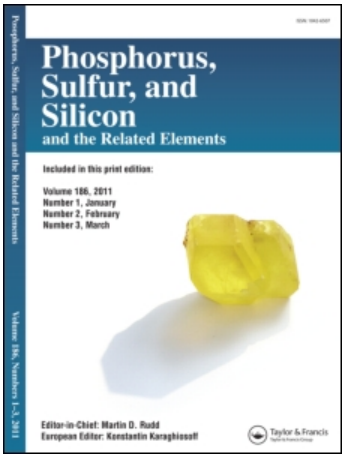

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Some 2'-Modified 4'-Thionucleosides via Sulfur Participation and Synthesis of Thio-Azt from 4'-Thiofuranoid 1,2-Glycal

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SOME 2′-MODIFIED 4′-THIONUCLEOSIDES VIA SULFUR PARTICIPATION AND SYNTHESIS OF THIO-AZT FROM 4′-THIOFURANOID 1,2-GLYCAL

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ThioAZT ***14*** *was synthesized in eight steps from D-arabinose derivative* ***4*** *via the new thiofuranoid 1,2-glycal, 5-O-Acetyl-1,2,4-trideoxy-1,4-epithio-3-O-p-toluenesulfonyl-D-*threo*-pent-1-enitol (****8****). Ribosylation of the thiosugar* ***6*** *with thymine afforded regioselectively the nucleoside* ***16****. Treatment of* ***16*** *with sodium azide in hot DMF gave, after spontaneous intramolecular displacment, the 2′-azido-xylo derivative* ***18****, which furnished the free nucleoside* ***19*** *on treatment with methanolic ammonia. Similarly, treatment of* ***16*** *with sodium ethylthiolate in boiling methanol led to inversion in configuration and gave, after several intramolecular displacments, via the sulfur participation, the 2′,3′-diethylthiolate-ribo derivative* ***23****. Deblocking of* ***23*** *with methanolic ammonia afforded the free nuclaoside* ***24****.*

Keywords: Antiviral agents; ribosylation; sulfur paricipation; thioAZT; 4′-thiofuraniod glycal

There has been increasing interest in recent years in the synthesis of nucleosides from sugar precursors in which the furanose ring atom is replaced by a sulfur atom and led to promising antiviral or antitumor nucleosides, such as 4′-thiothymidine (**1**), 4′-thio-2′deoxyxytidine (**2**),[1] and 4′-thioangustmycin C (**3**).[2] This interest has stimulated the synthesis of this class of nucleosides, especially those modified at

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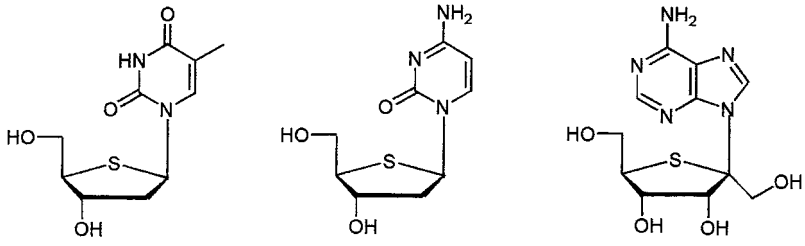

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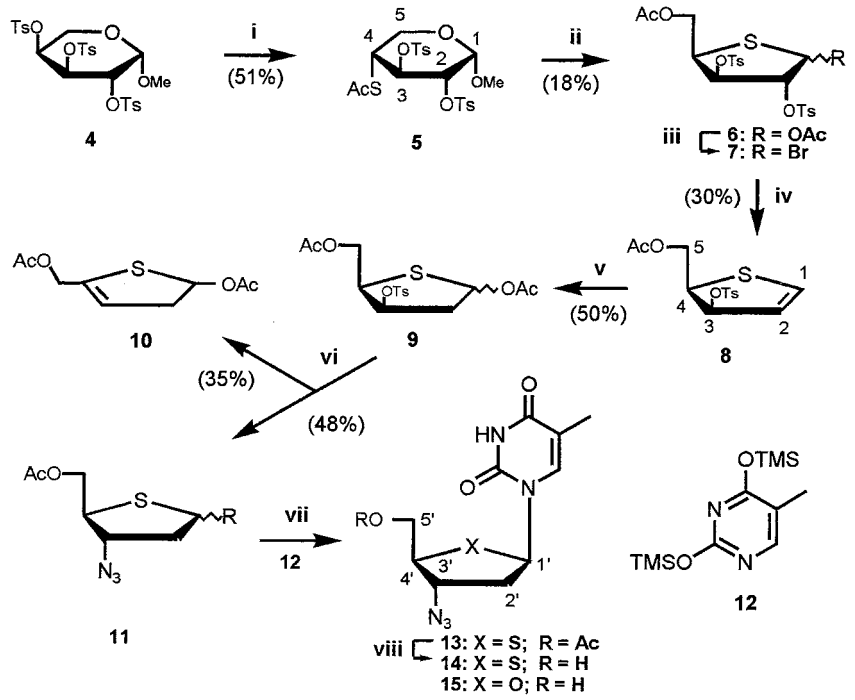
the sugar moiety.[3–7] 3′-Azido-3′-deoxy-thymidine **15** (AZT)[8,9] is the most widely used drug against infection by human immunodeficiency virus type 1 (HIV-1). Much interest is being shown in the synthesis of the thio analogue **14** with potentially higher activity and lower toxicity.[8,10,11] Recently, the 4′-thio analogue **14** has been synthesized by many laboratories[12] via different routes. We now report an alternative synthesis of **14** via the new thiofuranoid glycal **8**, a potentially useful intermediate for the synthesis of other deoxynucleoside analogues and in anomeric selective nucleoside synthesis.[13] Recently, some examples of synthesis of protected 4-thio-1,2-glycals were described via different methods.[14,15]

