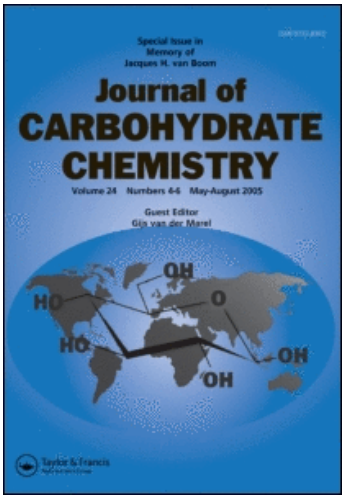

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Thiosugar Nucleosides. Effect of Sulfur in the Synthesis of Substituted Azido-5-Thio-D-Gluco- and Allopyranosyl-*N*-Nucleosides and New Isothionucleoside Derivatives Thereof

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To cite this Article Al-Masoudi, Najim A. , Al-Soud, Yaseen A. and Schuppler, Thilo(2005) 'Thiosugar Nucleosides. Effect of Sulfur in the Synthesis of Substituted Azido-5-Thio-D-Gluco- and Allopyranosyl-*N*-Nucleosides and New Isothionucleoside Derivatives Thereof', Journal of Carbohydrate Chemistry, 24: 3, 237 — 250

To link to this Article: DOI: 10.1081/CAR-200053715

URL: http://dx.doi.org/10.1081/CAR-200053715

Journal of Carbohydrate Chemistry, 24:237–250, 2005

ISSN: 0732-8303 print 1532-2327 online
DOI: 10.1081/CAR-200053715

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1-(2,3,4-tri-*O*-acety-6-azido-6-deoxy-5-thio-β-D-glucopyranosyl)thymine **5** and the 6-thio-septanosylthymine analogue **7** were obtained via the intramolecular displacement of the corresponding tosylate **2** by azide. Alternatively, **5** was obtained from bromination of alcohol **1** in the presence of azide. Deblocking of **5** afforded the nucleoside **6**. Glycosylation of the tetraacetate **11**, obtained by acetolysis of **10** with thymine, afforded the 3-*O*-tosyl-β-D-glucopyranosylthymine derivative **13**, which furnished the 3-azido-3-deoxy-β-D-allopyranosyl-thymine analogue **14** on reaction with azide ion. Alternatively, the glucoside **12** gave the corresponding *gluco* analogue **16** on treatment

Received August 10, 2004; accepted January 18, 2005.
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with azide. Acetolysis of **16** furnished the tetraacetate **17**, which was subjected for glycosylation to give the *gluco* nucleoside **18**. Deblocking of **14** and **18** afforded the free 3-azido-nucleosides **15** and **19**, respectively. The isothionucleoside **21** was prepared from treatment of thymine with the 2,3-epoxide derivative **20** in the presence of Ti(*i*-PrO)$_4$ and triethyl amine. Mild acid hydrolysis of **21** afforded **22**. Cycloaddition of the 2-azido-altroside **23** with dimethyl acetylenedicarboxylate gave the 1,2,3-triazole derivative **24**. Treatment of **24** with methanolic ammonia afforded the 4,5-carboxamide analogue **25**. The conformations of the new products were studied by NMR spectroscopy.

Keywords Biological activity, Glycosylation, Epimerization, Nucleosides, Isothionucleosides

INTRODUCTION

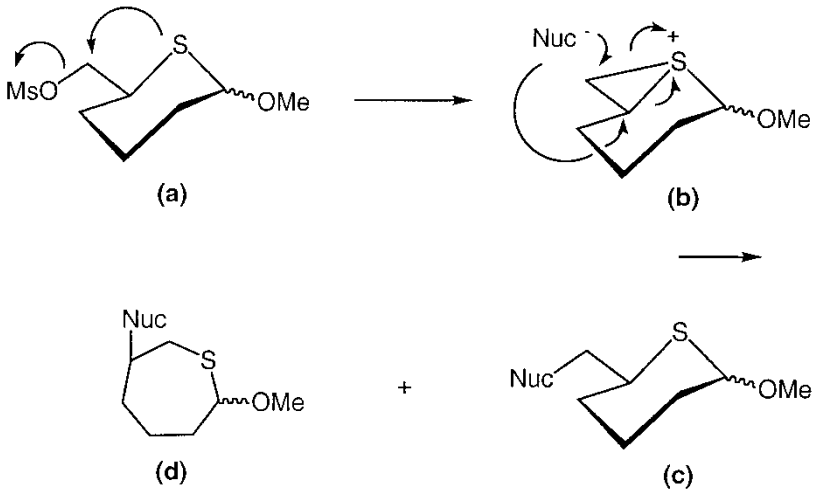
Nucleosides wherein the furanoside ring oxygen is replaced by sulfur were first described in the 1960s and were shown to have interesting biological activity.[1–6] Among these are the 4′-thio analogues of azidothymidine (AZT), dideoxyinosine, dideoxycytidine, (*E*)-5-(2-bromovinyl)-2′-deoxyuridine, and the 4′-thio analogues of the naturally occuring 2′-deoxynucleosides of which some have antiviral activity.[7–10] On the other hand, several laboratories[11–19] have described various 4′-thio analogues of purine and pyrimidine nucleosides with some remarkable potency against herpes simplex virus type 1 (HSV-1) and varicella zoster virus, but associated with high toxicity. To date, only the thionucleoside β-L-(-)-2′-deoxy-3′-thiacytidine[20] (lamivudine, 3TC™) has been licensed by the American Food and Drug Administration as both an anti-AIDS and an antihepatitis drug, since the 5′-*O*-carbamate derivatives[21] are found to be active against human immundiffiency virus type 1 (HIV-1) as well as human hepatitis B virus (HBV). Recently, we have reported the synthesis of nucleosides from 5-thio-D-xylose,[22] 5-thio-D-glucose,[23] and α-D,L-*arabino*-pentulopyranosyl derivatives.[24] The most significant attempts are the introduction of the bioactive azide or amino groups in these thionucleosides by substituting the OH-6 group or changing the chirality of the pyranosyl moiety at C-3 with an azido group, which might lead to potentially active candidates in comparison to the anti-HIV drug AZT and its derivatives.[25] We report here the synthesis of a new type of azido-thionucleosides carrying a 5-thio-β-D-glucopyranosyl moiety via sulfur participation and nucleophilic displacement, as well as some novel iso-thionucleosides. We have selected 5-thio-D-glucose[26] it acts as an active antimetabolite and exhibited interesting biological activities, such as inhibition of spermatogenesis.[27]

