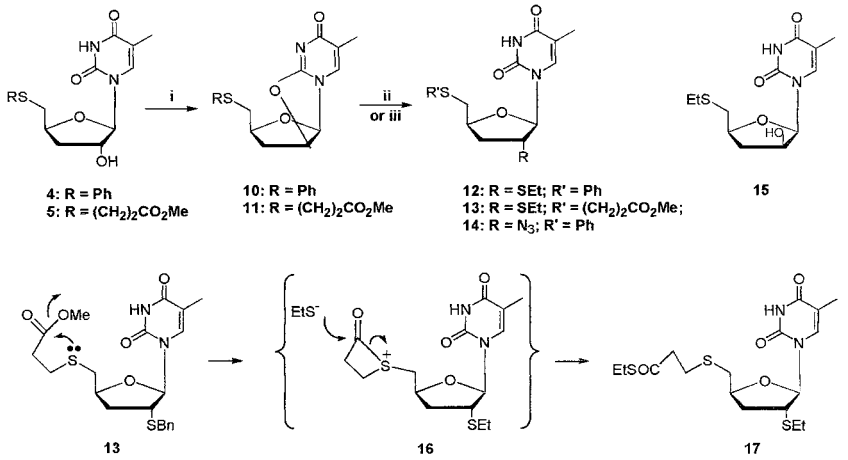
Treatment of **10** with sodioum ethanethiolate in MeOH at 23°C for 16 h gave, after chromatography, a foamy solid tentatively identified as **12** (87%). Interestingly, under the above condition, **11** gave two products, separated by chromatography. The higher running product



SCHEME 1 Conditions and reagents: (i) PhSNa, $HS(CH_2)_2CO_2Me$ or $NaSCH_2COCO_2Me$/DMF, 70°C, 3 h; (ii) MMPP, 1.0 eq., CH_2Cl_2/MeOH, reflux, 3 h; (iii) a) 0.5 eq. MMPP/as in **ii**, b) 0.50 M $NaIO_4$, aq. MeOH, 0–23°C, 18 h.

was assigned from the ^{1}H NMR and mass spectra [FABMS m/z 441 $(MNa)^+$] and identified as **17** (32%), while the second eluted product was the major, characterized as **13** (63%) (Scheme 2). Compounds **12**, **13**, and **17** showed almost a similar pattren of spectra, especially the thioethyl group which appeared as quartets at δ_H 2.46, 2.44, and 2.45 for methylenes of SEt group, respectively, meanwhile triplets at δ_H 1.18, 1.15, and 1.17 were asigned for the ethyl groups, respectively. The signals at δ_H 2.67, and 1.27 in **17** were attributed for the methylene and ethyl groups of the propionate moiety. The formation of **17** might be explained in terms of the intramolecular displacement of the methoxy group of **13**, via sulfur participation, leading to the episulphonium intermediate **16** which was ready for attack by the thiolate ion furnishing **17** as shown in Scheme 2.

Heating of **10** with lithium azide in DMF at 23°C afforded, after chromatography, the azide derivative **14** (70%). The appearance of a strong IR absorption at 2100 cm^{-1} was atrributed to the azido group. The structure of **14** was elucidated by the spectral analysis. The H-1′ signal appeared in the ^{1}H NMR spectrum as a doublet at δ_H 6.21 ($J_{1',2'}$ 2.3 Hz), while H-2′ appeared as doublets of doublet of doublets at δ_H 4.87 ($J_{2',3''(exo)} < 1.0$ Hz, $J_{2',3'\ (endo)}$ 4.4 Hz). The doublet and doublet of doublets of doublets at δ_H 2.09 ($J_{3'',4'}$ 4.3 Hz) and 1.60 ($J_{3',4'}$ 10.4 Hz, J_{gem} 13.5 Hz) were assigned to the *exo* proton H-3″ and the *endo*-proton



SCHEME 2 Conditions and reagents: (i) diphenyl sulphite, 156°C, Ac-NMe, 1-Me-imidazole; 1 h, then → 0°C, Et_3N; (ii) EtSNa, MeOH, 23°C, 16 h; (iii) LiN_3, DMF, 23°C, 16 h.

H-3′, respectively. These J values give an stereochemical proof of the *erythro* configuration.