RESULTS AND DISCUSSION

Potassium thioacetate reacted selectively with the readily avalaible tritosylate **4**[16] to give the crystalline *xylo* thioacetate **5** (51%). The thioacetyl group (SAc) in **5** was identified from the IR spectrum (ν_{max} 1695 cm^{-1}), since the structure of **5** was identified from the ^1H NMR spectrum. The H-1 appeared as a doublet at δ 4.98 with $J_{1,2} = 3.2$ Hz, indicating the α-anomer, while the large coupling ($J_{2,3} = J_{3,4} = 10.0$ Hz), was evidance for the *xylo*-configuration. Acetolysis of **5** with a mixture of acetic anhydride, acetic acid and sulfuric acid gave, after chromatography, the 1,5-di-*O*-acetyl-2,3-di-*O*-*p*-toluenesulfonyl-4-thio-D-xylofuranose (**6**) as a syrupy mixture of the α and β anomers (18%). The low yield of the recyclized product **6** arose from the fact that many products can be formed during this reaction due to the presence of the sulfur atom and the good leaving sulfonate groups. It is well known that 4-thioxylose and its adenine nucleoside was first prepared by Reist et al.[17] from the ring contraction of methyl 2,3-dibenzoyl-4-*S*-4-thio-α-D-xylopyranoside and recently was prepared by Marshal et al.[18] Obviously, the ring contraction to the furanose **6** occured in the similar manner to that observed by Reist et al. as well as in the 4-thioribose series.[19] The structure of **6** (β-anomer) was confirmed from the ^1H NMR

spectrum which showed H-1 as a doublet at δ 6.17 with $J_{1,2} = 3.0$ Hz, while the other J values ($J_{2,3} = 1.5$ Hz, $J_{3,4} = 2.7$ Hz) are typical for the *xylo*-configuration. Treatment of **6** with hydrogen bromide in the presence of acetic acid at 20°C gave the unstable bromo compound **7** which was converted directly into the furanoid thioglycal **8** (oil, 30%) by the action of zinc dust in acetic acid at 80°C. The glycal **8** is stable enough under nitrogen at −5°C to be purified by chromatography. The structure of glycal was characterized from the ^{1}H NMR and mass spectra. The anomeric proton and H-2 appeared as doublet and doublet of doublets at δ 6.43 ($J_{1,2} = 3.5$ Hz) and δ 5.67 ($J_{2,3} = 6.7$ Hz), respectively, which are in agreement with the results obtained by Miller et al.[14a] The H-3 appeared as a doublet of doublets with $J = 5.7$ Hz, which is indication of the *thereo*-configuration. Addition of sodium acetate and *p*-toluenesulfonic acid at 20°C to the thioglycal **8** furnished the 2-deoxy-4-thiofuranose diacetate **9** as an anomeric mixture (50%). The ^{1}H-NMR spectrum of **9** revealed the anomer ratio (α:β) to be about 2:1, since H-1 (α-anomer, from an HMBC experiment) appeared as a doublet of doublets at δ 6.20 ($J_{1,2a} = 5.6$ Hz; $J_{1,2b} = 2.7$ Hz) and similarly for H-1 (β-anomer) at δ 6.31 ($J_{1,2a} = 5.6$ Hz, $J_{1,2b} = 1.6$ Hz). The H-3 was characterized as a doublet of doublet of doublets at δ 4.90 with J values (6.3 Hz, 5.4 Hz, and difficult to measure $J_{2,3}$ since H-2 is a multiplet) which suggested the *thereo*-configuration of **9**β. Both elimination and substitution occurred when **9** was heated with lithium azide in DMF to give the olefin **10** (oil, 35%) as well as the desired azide **11** (oil, 48%). The structure of **11** (α,β-mixture) was elucidated from the ^{1}H NMR and mass spectra, which showed close resemblance to the authentic sample prepared by Villa et al.[20] Condensation of **11** with the silylated thymine **12**, by applying the modified Vorbrüggen method,[21,22] afforded, after purification by chromatography, the acetylated nucleoside **13** as an amorphous solid (36%, α,β mixture). Deacetylation of **13** with methanolic ammonia gave, after chromatographic purification (Et_2O-Me_2CO 99.5:0.5) and precipitation from ethyl acetate-hexane, the 3′azido-3′-deoxy-4′-thymidine (ThioAZT) (**14**) (m.p. 121–123°C, Lit.[20] 122–123°C) in 21% yield (Scheme 1). The β-configuration of **14** was confirmed by NOE experiment.[23] Thus, irradiation of the H-1′signal led to enhancement of the signal for H-4′ (2.9%) and irradiation of the H-6 signal resulted in the enhancement of the signals for H-3′ (3.0%) an H-5′,5″ (1.2%).