RESULTS AND DISCUSSION

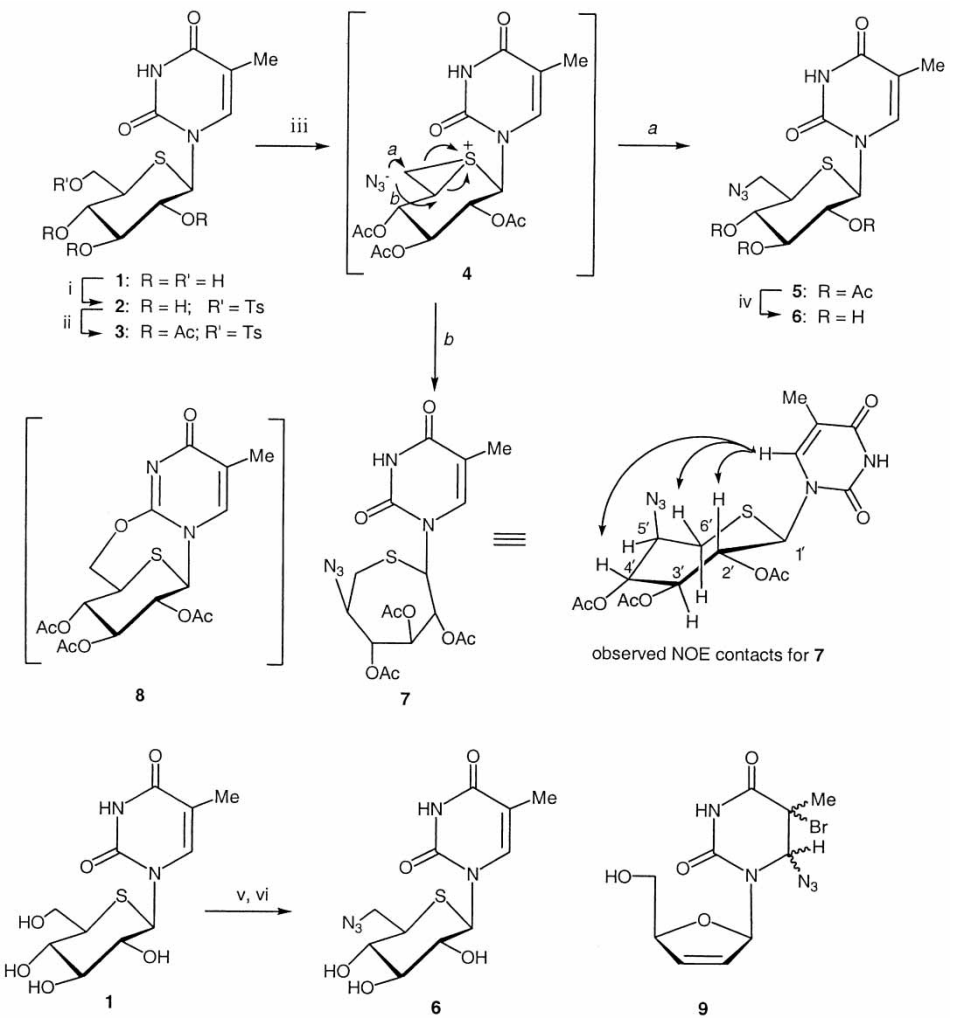
In earlier papers[28,29] it has been reported that nucleophilic displacement of 2- or 4-*O*-sulfonates of 5-thiopyranoside derivatives proceeded via transannular

sulphur participation, giving substituted products with retention of configuration or with ring contraction. Similarly,[30] a C-6-*O*-sulfonate of 5-thiopyranoside derivative **a** gave two products, the 6-substituted-5-thiopyranoside (**c**) and the corresponding 6-thioseptanoside **d**. It was suggested that these reactions proceeded *via* intermediate episulfonium ions **b** resulting from neighboring group participation from the ring sulphur atom (Sch. 1).

The nucleoside **3** was prepared from the readily available nucleoside **1** in two steps via the sulphonate ester **2**.[31] When **3** was stirred with lithium azide in dimethylformamide, two compounds were identified and separated by chromatography. In the NMR spectrum of the first isomeric product, H-1′ appeared as a doublet at δ 5.62 with a large $J_{1',2'}$ value (9.1 Hz), indicating the β-configuration, while other sugar protons H-2′–H-5′ were fully assigned. Furthermore, the observed NOE interactions between H-6 and both H-2′ and H-4′ and one of the two protons at C-6′ doubtlessly indicated the β-configuration. The compound was tentatively identified as 6-thio-α-L-idoseptanosyl)thymine derivative **7** in 37% yield. The second eluted product was identified as 5-thio-β-D-glucopyranosyl)thymine derivative **5** in 57% yield, which is consistent with the structure of a 5-thioglucopyrosides derivative previously prepared in our laboratory.[31] The ^{1}H-NMR spectrum of **5** showed large values of $J_{1',2'} = 9.0$ Hz; $J_{2',3'} = J_{3',4'}$ 9.5 Hz, $J_{4',5'} = 10.0$ Hz, indicative for the β-configuration and $^4C_1$-conformation of the sugar moiety. The proposed mechanism of formation of **5** and **7** might be explained in terms of opening of the episulphonium ion **4**, by azide ions via both routes *a* and *b* (Sch. 2). The reactivity of azide ion favors an "S_N2-like" attack at the primary C-6, thus explaining the formation of **5** as a major product. On the