Hydrolysis of **10** with 1N NaOH in 50% EtOH at 23°C, followed by neutralization with HOAc to pH 7.0 gave the *arabino* analogue **15** in 83% yield. The structural feature of **15** was depicted from the ^{1}H NMR and mass spectra. The $J_{1',2'}$ coupling in **15** (7.3 Hz) is in agreement with the *arabino*-configuration[34] of the glycosidic bond. The anticancer activity of compounds **4–8** and **12–14** is under investigation.

In conclusion, the electronic mobility, the lipophilic propreties and molecular distribution of the 2′-, 5′-alkylthio and 2′-azido groups in the new synthesized compounds have been adjusted to be close to those biological active substances reported previously and might show significant anticancer activity.

EXPERIMENTAL

General Procedure

Melting points are uncorrected. ^{1}H NMR spectra were determined at 300 and 600 MHz with TMS as internal standard and on a δ scale in ppm. 3-Nitrophenol (NBOH) or glycerol were used in the EI and FAB mass measurements as matrices. Some molecular ions were detected by doping the sample with Na^+ ion.

General Procedure for Preparation of 5′-S-Alkyl-5′-thio Derivatives of 3′-Deoxy-β-D-erythro-pentofuranosylthymine

A solution of **3** (1.00 g, 2.60 mmol) in DMF (15 ml) and the mercapto precursor (4.00 mmol) was heated at 70°C, with stirring, for 3 h under argon atmosphere. After cooling, the solution was evaporated under vaccum to dryness and the residue was partitioned between CH_2Cl_2 (3×20 ml) and water (20 ml). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness to give brown product. This was dissolved in CH_2Cl_2 (2 ml) and poured onto SiO_2 column (20 g) and eluted, in gradient, with MeOH (0-10%) and CH_2Cl_2 to give the desired products.

*1-(3-Deoxy-5-S-phenyl-5-thio-β-*D-erythro*pentofuranosyl)thymine* ***(4)***. From sodium thiophenolate (0.53 g). Yield: 0.45 g (52%), as a foam. ^{1}H NMR (DMSO-d_6/D_2O): δ 7.52 (s, 1H, H-6); 7.32–7.19 (m, 3H, Ar); 6.97 (m, 2H, Ar); 5.69 (d, 1H, $J_{1',2'} = 2.0$ Hz, H-1′); 4.60 (ddd, 1H, $J_{2',3'} < 1.0$ Hz, $J_{2',3''} = 4.5$ Hz, H-2′); 4.38 (m, 1H, $J_{4',5''} = 4.6$ Hz, H-4′); 2.79 (dd, 1H, $J_{4',5'} = 6.5$ Hz, H-5′); 2.69 (dd, 1H, $J_{5',5''} = 12.0$ Hz, H-5″); 2.10 (dd, 1H, $J_{3'',4'} = 4.5$ Hz, H-3″); 1.92 (s, 3H, C_5—Me); 1.67 (ddd, 1H, $J_{3',4'} = 10.2$ Hz, $J_{3',3''} = 13.5$ Hz, H-3′). Anal. calcd for $C_{16}H_{18}N_2O_4S$ (334.4): C, 57.47; H, 5.43; N, 8.38. Found: C, 57.28; H, 5.35; N, 8.19. MS: m/z (FAB) 335 $(MH)^+$.

*3-(3-Deoxy-β-*D-erythr*pentofuranosylthymin-5-ylsulfanyl)-propionic acid methyl ester* ***(5)***. From methyl 3-mercaptopropionate (0.43 g). Yield: 0.53 g (59%), m.p. 142-146°C. ^{1}H NMR (DMSO-d_6/D_2O): δ 7.50 (s, 1H, H-6); 5.66 (d, 1H, $J_{1',2'} = 2.1$ Hz, H-1′); 4.57 (ddd, 1H, $J_{2',3'} < 1.0$ Hz, $J_{2',3''} = 4.4$ Hz, H-2′); 4.37 (m, 1H, $J_{4',5''} = 4.5$ Hz, H-4′); 3.61 (s, 3H, OMe); 3.12 (t, 2H, J = 6.7 Hz, $COCH_2$); 2.76 (dd, 1H, $J_{4',5'} = 6.3$ Hz, H-5′); 2.65 (dd, 1H, $J_{5',5''} = 12.1$ Hz, H-5″); 2.52 (t, 2H, J = 6.7 Hz, SCH_2); 2.08 (dd, 1H, $J_{3'',4'} = 4.5$ Hz, H-3″); 1.91 (s, 3H, C_5—Me); 1.64 (ddd, 1H, $J_{3',4'} = 10.0$ Hz, $J_{3',3''} = 13.2$ Hz, H-3′). Anal. calcd for $C_{14}H_{20}N_2O_6S$ (344.4): C, 48.83; H, 5.85; N, 8.13. Found: C, 48.66; H, 5.76; N, 8.02. MS: m/z (FAB) 345 $(MH)^+$.