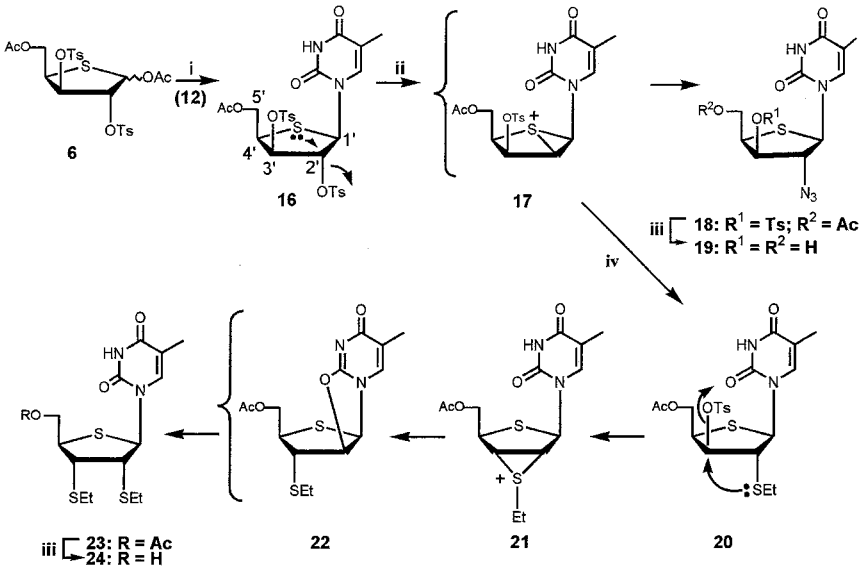
We next prepared the 4′-thioxylonucleoside **16** (67%) from ribosylation of the silylated thymine **12** with the sugar precursor **6**, by applyling Vorbrüggen method,[21,22] using TMSTfS as catalyst and dry 1,2-dichloroethane as solvent at 23°C. The ^{1}H NMR spectrum of **16** showed a doublet at δ 6.29, assigned to H-1′ with $J_{1,2} = 3.3$ Hz, which suggested the β-configuration. The two doublets of doublets at δ 5.00



SCHEME 1 *Reagents and conditions*: (i) KSAc, DMF, 100°C, 72 h; (ii) Ac_2O, HOAc, H_2SO_4, 0°C; (iii) HBr, HOAc, 20°C, 15 h; (iv) Zn, HOAc, 80°C, 4 h; (v) NaOAc, TSA, 20°C, 10 h; (vi) LiN_3, DMF, 100°C, 5 h; (vii) (**12**), TMSTfS, $ClCH_2CH_2Cl$, reflux °C, 4 h; (viii) NH3, MeOH, 5°C, 15 h.

($J_{3,4} = 3.0$ Hz,) and δ 4.87 ($J_{2,3} = 1.7$ Hz) were attributed to H-3′ and H-2′ respectively. These J values give an stereochemical proof of the *xylo*-configuration.

The action of nucleophile reagents on compound **16** was investigated. Thus, treatment of **16** with excess of a 1.5:1.0 mixture of sodium azide and ammonium chloride in DMF at 120°C for 2 h gave a syrupy mixture **18**. Deblocking of the syrup **18** with 16% methanolic ammonia resulted, after chromatographic purification, in the formation of a foam solid, tentatively identified as **19**. The IR spectrum of **19** was charactereized by the absorbtion at 2100 cm^{-1}, and assigned to the azide group. The ^1H NMR spectrum of **19** demonstrated H-1′ as a doublet at δ 6.19 with $J_{1',2'} = 5.5$ Hz which is a typical for the β-configuration. The H-2′ and H-3′ appeared at δ 3.98 ($J_{2',3'} = 1.7$ Hz); and δ 4.37 ($J_{3',4'} = 4.0$ Hz), and these J values supported the *xylo*-configuration. These results might be explained in terms of the intramolecular displacement with the



SCHEME 2 *Reagents and conditions*: (i) (**12**); TMSTfS, −78–23°C, 4 h; (ii) NaN_3, NH_4Cl, DMF, 120°C, 4 h; (iii) 16% NH_3/MeOH, 23°C, 16 h; (iv) NaSEt, MeOH, reflux, 4 h.