Scheme 1

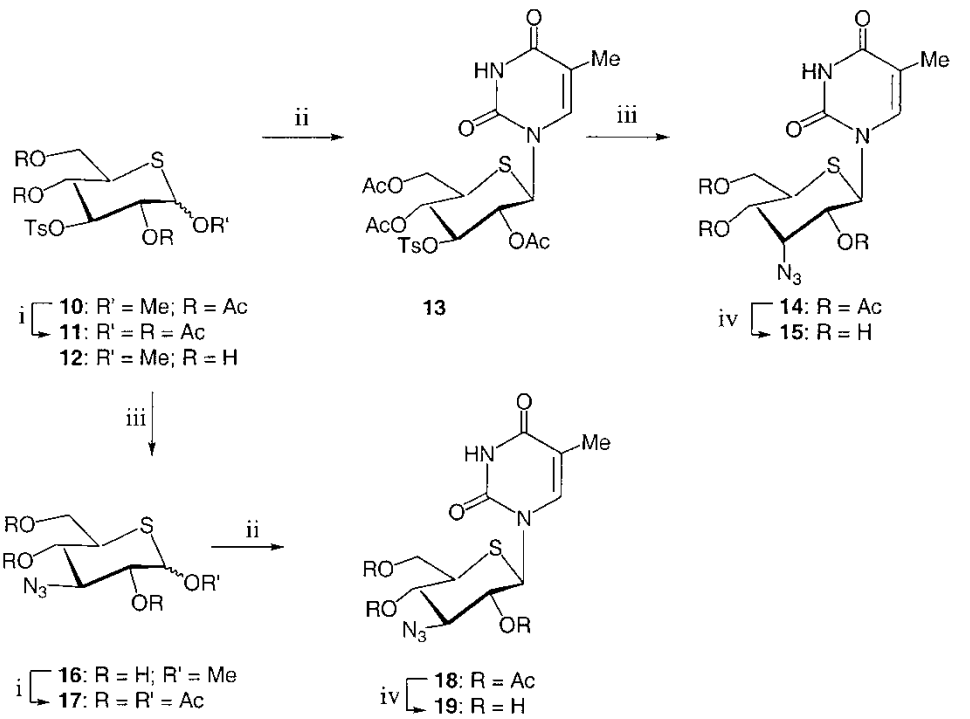


Scheme 2: *Reagents and conditions*: (i) TsCl-pyridine, 23°C, 16 hr; (ii) Ac_2O-pyridine, 23°C, 24 hr; (iii) LiN_3, DMF, 120°C, 6 hr; (iv) NaOMe-MeOH, 23°C, 16 hr; (v) Ph_3P, NBS, DMF, 55°C, 2 hr; (vi) NaN_3, 80°C, 5 hr.

other hand, there is a possibility of formation of the intermediate **8**, which would lead to **5** in the presence of azide ions. Deblocking of **5** with sodium methoxide in methanol afforded, after chromatographic purification, **6** in 79% yield. Alternatively, **5** was prepared from **1** in 39% yield, according to the literature procedure,[32] by reaction with triphenylphosphine and *N*-bromosuccinimide in dimethylformamide at 55°C, followed by reaction with azide ions at 80°C. The low yield of **5** might be explained in terms of addition of the azide group to the thymine ring, in comparison to the results obtained recently by Kumer et al.,[33] during the formation of **9** (Sch. 2).

Next, we examined the epimerization of an *O*-sulphonate at C-3 of the *gluco* isomer of the nucleoside analogues by nucleophilic displacement by the azide ions. Thus, glycosylation of the silylated thymine, devised by Vorbrüggen et al.[34] with **11**, obtained from acetolysis of **10** in 73% yield under trimethylsilyl triflate (TMSOTf) catalysis furnished, after chromatographic purification, **13** in 76% yield. Reaction of **13** with sodium azide in boiling dimethylformamide gave, after chromatography, the expected *allo*-azide **14** in 15% yield. Two minor products also formed, namely the unsaturated nucleosides 3- and 4-deoxy-5-thio-D-hexen-*eno*pyranosyl-thymines. The structures of **13** and **14** were followed from their ^{1}H NMR spectra.

The spectrum of **13** revealed large $J_{H,H}$ coupling values ($J_{1',2'} = J_{2',3'} = 9.4$ Hz, $J_{3',4'} = 9.5$ Hz, $J_{4',5'} = 10.0$ Hz), indicative of the β-configuration and the $^4C_1$-conformation of the sugar moiety. The spectrum of **14** showed only two large $J_{H,H}$ couplings ($J_{1',2'} = 9.1$ Hz, $J_{4',5'} = 10.0$ Hz) in keeping with an β-allopyranosylthymine in the $^4C_1$ conformation (Sch. 3). These results are consistent with our previously reported results[35] during the nucleophilic displacement of the sulphonate ester by the azide ions. Deblocking of **14** with sodium methoxide in methanol procceded smoothly to give **15** in 85% yield.