*3-(3-Deoxy-β-*D-erythro*pentofuranosylthymin-5-ylsulfanyl)-2-oxo-propionic acid methyl ester* ***(6)***. From methyl 3-mercapto-2-oxo-propionate (0.62 g). Yield: 0.52 g (56%), as a foam. ^{1}H NMR (DMSO-d_6/D_2O): δ 7.50 (s, 1H, H-6); 5.68 (d, 1H, $J_{1',2'} = 2.4$ Hz, 4.58 (ddd, 1H, $J_{2',3'} < 1.0$ Hz, $J_{2',3''} = 4.2$ Hz, H-2′); 4.39 (m, 1H, $J_{4',5''} = 4.4$ Hz, H-4′); 4.01 (s, 2H, SCH_2); 3.70 (s, 3H, OMe); 2.80 (dd, 1H, $J_{4',5'} = 6.2$ Hz, H-5′); 2.71 (dd, 1H, $J_{5',5''} = 12.0$ Hz, H-5″); 2.11 (dd, 1H, $J_{3'',4'} = 4.3$ Hz, H-3″); 1.92 (s, 3H, C_5—Me); 1.65 (ddd, 1H, $J_{3',4'} = 10.2$ Hz, $J_{3',3''} = 13.1$ Hz,

H-3′). Anal. calcd for $C_{14}H_{18}N_2O_7S$ (358.4): C, 46.92; H, 5.06; N, 7.82. Found: C, 46.75; H, 7.74; N, 7.73. MS: m/z (FAB) 359 $(MH)^+$.

*1-(3-Deoxy-5-*S*-phenylsulphonyl-5-thio-β-*D*-*erythro*pentofuranosyl)-thymine (**7**).* A solution of magnesium monoperoxyphthalate hexahydrate (MMPP) (0.30 g, 0.61 mmol, 1.0 eq.) in CH_2Cl_2 (7 ml) was added to a solution of **4** (0.20 g, 0.60 mmol) in CH_2Cl_2/MeOH (9:1, v/v, 10 ml). The solution was heated under reflux, with stirring, for 3 h. After cooling, the solution was filtered (hyflo) and evaporated to dryness at >40°C. The residue was purified on a SiO_2 column (5.00 g) using CH_2Cl_2—MeOH (9:1, v/v) as eluent to give **7** (0.16 g, 75%) as a white solid, m.p. 218–221°C. ^{1}H NMR (DMSO-d_6/D_2O): δ 7.53 (d, 1H, J = 1.2 Hz, H-6); 7.39–7.29 (m, 3H, Ar); 7.03 (m, 2H, Ar); 5.70 (d, 1H, $J_{1',2'} = 2.1$ Hz, H-1′); 4.63 (ddd, 1H, $J_{2',3'} < 1.0$ Hz, $J_{2',3''} = 4.3$ Hz, H-2′); 4.39 (m, 1H, $J_{4',5''} = 4.5$ Hz, H-4′); 2.81 (dd, 1H, $J_{4',5'} = 6.5$ Hz, H-5′); 2.76 (dd, 1H, $J_{5',5''} = 12.1$ Hz, H-5″); 2.14 (dd, 1H, $J_{3'',4'} = 4.4$ Hz, H-3″); 1.91 (d, 3H, J = 1.2 Hz, C_5—Me); 1.68 (ddd, 1H, $J_{3',4'} = 10.0$ Hz, $J_{3',3''} =$ 13.4 Hz, H-3′). Anal. calcd for $C_{16}H_{18}N_2O_6S$ (366.4): C, 52.45; H, 4.95; N, 7.65. Found: C, 52.34; H, 4.86; N, 7.49. MS: m/z (FAB) 367 $(MNa)^+$.