sulfonate group at C-2′, via sulfur participation, and led to the intermediate **17** which was spontaneously attacked by the azide ion at C-2′ to give, with the retention in configuration, the 2′-azido-xylo derivative **18** (Scheme 2). These findings are in accordance with the results obtained by Miller et al.[14a]

Treatment of **16** with sodium ethylthiolate in refluxing methanol for 5 h might proceeded similarly as in the previous mechanism by the intramolecular displacement to give the episulfonium ion **17** which, attacked by the thiolate ion at C-2′, could give, with the retention of configuration, the unseparable 2-ethylthiolate nucleoside **20**. The latter compound might suffer another displacement via sulfur participation with the sulfonate group at C-3′ to give the episulfonium ion **21** which and again would be attacked by the amido group at C-2 giving the unseparable 2,2′-anhydro derivative **22**. The presence of excess of sodium ethylthiolate in refluxing methanol might lead to the opening of the anhydro ring at **22** and result in inversion of configuraton and formation of the syrupy ribo compound **23**. Deblocking of **23** afforded the free nucleoside **24** (38%) as a crystalline compound (Scheme 2). The structure of **24** was elucidated by spectral analysis (Scheme 2). The H-2′ and H-3′ signals appeared in the ^1H NMR spectrum as two doublet of doublets at δ 3.98 and 4.37 with $J_{2',3'} = 3.0$ Hz and $J_{3',4'} = 4.0$ Hz

respectively. These values are an indication of the *ribo* configuration and again are in agreement with those of the previously reported xylo and ribo derivatives.[24] More evidence for the formation of **23** is concluded from the NOE irradiation experiment of the H-1′ signal, which led to enhancement of the signal for H-4′ (2.8%) and irradiation of the H-6 signal which resulted in the enhancement of the signals for H-3′ (2.9%). The HMQC spectrum of **24** showed a $^3J_{C,H}$ correlation between C-5′ and H-3′, as additional evidence for the *endo*-H-3′ (the *ribo*-configuration).

EXPERIMENTAL

General Procedure

Melting points are uncorrected. ^{1}H NMR spectra were recorded on AC 250 and 600 MHz spectrometers [^{13}C NMR (62.9 MHz)] using tetramethylsilane (TMS) as internal standard with δ: chemical shift in ppm, and coupling constants in Hz. Mass were measured in glycerol as matrix and some ions were measured with sodium ions.

Methyl 4-*S*-acetyl-4-deoxy-2,3-di-*O*-*p*-toluenesulfonyl-α-D-xylopyranoside (5). A solution of **4** (4.0 g, 6.38 mmol) in DMF (35 ml) was stirred under nitrogen with potassium thioacetate (1.0 g, 8.76 mmol) at 117°C for 24 h. After cooling, the brown solution was evaporated to dryness, and the residue was partitioned between $CHCl_3$ (3 × 50 ml) and water (50 ml). The combined organic extract was dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was dissolved in toluene (5 ml) and poured onto a column of SiO_2 (100 g) and eluted, in gradient, with ethyl acetate (0–10%) and toluene to give **5** (1.78 g, 51%) as a crystalline product, m.p. 145–147°C. ν_{max} 1695 (-SAc), 1740 cm^{-1}(-OAc). ^{1}H NMR ($CDCl_3$): δ 7.79–7.45 (m, 8H, Ar); 5.05 (dd, 1H, $J_{3,4} = 10.0$ Hz, H-3); 4.98 (d, 1H, $J_{1,2} = 3.2$ Hz, H-1); 4.70 (dd, 1H, $J_{2,3} = 10.0$ Hz, H-2); 4.22 (m, 1H, H-4); 4.09 (dd, 1H, $J_{4,5b} = 2.3$ Hz, H-5b); 3.60 (dd, 1H, $J_{5a,5b} = 12.5$ Hz, H-5a); 3.37 (s, 3H, OMe); 2.47 (s, 3H, C_6H_4*Me*); 2.35 (s, 3H, SAc); 2.27 (s, 3H, C_6H_4*Me*); 2.08, 1.97 (2s, 6H, 2 × OAc). Anal. calc. for $C_{22}H_{26}S_3O_{10}$ (546.6): C, 48.34; H, 4.79. Found: C, 48.21; H, 4.68. MS: m/z (FAB) 547 (MH^+).