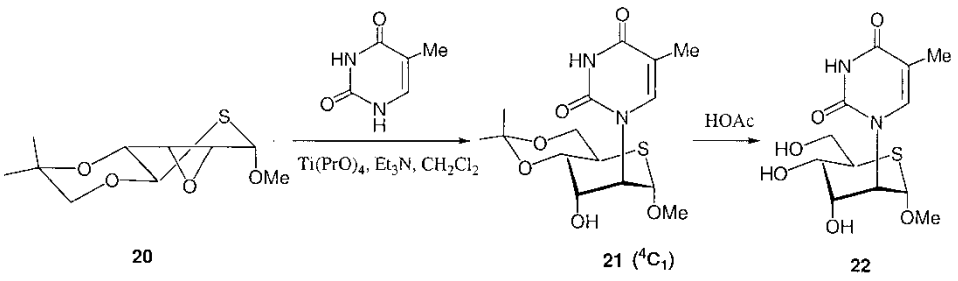


Scheme 3: *Reagents and conditions*: (i) Ac_2O-HOAc-H_2SO_4, 23°C, 2hr; (ii) silyl. thymine, TMSOTf, $(CH_2)_2Cl_2$, 23°C, 3 hr; (iii) LiN_3, DFM, reflux, 7 hr; (iv) NaOMe-MeOH, 23°C 16 hr.

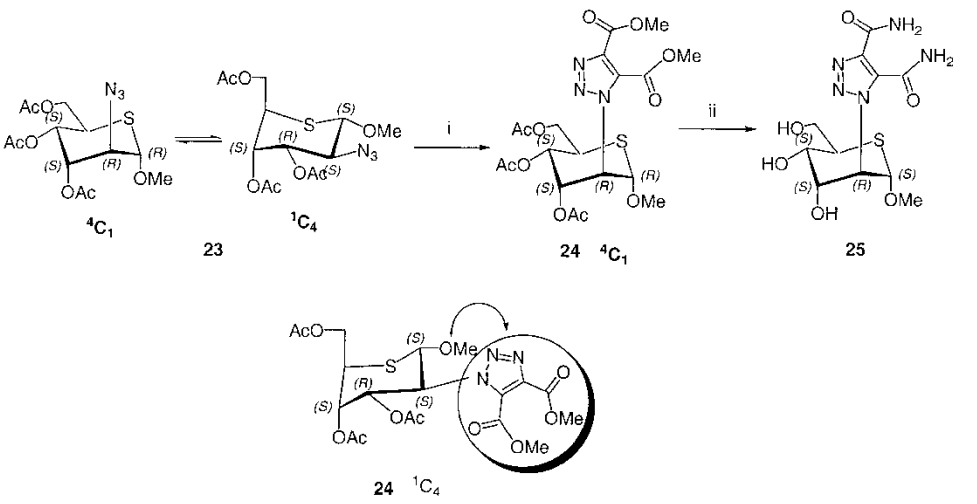
Alternatively, heating of **12** with sodium azide in dimethylformamide afforded **16** as the main product and isolated as the syrupy tetraacetate **17**[35] after acetolysis. The formation of **16** can be explained as a result of double inversion, where **12** is converted first into the *allo*-epoxide, which then underwent azide ion opening,[36] leading mainly to **16**. Condensation of the silylated thymine, devised by Vorbrüggen et al.,[34] with **17** in the presence of TMSOTf as a catalyst gave, after chromatographic purification, **18** in 72% yield. Deblocking of **18** with sodium methoxide in methanol furnished **19** in 83% yield. The structures of **18** and **19** were confirmed by their ^{1}H NMR and mass spectra. The large value of $J_{1',2'}$ (9.1 Hz and 10.0 Hz, respectively), is indicative for the β-configuration, while the large couplings of $J_{2',3'} = 10.0$ Hz, $J_{3',4'} = 9.5$ Hz, $J_{4',5'} = 10.0$ Hz, respectively, confirmed the $^4C_1$ conformation of the sugar moiety.

By emplyoing Lopez' procedure,[37] **20** was subjected for opening of the 2,3-epoxy ring by the azide ions, using titanium tetraisopropoxide [Ti(*i*-PrO)$_4$] as a Lewis acid catalyst in the presence of triethyl amine (Sch. 4) to afford **21** in 52% yield. Although the *altro* isomer favors the $^1C_4$ conformation, the ^{1}H NMR data confirmed that **21** existed mainly in the $^4C_1$ conformation, due to the *trans*-fused 4,6-*O*-isopropylidene ring. Mild acid hydrolysis of **21** with 80% acetic acid afforded **22** in 83% yield, which the ^{1}H NMR spectrum suggested to exist mainly in the $^4C_1$ conformation. These data are consistent with those of the altroside derivatives reported previously.[38]

The significant cytotoxic properties and anticancer activity of several triazolated compounds prompted us to synthesize a new 1,2,3-triazole derivative of a 5-thio-*altro*-isonucleoside by employing our recent synthetic approaches[39] starting from **23**, prepared previously in our laboratory.[38] Thus, reaction of **23** (Sch. 5) with dimethyl acetylenedicarboxylate (DMAD) furnished **24** (74%) and subsequently gave the 4,5-dicarboxamide derivative **25** (84%) on treatment with 16% methanolic ammonia. The structures of **24** and **25** were identified from their ^{1}H NMR and mass spectra. Although **24** existed in equilibrium between $^4C_1$ and $^1C_4$ conformations as proved previously,[39] the large $J_{4',5'}$ values (10.3 Hz, and 9.5 Hz, respectively) and low coupling values of the



Scheme 4



Scheme 5: *Reagents and conditions*: (i) $MeO_2C-\equiv-CO_2Me$; toluene, 60°C; (ii) NH_3/MeOH, 23°C, 16 hr.

other sugar protons indicated that both **24** and **25** preferred the $^4C_1$ conformation, possibly due to the repulsion between the triazole ring at C-2′ and OMe at C-1′ in the case of the $^1C_4$ conformation, as shown in Scheme 5.