*3-(3-Deoxy-β-*D*-*erythro*pentofuranosylthymin-5-ylsulfonyl)-propionic acid methyl ester **(8)**.* From **5** (0.20 g, 0.58 mmol) and magnesium monoperoxyphthalate (MMPP) (0.29 g, 0.58 mmol, 1.0 eq.) in the manner described for **7**. Yield: .0.15 g (69%) as a white solid, m.p. 168–170°C. ^{1}H NMR (DMSO-d_6/D_2O): δ 7.52 (d, 1H, J = 1.2 Hz, H-6); 5.72 (d, 1H, $J_{1',2'} = 2.0$ Hz, H-1′); 4.61 (ddd, 1H, $J_{2',3'} < 1.0$ Hz, $J_{2',3''} =$ 4.6 Hz, H-2′); 4.48 (m, 1H, $J_{4',5''} = 4.5$ Hz, H-4′); 3.75 (s, 3H, OMe); 3.25 (m, 2H, $COCH_2$); 2.99 (m, 2H, SO_2CH_2); 2.90 (dd, 1H, $J_{4',5'} = 6.2$ Hz, H-5′); 2.80 (dd, 1H, $J_{5',5''} = 12.0$ Hz, H-5″); 2.10 (dd, 1H, $J_{3'',4'} = 4.5$ Hz, H-3″); 1.91 (d, 3H, J = 1.2 Hz, C_5—Me); 1.66 (ddd, 1H, $J_{3',4'} = 10.1$ Hz, $J_{3',3''} = 13.5$ Hz, H-3′). Anal. calcd for $C_{14}H_{20}N_2O_8S$ (376.4): C, 44.68; H, 5.36; N, 7.44. Found: C, 44.49; H, 5.28; N, 7.26. MS: m/z (FAB) 399 $(MNa)^+$.

*(*R*)- and (*S*)-Sulfoxides of 1-(3-Deoxy-5-*S*-phenyl-5-thio-β-*D*-erythro-pentofuranosyl) thymine (**9**).*

Method A. From **4** (0.20 g, 0.60 mmol) and MMPP (0.15 mg, 0.30 mmol, 0.50 eq.) in the manner described for **7**. The product was purified on a SiO_2 column (5.00 g), using CH_2Cl_2—MeOH 4:1, v/v) as eluent. Yield: 0.15 g, (70%), m.p. 176–179°C. ^{1}H NMR (DMSO-d_6/D_2O): δ 7.54 (s, 1H, H-6); 7.40–7.31 (m, 3H, Ar); 7.03 (m, 2H, Ar); 5.74 (d, 1H, $J_{1',2'} = 2.0$ Hz, H-1′); 4.67 (ddd, 1H, $J_{2',3'} < 1.0$ Hz, $J_{2',3''} = 4.4$ Hz, H-2′); 4.47 (m, 1H, $J_{4',5''} = 4.5$ Hz, H-4′); 2.95 (dd, 1H, $J_{4',5'} = 6.5$ Hz, H-5′); 2.81 (dd, 1H, $J_{5',5''} = 12.0$ Hz, H-5″); 2.12 (dd, 1H, $J_{3'',4'} = 4.5$ Hz, H-3″); 1.90 (s, 3H,

C_5—Me); 1.70 (ddd, 1H, $J_{3',4'} = 10.0$ Hz, $J_{3',3''} = 13.4$ Hz, H-3′). Anal. calcd for $C_{16}H_{18}N_2O_5S$ (350.4): C, 54.85; H, 5.18; N, 7.99. Found: C, 54.62; H, 5.02; N, 7.78. MS: m/z (FAB) 351 $(MH)^+$; 373 $(MNa)^+$.

Method B. To a stirred solution of **4** (0.30 g, 0.90 mmol) in water (13 ml) and MeOH (13 ml) at 0°C was added a 0.05 M aq. solution of soudium metaperiodate (35 ml) . The reaction mixture was then left to warm to room temperature (23°C) for 18 h, followed by purification of the product by column chromatography (SiO_2, CH_2Cl_2/MeOH 4:1, v:v) to afford **9** (0.21 g, 65%). All the physical properties are identical to those of the authetic sample prepared in method a.