1,5-Di-*O*-acetyl-2,3-di-*O*-*p*-toluenesulfonyl-4-thio-D-xylofuranose (6). To a cooled (−15°C), stirred solution of **5** (2.0 g, 3.66 mmol) in a mixture of acetic anhydride (25 ml) and acetic acid (25 ml) was added conc. sulfuric acid (1.5 ml) dropwise. The solution was left at 23°C for 2 days, then mixed with anhydrous sodium acetate (8.0 g) and evaporated to dryness below 25°C. The residue was partitioned between chloroform (50 ml) and water (50 ml), and the organic layer was washed with aqueous solution of sodium bicabonate (50 ml) and

finally with water (50 ml). The organic extract was decolourized by warming with charcoal in methanol and then evaporated to dryness. The residue was dissolved in toluene and poured onto acolumn of SiO_2 (50 g). Elution, in gradient, with ethyl acetate (0–10%) and toluene afforded **3** (α,β-anomeric mixture 3:1) (0.37 g, 18%) as oil. ^{1}H NMR ($CDCl_3$) (β-anomer): δ 7.81-7.43 (m, 8H, Ar); 6.19 (d, 1H, $J_{1,2} = 3.0$ Hz, H-1); 5.09 (dd, 1H, $J_{3,4} = 2.7$ Hz, H-3); 4.85 (dd, 1H, $J_{2,3} = 1.5$ Hz; H-2); 4.80 (dd, 1H, $J_{5a,5b} = 11.5$ Hz, H-5b); 4.54 (dd, 1H, $J_{4,5a} = 4.7$ Hz, H-5a); 4.19 (m, 1H, $J_{4,5b} = 3.7$ Hz, H-4); 2.46 (s, 3H, C_6H_4*Me*); 2.42 (s, 3H, C_6H_4*Me*); 2.00, 1.90 (2s, 6H, 2 × OAc). MS: m/z (FAB) ($C_{23}H_{26}S_3O_{10}$) 581 (MNa^+).

5-*O*-Acetyl-1-bromo-2,3-di-*O*-*p*-toluenesulfonyl-4-thio-D-xylofuranose (7). A solution of **6** (1.94 g, 3.48 mmol) in a mixture of HBr/acetic acid solution (30 ml) was stirred at 20°C for 15 h. The solution was evaporated under high vaccum below 23°C to dryness. The residue was partitioned between water (50 ml) and chloroform (2 × 50 ml), and the combined organic extracts was dried (Na_2SO_4), filtered, and evaporated below 23°C to dryness to give **6** (1.15 g, 57%) as oil, which used directly for the next step. MS: m/z (FAB) ($C_{21}H_{26}BrS_3O_8$) 601/603 (MNa^+).

5-*O*-Acetyl-1,2,4-trideoxy-1,4-epithio-3-*O*-*p*-toluenesulfonyl-D-*threo*pent-1-enitol (8). A solution of **7** (1.0 g, 1.72 mmol) in acetic acid (10 ml) was treated with zinc dust (2.0 g) and stirred at 80°C for 4 h. After cooling, chloroform (50 ml) was added and washed successively with water (30 ml), dil. hydrochloric acid (30 ml), an aqueous solution of sodium bicabonate (30 ml), and finally with water (30 ml). The organic extract was dried (Na_2SO_4), filtered, and dried to dryness. The residue was purified by flash chromatography using toluene-ether (9:1) to give the desired glycal **5** (0.20 g, 35%) as a pure (TLC) oil. ^{1}H NMR ($CDCl_3$): δ 7.69, 7.58 (2d, 4H, Ar); 6.43 (d, 1H, $J_{1,2} = 3.5$ Hz, H-1); 5.67 (dd, 1H, $J_{2,3} = 6.7$ Hz; H-2); 5.10 (dd, 1H, $J_{3,4} = 5.7$ Hz, H-3); 4.88 (dd, 1H, $J_{4,5b} = 6.7$ H, H-5b); 4.64 (dd, 1H, $J_{5a,5b} = 11.3$ Hz, H-5b); 4.19 (m, 1H, H-4); 2.43 (s, 3H, C_6H_4*Me*); 2.01 (s, 3H, OAc). MS: m/z (FAB) ($C_{14}H_{16}S_2O_5$) 351 (MNa^+).

1,5-Di-*O*-acetyl-2-deoxy-4-thio-3-*O*-*p*-toluenesulfonyl-D-*threo*-pentofuranose (9). A solution of **8** (0.70 g, 2.13 mmol) in acetonitrile (30 ml) containing sodium acetate (0.41 g, 5.0 mmol) and p-toluenesulfonic acid (0.17 g, 1.0 mmol) was stirred at 20°C for 10 h. Chloroform (50 ml) was added, and the reaction mixture was extracted with aqueous solution of sodium bicarbonate (3 × 30 ml). The organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was chromatographed on a SiO_2 column (40 g) using hexane-ether (1:1) as eluent to give **6** (mixture of stereoisomers)

(0.41, 50%) as a syrup.^{1}H NMR ($CDCl_3$): δ 7.52, −7.42 (2d, 4H, Ar); 6.26 (dd, 0.4 H, J = 5.5, 1.6 Hz, H-1); 6.22 (dd, 0.6 H, J = 5.4, 2.0 Hz; H-1); 5.09 (dt, 0.6 H, J = 7.6, 5.9 Hz, H-3); 4.90 (ddd, 0.4 H, J 6.3, 5.4 Hz, H-3); 4.59 (m, 1H, $J_{4,5b} = 5.5$ Hz, $J_{5a,5b} = 11.0$ Hz, H-5b); 4.42 (m, 1H, $J_{4,5a} = 8.3$ Hz, H-5a); 4.09 (m, 1H, H-4); 2.65–2.55 (m, 2H, H-2a, H-2b); 2.02, 2.40 (s, 3H, C_6H_4*Me*); 2.01, 1.98 (2s, 6H, 2 × OAc). MS: m/z (FAB) ($C_{16}H_{20}S_2O_7$) 411 (MNa^+).