EXPERIMENTAL

General

See references [24,39].

Reaction of 1-(1,2,4,6-tetra-*O*-acetyl-3-*O*-toluene-*p*-sulphonyl-5-thio-D-glucopyranosyl) thymine (3) with azide ions. A solution of **3**[31] (500 mg, 0.86 mmol) in dimethylformamide (15 mL) was stirred with lithium azide at 23°C for 16 hr. After cooling, the mixture was evaporated to dryness and the residue was partitioned between chloroform (30 mL) and water (4 × 20 mL). The organic extract was dried (Na_2SO_4), filtered, and evaporated to dryness to give a foam, which was chromatographed on a silical gel column (50 g). Elution with dichloromethane and methanol (0–3%) gave first a foam identified as 1-(2,3,4-tri-*O*-acety-5-azido-5-deoxy-6-thio-α-L-idopseptanosyl)thymine (**7**, 145 mg, 37%). ^1H NMR ($CDCl_3$): δ 6.56 (s, 1H, H-6), 5.62 (d, 1H, $J_{1',2'} = 9.1$ Hz, H-1′), 5.42 (dd, 1H, $J_{2',3'} = 8.4$ Hz, H-2′), 5.21 (dd, 1H, $J_{3',4'} = 6.0$ Hz, H-4′), 5.01 (dd, 1H, $J_{4',5'} = 2.6$ Hz, H-4′), 3.53 (ddd, 1H, $J_{5',6'a} = 5.8$ Hz, H-5′), 2.65 (dd, 1H, $J_{5',6'b} = 2.7$ Hz, H-6′b), 2.32 (dd, 1H, $J_{6'a,6'b} = 13.0$ Hz, H-6′a), 2.09, 1.96, 1.86 (3 × s, 9H, 3 × OAc), 1.93

(s, 3H, C_5-Me). Anal. Calcd $C_{17}H_{21}N_5O_8S$ (455.45): C, 44.83; H, 4.65; N, 15.38. Found: C, 44.51; H, 4.54; N, 15.19. MS: m/z (FAB) 456 ($M + H^+$). Further elution gave an amorphous solid identified as 1-(2,3,4-tri-*O*-acety-6-azido-6-deoxy-5-thio-β-D-glucopyranosyl)thymine (**5**, 223 mg, 57%). ^{1}H NMR ($CDCl_3$): 10.12 (s, 1H, NH), 7.54 (s, 1H, H-6), 5.84 (d, 1H, $J_{1',2'} = 9.0$ Hz, H-1′), 5.70 (t, 1H, $J_{2',3'} = 9.0$ Hz, H-2′), 5.29 (dd, 1H, $J_{3',4'} = 9.5$ Hz, H-3′), 5.12 (dd, 1H, $J_{4',5'} = 10.0$ Hz, H-4′), 3.50 (ddd, 1H, $J_{5',6'b} = 3.3$ Hz, H-5′), 3.41 (dd, 1H, $J_{5',6'a} = 6.0$ Hz, H-6′a), 3.30 (dd, 1H, $J_{6'a,6'b} = 13.5$ Hz, H-6′b), 2.08, 1.96, 1.87 (3 × s, 9H, 3 × OAc), 1.91 (s, 3H, C_5-Me). Anal. Calcd $C_{17}H_{21}N_5O_8S$ (455.45), C, 44.83; H, 4.65; N, 15.38. Found: C, 44.42; H, 4.57; N, 15.18. MS: m/z (FAB) 456 (MH^+).

1-(6-Azido-6-deoxy-5-thio-β-D-glucopyranosyl)thymine (6).

a. A solution of **5** (300 mg, 0.66 mmol) in 0.3 M sodium methoxide (10 mL) was stirred at 23°C for 16 hr. The solution was neutralized with acetic acid to pH 5, then 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 coevaporated with ethanol (3 × 10 mL) and then crystallized from ethanol to give **6** (172 mg, 79%) as a solid, m.p. 157–162°C. ^{1}H NMR (DMSO-d_6/D_2O): δ 7.51 (s, 1H, H-6), δ 5.47 (d, 1H, $J_{1',2'} = 9.5$ Hz, H-1′), 3.87 (dd, 1H, $J_{6'a,6'b} = 13.0$ Hz, H-6′b), 3.74 (dd, 1H, $J_{5',6'a} = 6.2$ Hz, H-6′a), 3.71 (t, 1H, $J_{2',3'} = 9.5$ Hz, H-2′), 3.07 (t, 1H, $J_{3',4'} = 9.2$ Hz, H-3′), 3.29 (dd, 1H, $J_{4',5'} = 9.6$ Hz, H-4′), 2.94 (ddd, 1H, $J_{5',6'b} = 2.4$ Hz, H-5′), 1.90 (s, 3H, C_5-Me). Anal. Calcd for $C_{11}H_{15}N_5O_5S$ (329.33), C, 40.12; H, 4.59; N, 21.27. Found: C, 39.91; H, 4.46; N, 21.05. MS: m/z (FAB) 352 ($M + Na^+$).

b. To a cooled solution of **1** (350 mg, 1.15 mmol), and triphenyl phosphine (0.61 g, 2.30 mmol) in dry dimethylformamide (7.0 mL) was added *N*-bromosuccinimide (NBS, 0.40 g, 2.23 mmol), and the solution was heated for 2 hr at 55°C with stirring. After cooling, methanol (0.5 mL) was added to decompose the excess of NBS, followed by addition of sodium azide (1.30 g, 2.00 mmol). The suspension was heated for 5 hr at 80°C, with stirring. After cooling, the solvent was evaporated to dryness, and the residue was partitioned between water (30 mL) and 1:1 choloroform-hexane (3 × 15 mL). The water phase was evaporated to dryness, and the residue was coevaporated with methanol with 1.0 g of silica gel and then poured onto a column of silica gel. Elution with dichoromethane and methanol (0–10%) afforded **6** (0.30 g, 39%) as a solid. The physical data were identical to the authentic sample prepared by method a.