Formation of 2,2′-anyhro derivatives of 1-(5-S-*alkyl-5-thio-3-dexoy-β*-D-threo*pentofuranosyl)thymines.* A mixture of **4** or **5** (1.49 mmol), diphenyl sulphite (1.39 g, 5.96 mmol), 1-methylimidazole (0.03 ml, 0.31 mmol), and *N*,*N*-dimethylacetamide (15 ml) was stirred at 156 ± 1°C. After 1 h, the products were cooled to 0°C and then poured, with stirring, into a cooled (ice-bath) mixture of Et_3N (8 ml) and water (15 ml). After almost 40-45 min, where the temperature raised to 23°C, the resulting solution was extracted with CH_2Cl_2 (4 × 14 ml). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to dryness. The residue was chromatographed on a SiO_2 column (10.00 g) using CH_2Cl_2—MeOH 9:1, v/v) as eluent to give **10** or **11** as a gumy product.

2,2′-Anhydro-1-(3′-deoxy-5′-S-*phenylsulphonyl-5′-thio-β*-D-threo*pentofuranosyl)thymine **(10)**.* From **4** (0.50 g). Yield: 0.33 g (70%). ^{1}H NMR (DMSO-d_6): δ 7.52 (s, 1H, H-6); 7.32-7.19 (m, 3H, Ar); 6.97 (m, 2H, Ar); 5.97 (d, 1H, $J_{1',2'} = 5.5$ Hz, H-1′); 4.98 (m, 1H, H-2′); 4.38 (m, 1H, $J_{4',5''} = 4.6$ Hz, H-4′); 2.79 (dd, 1H, $J_{4',5'} = 6.5$ Hz, H-5′); 2.69 (dd, 1H, $J_{5',5''} = 12.0$ Hz, H-5″); 2.10 (m, 1H, H-3″); 1.92 (s, 3H, C_5-Me); 1.67 (m, 1H, H-3′). MS ($C_{16}H_{16}N_2O_3S$): m/z (FAB) 317 $(MH)^+$; 339 $(MNa)^+$.

3-(2,2′-Anhydro-3-deoxy-β-D-threo*pentofuranosylthymin-5-ylsulfonyl)-propionic acid methyl ester (**11**).* From **5** (0.51 g). Yield: 0.29 g (59%). ^{1}H NMR (DMSO-d_6): δ 7.50 (s, 1H, H-6); 5.96 (d, 1H, $J_{1',2'} = 5.7$ Hz, H-1′); 4.87 (m, 1H, H-2′); 4.48 (m, 1H, H-4′); 3.61 (s, 3H, OMe); 3.14 (t, 2H, J = 6.7 Hz, $COCH_2$); 2.79 (dd, 1H, $J_{4',5'} = 6.3$ Hz, H-5′); 2.65 (dd, 1H, $J_{5',5''} = 12.1$ Hz, H-5″); 2.52 (t, 2H, J = 6.7 Hz, SCH_2); 2.08 (dd, 1H, $J_{3'',4'} = 4.5$ Hz, H-3″); 1.91 (s, 3H, C_5-Me); 1.64 (ddd, 1H, $J_{3',4'} = 10.0$ Hz, $J_{3',3''} = 13.2$ Hz, H-3′). MS ($C_{14}H_{18}N_2O_5S$): m/z (FAB) 327 $(MH)^+$; 349 $(MNa)^+$.

1-(3′-Deoxy-2′-S-*ethyl-5′*-S-*phenyl-2′,5′-dithio-β*-D-erythro*pentofuranosyl)thymine (**12**).* Ethanethiol (0.37 ml, 5.04 mmol), NaH (60%, dispersion in mineral oil, 0.06 g, 2.52 mmol) and dry DMF (10 ml) were