1,5-Di-*O*-acetyl-3-azido-2,3-deoxy-4-thio-α,β-D-*erythro*-pentofuranose (11). A solution of 9 (1.2 g, 3.1 mmol) in DMF (30 ml) was treated with lithium azide (0.40 g, 15.4 mmol) with stirring under nitrogen at 100°C for 5 h. After cooling, the solvent was evaporated to dryness, and the residue was taken in chloroform (3 × 30 ml) and partitioned with water (40 ml). The combined organic extract was dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was chromatographed on a SiO_2 (50 g) and eluted, in gradient, with ether (0–50%) and hexane to give two components. The first eluted component (0.23 g, 35%), as an oil, was tentatively identified as the olefin **10** (MS: m/z (FAB) ($C_9H_{12}SO_4$) 217 (MH^+). The second fraction(0.37 g, 48%), as a pale yellow syrup, was identified as the anomeric mixture of **11** (α:β ratio 1:1). The ^{1}H NMR spectrum ($CDCl_3$) of the mixture showed close similarity to those anomers obtained by Villa et al.[20]MS: m/z (FAB) ($C_9H_{13}N_3SO_4$) 260 (MH^+). The mixture was used directly for ribosylation without separation

3′-Azido-3′-deoxy-4′-thiothymidine (14β) and the corresponding α-anomer (14α). A suspension of thymine (200 mg, 1.60 mmol) in hexamethyldisilazane (10 ml) containing few crystals of ammonium sulfate was heated under reflux for 5 h. After cooling, the solution was evaporated to dryness, and the residue was dissolved in anhydrous acetonitrile (10 ml). To the clear solution, was added compound **11** (207 mg, 1.60 mmol) in anhydrous acetonitrile (10 ml) and trimethylsilyl trifluoromethanesulfonate (TMSTfS) (290 μl) the mixture of which was then heated under refulx for 4 h. After cooling, the reaction mixture was diluted with dichloromethane (15 ml) and stirred with saturated aqueous solution of sodium bicarbonate (30 ml) for 30 min. The organic layer was dried, filtered, and evaporated to dryness. The residue was stirred at 23°C with 16% methanolic ammonia solution for 15 h and then evaporated to dryness. The residue was separated on a column of SiO_2 (5.0 g) using (ether-aceton 99:0.5) as eluent. The first fraction was assigned to **14α** (65 mg, 16%) as a syrup. The ^{1}H NMR (DMSO-d_6) spectrum was identical to that of the sample prepard by Villa et al.[20]

The second eluted fraction was identified as compound 14β (89 mg, 22%); m.p. 120–123°C (from EtOAc-hexane) (Lit.[18] m.p. 122–123°C). ^{1}H NMR (DMSO-d_6): δ 11.31 (br s, 1H, NH), 7.83 (d, 1H, J 1.0 Hz, H-6);

6.15 (t, 1H, $J_{1',2'a} = 7.1$ Hz, $J_{1,2b} = 7.6$ Hz, H-1′); 4.50 (q, 1H, H-3′); 3.64 (m, 2H, H-5′a, H-5′b); 3.37 (q, 1H, H-4); 2.45 (m, 1H, $J_{2'b,3'} = 5.0$ Hz, H-2′b); 2.30 (m, 1H, $J_{2'a,3'} = 5.0$ Hz, $J_{2'a,2'b} = 13.5$ Hz, H-2a′); 1.81 (d, 3H, Me). ^{13}C NMR (163.3 (C-4), 150.6 (C-6); 109.8 (C-5); 64.2 (C-1′); 63.0 (C-5′); 59.5 (C-4′); 55.2 (C-3′); 38.0 (C-2′); 12.3 (Me). Anal. calc. for $C_{10}H_{13}N_3SO_3$ (255.3): C, 47.05; H, 5.13. Found: 46.92; H, 5.04. MS: m/s (FAB) 256 (MH^+).