1,2,4,6-Tetra-*O*-acetyl-3-*O*-toluene-*p*-sulphonyl-5-thio-D-glucopyranose (11). To a solution of **10**[40] (300 mg, 0.61 mmol) in acetic acid (1.0 mL) and acetic anhydride (2.0 mL) was added sulphuric acid (0.1 mL) at 0°C, and the mixture was kept at 23°C for 2 d. A dil. solution of sodium bicarbonate

(15 mL) was added, and the mixture was stirred for 30 min followed by addition of water (10 mL). The mixture was partitioned between dichloromethane (30 mL) and sodium bicarbonate solution (3 × 15 mL), and the organic layer was washed with water (20 mL), dried (Na_2SO_4), filtered, and evaporated to dryness. The oily residue was chromatographed on silica gel, (7 g), using toluene-ethyl acetate (7:3) as eluent to give **11** (241 mg, 73%) as a syrup. ^{1}H NMR ($CDCl_3$): δ 6.12 (d, 1H, $J_{1',2'} = 9.4$ Hz, H-1′), 5.60–5.14 (m, 3H, H-2′, H-3′, H-4′), 4.40 (dd, 1H, $J_{5',6'a} = 4.7$ Hz, H-6′a), 4.20 (dd, 1H, $J_{6'a,6'b} = 12.0$ Hz, H-6′b), 3.42 (ddd, 1H, $J_{5',6'b} = 3.5$ Hz, H-5′), 2.45 (s, 3H, Ar*Me*), 2.19, 2.17, 2.09, 2.00 (4 × s, 12H, 4 × OAc). MS: ($C_{21}H_{26}O_{11}S_2$) m/z (FAB) 541 $(M + Na)^+$.

1-(2,4,6-Tri-*O*-acetyl-3-*O*-toluene-*p*-sulphonyl-5-thio-β-D-glucopyranosyl)thymine (13). A suspension of thymine (360 mg, 2.88 mmol) in hexamethyldisilazane (10 mL) containing a few crystals of ammonium sulphate was boiled for 5 hr. After cooling, a solution of **11** (700 mg, 0.96 mmol) in dry dichloroethane (15 mL) was added to the clear solution of the silylated thymine, followed by the addition of the trimethylsilyl trifluoromethanesulfonate (0.1 mL), with stirring. After 3 hr, the solution was evaporated to dryness and the residue was partitioned between dicholoromethane (35 mL) and a dil. solution of sodium bicarbonate (3 × 15 mL), and the organic layer was washed with water (20 mL), dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was poured onto a column of silica gel (20 g) and eluted with dicholoromethane and methanol (0–0.2%) to give **13** (426 mg, 76%) as a solid, m.p. 162–166°C. ^{1}H NMR ($CDCl_3$): δ 10.70 (s, 1H, NH), 7.57 (s, 1H, H-6), 5.84 (d, 1H, $J_{1',2'} = 9.4$ Hz, H-1′), 5.68 (t, 1H, $J_{3',4'} = 9.5$ Hz, H-3′), 5.59 (t, 1H, $J_{2',3'} = 9.4$ Hz, H-2′), 5.17 (dd, 1H, $J_{4',5'} = 10.0$ Hz, H-4′), 4.28 (dd, 1H, $J_{5',6'a} = 4.5$ Hz, H-6′a), 4.10 (dd, 1H, $J_{6'a,6'b} = 12.0$ Hz, H-6′b), 3.39 (ddd, 1H, $J_{5',6'b} = 3.5$ Hz, H-5′), 2.40 (s, 3H, *Me*Ar), 2.10, 2.04, 1.96 (3 × s, 9H, 3 × OAc), 1.94 (s, 3H, C_5-Me). Anal. Calcd. for $C_{24}H_{28}N_2O_{11}S_2$ (584.62): C, 49.62; H, 4.83; N, 4.79. Found: C, 49.41; H, 4.68; N, 4.49. MS: m/z (FAB) 585 $(M + H)^+$.

1-(2,4,6-Tri-*O*-acetyl-3-azido-3-deoxy-5-thio-β-D-allopyranosyl)thymine (14). A solution of **13** (570 mg, 0.97 mmol) in dimethylformamide (15 mL) containing lithium azide (131 mg, 2.91 mmol) was heated under reflux for 7 hr, then concentrated in *vacuo*. The residue was partitioned between water (20 mL) and dicholoromethane (3 × 15 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was poured onto a column of silica gel (20 g) and eluted, in gradient, with methanol (0–0.3%) and dichloromethane. The last fractions were tentatively identified as **14** (66 mg, 15%) as amorphous solid. ^{1}H NMR ($CDCl_3$): δ 10.21 (s, 1H, NH), 7.56 (s, 1H, H-6), 5.81 (d, 1H, $J_{1',2'} = 9.1$ Hz, H-1′), 5.60 (dd, 1H, $J_{4',5'} = 10.0$ Hz, H-4′), 4.15 (dd, 1H, $J_{2',3'} = 4.1$ Hz, H-2′), 3.97 (dd,

1H, $J_{3',4'} = 5.1$ Hz, H-3′), 4.28 (dd, 1H, $J_{5',6'a} = 5.0$ Hz, H-6′a), 4.08 (dd, 1H, $J_{6'a,6'b} = 12.0$ Hz, H-6′b), 3.36 (ddd, 1H, $J_{5',6'b} = 4.0$ Hz, H-5′), 2.14, 2.13, 2.12 (3 × s, 9H, 3 × OAc), 1.93 (s, 3H, C_5-Me). Anal. Calcd for $C_{17}H_{21}N_5O_8S$ (455.45): C, 44.83; H, 4.65; N, 15.38. Found: C, 44.62; H, 4.53; N, 15.01. MS: m/z (FAB) 456 $(M + H)^+$.