stirred together at 23°C for 5 min. Compound **10** (0.40 g, 1.26 mmol) was added to the resulting solution, and the reactants were stirred at 23°C. After 18 h, solid CO_2 (0.60 g) was added, and the products were evaporated (<100°C) under reduced pressure. The residue was poured onto SiO_2 column using, in gradient, MeOH (0–10%) and CH_2Cl_2 as eluent to give **12** (0.42 g, 87%) as a pure foamy solid. ^{1}H NMR (DMSO-d_6: δ 10.28 (s, 1H, NH); 8.10 (s, 1H, H-6); 7.34-7.22 (m, 3H, Ar); 6.96 (m, 2H, Ar); 6.50 (d, 1H, $J_{1',2'} = 3.5$ Hz, H-1′); 5.19 (ddd, 1H, $J_{2',3'} < 1.0$ Hz, $J_{2',3''} = 4.1$ Hz, H-2′); 4.32 (m, 1H, H-4′); 2.80 (dd, 1H, $J_{4',5'} = 6.4$ Hz, H-5′); 2.74 (dd, 1H, $J_{5',5''} = 12.8$ Hz, H-5″); 2.46 (q, 2H, J = 7.4 Hz, S*CH*$_2$CH$_3$); 2.09 (dd, 1H, $J_{3'',4'} = 4.3$ Hz, H-3″); 1.89 (s, 3H, C_5—Me); 1.60 (ddd, 1H, $J_{3',4'} = 10.4$ Hz, $J_{3',3''} = 13.5$ Hz, H-3′); 1.18 (t, 3H, SCH$_2$*CH*$_3$). Anal. calcd for $C_{18}H_{22}N_2O_3S_2$ (378.5): C, 57.12; H, 5.86; N, 7.40. Found: C, 56.93; H, 5.78; N, 7.21. MS: m/z (FAB) 379 $(MH)^+$.

*3-(3-Deoxy-2-*S*-ethyl-2,5-dithio-β-*D-erythro*pentofuranosylthymin-5-ylsulfanyl)-propionic acid methyl ester (**13**) and 3-(3-deoxy-2-S-ethyl-2, 5-dithio-β-*D-erythro*pentofuranosyl-thymin-5-ylsulfanyl)-propionic acid thioethyl ester (**17**).* From **11** (0.40 g, 1.22 mmol), NaH (0.06 g, 2.44 mmol) and ethanethiol (0.36 ml, 4.88 mmol) in the manner described for **12**. After working up the reaction mixture, the crude products were chromatographed on a SiO_2 column (10 g), using, in gradient, MeOH (0–5%) and CH_2Cl_2 as eluent to give first a foam, tentatively identified as **17** (0.16 g, 32%). ^{1}H NMR (DMSO-d_6): 10.20 (s, 1H, NH); 7.96 (br s, 1H, H-6); 6.42 (d, 1H, $J_{1',2'} = 2.3$ Hz, H-1′); 4.49 (m, 1H, H-2′); 4.29 (m, 1H, H-4′); 3.01 (t, 2H, J = 6.6 Hz, COCH$_2$); 2.75 (dd, 1H, $J_{4',5'} = 6.2$ Hz, H-5′); 2.62 (dd, 1H, $J_{5',5''} = 12.0$ Hz, H-5″); 2.67 (q, 2H, J = 7.1 Hz, COS*CH*$_2$CH$_3$); 2.50 (t, 2H, J = 6.6 Hz, SCH$_2$); 2.44 (q, 2H, J = 7.2 Hz, S*CH*$_2$CH$_3$); 1.98 (dd, 1H, $J_{3'',4'} = 4.5$ Hz, H-3″); 1.91 (s, 3H, C_5—Me); 1.57 (ddd, 1H, $J_{3',4'} = 10.2$ Hz, $J_{3',3''} = 13.3$ Hz, H-3′); 1.27 (t, 3H, COSCH$_2$*CH*$_3$); 1.15 (t, 3H, SCH$_2$*CH*$_3$). Anal. calcd for $C_{17}H_{26}N_2O_4S_3$(418.6): C, 48.78; H, 6.26; N, 6.69. Found: C, 48.52; H, 6.17; N, 6.39. MS: m/z (FAB) 441 $(MNa)^+$.

Further elution with CH_2Cl_2—MeOH (93:7, v:v) afforded a foamy solid, tentatively identified as **13** (0.26 g, 63%). ^{1}H NMR (DMSO-d_6): δ 10.23 (s, 1H, NH); 8.06 (s, 1H, H-6); 6.43 (d, 1H, $J_{1',2'} = 2.3$ Hz, H-1′); 4.50 (m, 1H, H-2′); 4.37 (m, 1H, H-4′); 3.60 (s, 3H, OMe); 3.06 (t, 2H, J = 6.5 Hz, COCH$_2$); 2.79 (dd, 1H, $J_{4',5'} = 6.0$ Hz, H-5′); 2.67 (dd, 1H, $J_{5',5''} = 12.0$ Hz, H-5″); 2.52 (t, 2H, J = 6.5 Hz, SCH$_2$); 2.45 (q, 2H, J = 7.0 Hz, S*CH*$_2$CH$_3$); 2.02 (dd, 1H, $J_{3'',4'} = 4.4$ Hz, H-3″); 1.89 (s, 3H, C_5—Me); 1.63 (ddd, 1H, $J_{3',4'} = 10.0$ Hz, $J_{3',3''} = 13.1$ Hz, H-3′); 1.17 (t, 3H, SCH$_2$*CH*$_3$). Anal. calcd for $C_{16}H_{24}N_2O_5S_2$(388.5): C, 49.47; H, 6.23; N, 7.21. Found: C, 49.27; H, 6.14; N, 7.00. MS: m/z (FAB) 389 $(MH)^+$.