1-(5-*O*-Acetyl-2,3-di-*O*-*p*-toluenesulfonyl-4-thio-β-D-xylofuranosyl)thymine (16). A solution of **6** (500 mg, 0.89 mmol) in dry 1,2-dichloroethane (15 ml) was added to a solution of silylated thymine [prepared by refluxing thymine (200 mg, 1.59 mmol) and hexamethyldisilzane (HMDS, 15 ml) for 5 h and concentrating the mixture to a gum] in dry 1,2-dichloroethane (15 ml). During the stirring at 23°C, trimethylsilyl triflouromethylsulfonate (TMSTfS) (150 μl) was added dropwise, and the solution was continued with stirring at the same temperature for 5 h. The mixture was then diluted with dichloromethane (30 ml) and then partitioned with saturated aqueous solution of sodium bicarbonate (3 × 30 ml). The organic extract was dried, filtered, and evaporated to dryness. The residue was purified on a column of SiO_2 (20 g), using, in gradient, methanol (0–2%) and dichloromethane as eluents to give **16** (0.36 g, 67%) as a crystalline product, m.p. 130–134°C. ^{1}H NMR ($CDCl_3$): δ 7.91 (d, 1H, J 1.1 Hz, H-6); 7.75–7.40 (m, 8H, Ar); 6.29 (d, 1H, $J_{1,2} = 3.3$ Hz, H-1); 5.00 (dd, 1H, $J_{3,4} = 3.0$ Hz, H-3); 4.87 (dd, 1H, $J_{2,3} = 1.7$ Hz; H-2); 4.76 (dd, 1H, $J_{5a,5b} = 11.1$ Hz, H-5b); 4.53 (dd, 1H, $J_{4,5a} = 4.5$ Hz, H-5a); 4.18 (m, 1H, $J_{4,5b} = 3.7$ Hz, H-4); 2.47 (s, 3H, C_6H_4*Me*); 2.40 (s, 3H, C_6H_4*Me*); 2.01, 1.92 (2s, 6H, 2 × OAc). Anal. calc. for $C_{26}H_{28}N_2S_3O_{10}$(624.7): C, 49.99; H, 4.52; N, 4.48. Found: 49.73; H, 4.44; N, 4.26. MS: m/z (FAB) 625 (MH^+).

Reaction of 16 with azide ion. A solution of **16** (250 mg, 0.40 mmol), sodium azide (160 mg, 2.40 mmol), and ammonium chloride (86 mg, 1.60 mmol) in DMF (15 ml) was stirred at 120°C. After 2 h, additional sodium azide (76 mg, 1.17 mmol) and ammonium chloride (44 mg, 0.82 mmol) were added, and the reaction was continued for another 3 h at the same temperature. The micture was cooled to 23°C, the salts were filtered off, and the filtrate was evaporated to a syrupy mixture. A solution of 16% methanolic ammonia (10 ml) was added to the syrup, and the solution was stirred at 23°C for 16 h. The solution was evaporated to dryness, and the residue was partitioned between water (15 ml) and ether (3 × 15 ml). The aqueous layer was evaporated to dryness, and the residue was co-evaporated to dryness. The residue was chromatographed on a SiO_2 column (15 g) with methanol, in gradient (0–10%), and chloroform as eluents to give a foam, tentatively

characterized as (1-(2-azido-2-deoxy-4-thio-β-D-xylofuranosyl)thymine (**19**). Crystallization from ethanol-petrolium ether gave 48 mg of **16** (40%), m.p. 96–99°C. ^{1}H NMR (CD_3OD): 7.93 (d, 1H, J 1.0, H-6); 6.19 (d, 1H, $J_{1',2'} = 5.5$ Hz, H-1′); 4.80 (br s, 2H, 2 × OH); 4.37 (dd, 1H, $J_{3',4'} = 4.0$ Hz, H-3′); 3.98 (dd, $J_{2',3'} = 1.7$ Hz, H-2′); 3.68 (m, 2H, H-5a′,H-5′b); 3.43 (m, 1H, H-4′); 1.83 (d, 3H, Me). Anal. calc. for $C_{10}H_{13}N_5SO_4$(299.3): C, 40.13; H, 4.38; N, 23.40. Found: 39.82.; H, 4.30; N, 22.98. MS: m/s (FAB) 322 (MNa^+).

Reaction of 16 with ethylthiolate ion. A solution of **16** (250 mg, 0.40 mmol) in dry methanol (10 ml) containing sodium ethylthiolate (45 mg, 0.50 mmol) was boiled for 5 h. After cooling, the solvent was evaporated to dryness, and the residue was worked up as in the previous experiment after treatment with 16% methanolic ammonia (10 ml) to give a syrup (120 mg). The syrupy product was chromatographed on a SiO_2 column (15 g), using, in gradient, methanol (0–0.5%), and chloroform as eluents to give a pure foamy solid tentatively identified as 1-(2,3-dideoxy-2,3-*S*,*S*-diethyl-4-thio-β-D-ribofuranosyl)thymine (**24**). (55 mg, 38%); m.p. 79-85°C. ^{1}H NMR (CD_3OD): 7.87 (d, 1H, J 1.1 Hz, H-6); 6.59 (d, 1H, $J_{1',2'} = 5.2$ Hz, H-1′); 4.76 (t, 1H, J = 5.2 Hz, OH); 4.37 (dd, 1H, $J_{3',4'} = 4.0$ Hz, H-3′); 3.98 (dd, $J_{2',3'} = 3.0$ Hz, H-2′); 3.68 (m, 2H, H-5a′, H-5′b); 3.43 (m, 1H, H-4′); 2.75, 2.72 (2q, 4H, J 6.8 Hz, 2 × S*CH2*CH_3); 1.83 (d, 3H, Me); 1.37, 1.35 (2t, 6H, 2 × SCH_2*CH_3*). Anal. calc. for $C_{14}H_{22}N_2S_3O_3$(362.5): C, 46.38; H, 6.12; N, 7.73. Found: 46.02.; H, 6.01; N, 7.53. MS: m/z (FAB) 385 (MNa^+).