1-(3-Azido-3-deoxy-5-thio-β-D-allopyranosyl)thymine (15). A solution of **14** (50 mg, 0.11 mmol) in 0.3 M sodium methoxide (5 mL) was stirred at 23° for 16 hr, then worked up as in **6**, to give **15** (31 mg, 85%) as a solid, m.p. 135–139°C. ^{1}H NMR (DMSO-d_6/D_2O): δ 7.56 (s, 1H, H-6), 5.49 (d, 1H, $J_{1',2'} = 9.0$ Hz, H-1′), 4.03 dd, 1H, $J_{2',3'} = 5.0$ Hz, H-3′), 3.80 (dd, 1H, $J_{5',6'a} =$ 5.1 Hz, H-6′a), 3.41 (dd, 1H, $J_{2',3'} = 4.1$ Hz, H-2′), 3.39 (dd, 1H, $J_{6'a,6'b} = 12.0$ Hz, H-6′b), 3.29 (dd, 1H, $J_{4',5'} = 10.5$ Hz, H-4′), 2.75 (ddd, 1H, $J_{5',6'b} = 4.0$ Hz, H-5′), 1.92 (s, 3H, C_5-Me). Anal. Calcd for $C_{11}H_{15}N_5O_5S$ (329.33): C, 40.12; H, 4.59; N, 21.27. Found: C, 39.96; H, 4.4.7; N, 20.95. MS: m/z (FAB) 352 $(M + Na)^+$.

1-(2,4,6-Tri-*O*-acetyl-3-azido-3-deoxy-5-thio-β-D-glucopyranosyl)thymine (18). A suspension of thymine (650 mg, 5.20 mmol) in hexamethyldisilazane (20 mL) containing a few crystals of ammonium sulphate was heated under reflux for 5 hr. After cooling, a solution of **17**[35] (680 mg, 1.74 mmol) in dry dichloroethane (15 mL) was added, followed by the addition of the trimethylsilyl trifluoromethanesulfonate (0.1 mL), with stirring. After 3 hr, the solution was evaporated to dryness, and the residue was partitioned between dichloromethane (35 mL) and a dil. solution of sodium bicarbonate (3 × 15 mL), and the organic layer was washed with water (20 mL), dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was poured onto a column of silica gel (20 g) and eluted, in gradient, with methanol (0–0.2%) and dichloromethane to give **18** (570 mg, 72%) as amorphous solid. ^{1}H NMR ($CDCl_3$): δ 10.32 (s, 1H, NH), 7.56 (s, 1H, H-6), 5.92 (d, 1H, $J_{1',2'} = 9.1$ Hz, H-1′), 5.44 (t, 1H, $J_{2',3'} = 10.0$ Hz, H-2′), 4.48 (t, 1H, $J_{4',5'} = 10.0$ Hz, H-4′), 4.26 (dd, 1H, $J_{5',6'a} =$ 5.0 Hz, H-6′a), 4.11 (dd, 1H, $J_{6'a,6'b} = 12.0$ Hz, H-6′b), 3.74 (t, 1H, $J_{3',4'} = 10.0$ Hz, H-3′), 3.56 (ddd, 1H, $J_{5',6'b} = 3.5$ Hz, H-5′), 2.10, 1.98, 1.88 (3 × s, 9H, 3 × OAc), 1.92 (s, 3H, C_5-Me). Anal. Calcd for $C_{17}H_{21}N_5O_8S$ (455.45): C, 44.83; H, 4.65; N, 15.38. Found: C, 44.542; H, 4.55; N, 15.09. MS: m/z (FAB) 456 $(M + H)^+$.

1-(3-Azido-3-deoxy-5-thio-β-D-glucopyranosyl)thymine (19). A solution of **18** (200 mg, 0.44 mmol) in 0.3 M sodium methoxide (10 mL) was stirred at 23°C for 16 hr, then worked up as in **6**, to give **19** (120 mg, 83%) as a solid, m.p. 141–145°C. ^{1}H NMR (DMSO-d_6/D_2O): δ 7.56 (s, 1H, H-6), 5.52 (d, 1H, $J_{1',2'} = 10.0$ Hz, H-1′), 3.90 (t, 1H, $J_{2',3'} = 9.5$ Hz, H-3′), 3.74 (dd, 1H, $J_{5',6'a} = 5.0$ Hz, H-6′a), 3.70 (t, 1H, $J_{2',3'} = 9.5$ Hz, H-2′), 3.37 (dd, 1H, $J_{6'a,6'b} =$ 12.0 Hz, H-6′b), 3.42 (dd, 1H, $J_{4',5'} = 10.0$ Hz, H-4′), 2.94 (ddd, 1H,

$J_{5',6'b} = 4.0$ Hz, H-5′), 1.92 (s, 3H, C_5-Me). Anal. Calcd for $C_{11}H_{15}N_5O_5S$ (329.33): C, 40.12; H, 4.59; N, 21.27. Found: C, 39.83; H, 4.4.5; N, 20.89. MS: m/z (FAB) 452 $(M + Na)^+$.