2′-Azido-2′,3′-dideoxy-5′-S-*phenyl-5′-thio-β*-D-erythro*pentofuranosylthymine (**14**).* A solution of **10** (0.35 g, 1.11 mmol) in *N*,*N*-dimethylacetamide (10 ml) and LiN_3 (0.10 g, 0.32 mmol) was stirred at 23°C for 16 h under nitrogen atmosphere. After cooling the solution was evaporated to dryness at temperature <40°C and the residue was partitioned between water (20 ml) and CH_2Cl_2 (3 × 15 ml). The combined organic extracts were dried (Na_2SO_4), filetered and evaporated and the residue was poured onto short SiO_2 column and eluted CH_2Cl_2—MeOH (95:5, v/v) to give **12** (0.28 g, 70%)) as a foam. ^{1}H NMR (DMSO-d_6): δ 10.12 (s, 1H, NH); 7.52 (s, 1H, H-6); 7.39–7.29 (m, 3H, Ar); 7.03 (m, 2H, Ar); 6.21 (d, 1H, $J_{1',2'} = 2.3$ Hz, H-1′); 4.87 (ddd, 1H, $J_{2',3'} < 1.0$ Hz, $J_{2',3''} = 4.4$ Hz, H-2′); 4.27 (m, 1H, $J_{4',5''} = 4.6$ Hz, H-4′); 2.84 (dd, 1H, $J_{4',5'} = 6.4$ Hz, H-5′); 2.79 (dd, 1H, $J_{5',5''} = 12.0$ Hz, H-5″); 2.21 (dd, 1H, $J_{3'',4'} = 4.0$ Hz, H-3″); 1.91 (d, 3H, J = 1.2 Hz, C_5-Me); 1.72 (ddd, 1H, $J_{3',4'} = 10.1$ Hz, $J_{3',3''} = 13.5$ Hz, H-3′). Anal. calcd for $C_{16}H_{17}N_5O_3S$(359.4): C, 53.47; H, 4.77; N, 19.49. Found: C, 54.26; H, 4.70; N, 19.29. MS: m/z (FAB) 360 $(MH)^+$.

1-(3-Deoxy-2-S-*ethyl-5-S-phenyl-β*-D-threo*pentofuranosyl)thymine (**15**).* A mixture of **10** (0.30 g, 0.95 mmol), 1 M NaOH (2.4 ml), and 50% EtOH (20 ml) was stirred at 23°C for 3 h. The solution was neutralized with HOAc/EtOH (1:1, v/v) to pH 7.0 and then evaporated to dryness. The residue was co-evaporated with EtOH (4 × 20 ml) and the residue was chromatographed on a SiO_2 column (10 g) by eluting, in gradient, with MeOH (0–10%) and CH_2Cl_2 to give **15** (0.26 g, 83%) as a foam. ^{1}H NMR (DMSO-d_6/D_2O): δ 7.58 (s, 1H, H-6); 7.37–7.24 (m, 3H, Ar); 7.01 (m, 2H, Ar); 6.30 (d, 1H, $J_{1',2'} = 7.3$ Hz, H-1′); 4.71 (m, 1H, H-2′); 4.46 (m, 1H, H-4′); 2.81 (dd, 1H, $J_{4',5'} = 6.3$ Hz, H-5′); 2.70 (dd, 1H, $J_{5',5''} = 12.1$ Hz, H-5″); 2.20 (m, 1H, H-3″); 1.91 (s, 3H, C_5-Me); 1.75 (m, 1H, H-3′). Anal. calcd for $C_{16}H_{18}N_2O_4S$ (334.4): C, 57.47; H, 5.43; N, 8.38. Found: C, 57.13; H, 5.32; N, 8.08. MS: m/z (FAB) 357 $(MNa)^+$.

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