REFERENCES

[1] a) M. R. Dyson, P. L. Coe, and R. T. Walker, *J. Med. Chem*., **34,** 2782 (1991); b) J. A. Secrist, K. N. Tiwari, J. M. Riodran, and J. A. Montgomery, *J. Med. Chem*., **34,** 2361 (1991).

[2] E. Ichikawa, S. Yamamura, and K. Kato, *Tetrahedron Lett*., **40,** 7385 (1999).

[3] a) Y. Yoshimura, K. Kitano, H. Satoh, M. Watanabe, S. Miura, S. Sakata, T. Sasaki, and A. Matsuda, *J. Org. Chem.,* **61,** 822 (1996); b) D. Kaga, N. Minakawa, and A. Matsuda, *Nucleic Acids Res. Suppl.,* **1,** 103 (2001).

[4] J. Branalt, I. Kvarnstrom, G. Niklasson, S. C. T. Svensson, B. Classon, and B. Samuelson, *J. Org. Chem.,* **59,** 1783 (1994).

[5] J. Uenish, *J. Synth. Org. Chem. Japan,* **55,** 186, (1997).

[6] N. A. Al-Masoudi, W. Pfleiderer, and H. B. Lazrek, *Nucleos. & Nucleot.*, **12,** 687 (1993).

[7] N. A. Al-Masoudi, and W. Pfleiderer, *Tetrahedron,* **49,** 7579 (1993).

[8] M. E. Jung, and J. M. Gardiner, *J. Org. Chem.,* **56,** 2614 (1991).

[9] H. Mitsuya, K. J. Weinhold, P. A. Furman, et al., *Proc. Natl. Acad. Sci. USA,* **82,** 7096 (1985).

[10] H. Mitsuya and S. Broder, *Proc. Natl. Acad. Sci. USA,* **83,** 1911 (1986).

[11] E. De Clercq, *Nucleos. & Nucleot.,* **13,** 1271 (1994).

[12] J. G. Fernandez-Bolanos, N. A. Al-Masoudi, and I. Maya, *Advances in Carbohydrate Chemistry and Biochemistry: Sugar Derivatives Having Sulfur in the Ring*, edited by D. Horton (Academic Press, London, 2001), vol. 57, p. 21.
[13] a) A. El-Laghdach, Y. Diaz, and S. Castillon, *Tetrahedron Lett.,* **34,** 2821 (1993); b) Y. Diaz, A. El-Laghdach, and S. Castillon, *Tetraherdon,* **53,** 10921 (1997).
[14] a) J. A. Miller, A. W. Pugh, and G. M. Ullah, *Tetrahedron Lett.,* **41,** 3265 (2000); b) J. A. Miller, A. W. Pugh, and G. M. Ullah, *Nucleos. Nucleot. & Nucleic Acids*, **19,** 1475 (2000).
[15] a) K. Haraguchi, H. Takahashi, and H. Tanaka, *Tetrahedron Lett.* **43,** 5657 (2002); b) K. Haraguchi, A. Nishikawa, E. Sasakura, H. Tanaka, K. T. Nakamura, and T. Miyasaka, *Tetrahedron Lett*., **39,** 3713 (1998).
[16] J. G. Buchanan and J. Fletcher, *Chem. Soc. C.,* 1926 (1966).
[17] E. J. Reist, L. V. Fisher, and L. Goodman, *Org. Chem.*, **33,** 189 (1968).
[18] S. A. Hartsel and W. S. Marshal, *Tetrahedron Lett.,* **39,** 205 (1998).
[19] E. J. Reist, D. E. Gueffroy, R. W. Blackford, and L. Goodman, *J. Org. Chem.*, **31,** 4025 (1966).
[20] B. Tber, N.-E. Fahmi, G. Ronco, P. Villa, D. F. Ewing, and G. MacKenzie, *Carbohydr. Res.*, **267,** 203 (1995).
[21] H. Vorbrüggen, K. Krollikiewicz, K., and B. Bennua, *Chem. Ber.*, **114,** 1234 (1981).
[22] H. Vorbrüggen and B. Bennua, *Tetrahedron Lett.*, **15,** 1339 (1978).
[23] H. Roseymer, G. Toth, and F. Seela, *Nucleos. & Nucleot.*, **8,** 587 (1989).
[24] N. A. Al-Masoudi and W. Pfleiderer, *Carbohyd. Res.*, **275,** 95 (1995).