Reaction of the anhydro derivative 20 with thymine (synthesis of isothionucleoside). To a solution of **20**[41] (400 mg, 1.72 mmol) in dichloromethane (15 mL) contaning triethyl amine (2 mL) was added Ti(*i*-PrO)$_4$ (142 mg, 0.50 mmol), and the mixture was boiled for 6 hr. After cooling, the solution was evaporated to dryness, and the residue was partitioned between water (15 mL) and dichloromethane (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to dryness, and the residue was chromatographed on silica gel (20 g). Elution, in gradient, with methanol (0–0.5%) and dichloromethane afforded an amorphous solid, identified as 1-(methyl-4,6-*O*-isopropylidene-5-thio-α-D-altropyranosid-2-yl)thymine (**21**) (320 mg, 52%). ^{1}H NMR ($CDCl_3$): δ 7.58 (s, 1H, H-6), 4.84 (t, 1H, $J_{2',3'} = 3.5$ Hz, H-2′), 4.41 (d, 1H, $J_{1',2'} = 2.8$ Hz, H-1′), 4.17 (dd, 1H, $J_{4',5'} = 9.5$ Hz, H-4′), 4.02 (dd, 1H, $J_{3',4'} = 2.8$ Hz, H-3′), 3.82 (dd, 1H, $J_{5',6'a} = 6.5$ Hz, H-6′a), 3.78 (dd, 1H, $J_{6'a,6'b} = 11.3$ Hz, H-6′b), 3.49 (ddd, 1H, $J_{5',6'b} = 10.5$ Hz, H-5′), 3.23 (s, 3H, OMe), 2.27 (t, 1H, $J_{3,OH} = 5.0$ Hz, C_3-OH), 1.92 (s, 3H, C_5-Me), 1.54, 1.46 (2 × s, 6H, CMe_2). Anal. Calcd for $C_{15}H_{22}N_2O_6S$ (358.41): C, 50.27; H, 6.19; N, 7.82. Found: C, 50.02; H, 6.04; N, 7.57. MS: m/z (FAB) 359 $(M + H^+$.

1-(Methyl-5-thio-β-D-altropyranosid-2-yl)thymine (22). A solution of **21** (250 mg, 0.70 mmol) in 80% acetic acid (4 mL) was left at 23°C for 16 hr and then was evaporated to dryness. The residue was coevaporated with ethanol (4 × 10 mL), and the residue was poured onto a column of silica gel (1.0 g). Elution, in gradient, with methanol (0–10%) and dichloromethane gave **22** (208 mg, 83%) as amorphous solid. ^{1}H NMR (DMSO-d_6/D_2O): δ 7.59 (s, 1H, H-6), 4.59 (d, 1H, $J_{1',2'} = 4.0$ Hz, H-1′), 4.09 (dd, 1H, $J_{4',5'} = 9.4$ Hz, H-4′), 3.93 (dd, 1H, $J_{5',6'a} = 4.5$ Hz, H-6′a), 3.89 (dd, 1H, $J_{3',4'} = 4.7$ Hz, H-3′), 3.80 (dd, 1H, $J_{6'a,6'b} = 11.7$ Hz, H-6′b), 3.35 (ddd, 1H, $J_{5',6'b} = 5.5$ Hz, H-5′), 1.93 (s, 3H, C_5-Me). Anal. Calcd for $C_{12}H_{18}N_2O_6S$ (318.35): C, 45.27; H, 5.70; N, 8.80. Found: C, 45.96; H, 5.57; N, 8.51. MS: m/z (FAB) 341 $(M + Na^+)$.

Dimethyl-1-(methyl-3,4,6-tri-*O*-acetyl-5-thio-α-D-glucopyranosid-2-yl)-1,2,3-triazole-4,5-dicarboxylate (24). To a solution of **23**[38] (600 mg, 1.66 mmol) in dry toluene (20 mL) was added dimethyl-acetylenedicarboxylate (3 mL, in excess), and the reaction mixture was stirred at 80°C under nitrogen for 24 hr. After cooling, the solution was evaporated to dryness, and the residue was partioned between dichloromethane (3 × 25 mL) and water (30 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to dryness, and the residue was chromatographed on a column of silica gel

(20 g). Elution, in gradient, with methanol (0–0.2%) and dichloromethane afforded **24** (618 mg, 74%), as amorphous solid. ^{1}H NMR ($CDCl_3$): δ 7.58 (s, 1H, H-6), 5.38 (dd, 1H, $J_{4',5'} = 10.3$ Hz, H-4′), 5.20 (dd, 1H, $J_{3',4'} = 3.0$ Hz, H-3′), 4.79 (dd, 1H, $J_{2',3'} = 3.7$ Hz, H-2′), 4.35 (d, 1H, $J_{1',2'} = 2.6$ Hz, H-1′), 4.40 (dd, 1H, $J_{5',6'a} = 3.4$ Hz, H-6′a), 4.11 (dd, 1H, $J_{6'a,6'b} = 12.0$ Hz, H-6′b), 4.01, 3.97 (2 × s, 6H, 2 × COMe), 3.70 (s, 3.70 (ddd, 1H, $J_{5',6'b} = 5.2$ Hz, H-5′), 3.47 ($C_{1'}$-OMe), 2.10, 2.06, 2.00 (3 × s, 9H, 3 × OAc). Anal. Calcd for $C_{19}H_{25}N_3O_{11}S$ (503.48): C, 45.33; H, 5.00; N, 8.35. Found: C, 45.04; H, 4.87; N, 7.95. MS: m/z (FAB) 504 ($M + H^+$).

1-(Methyl-5-thio-α-D-glucopyranosid-2-yl)-1,2,3-triazole-4,5-dicarboxamide (25). A solution of **24** (250 mg, 0.49 mmol) in 16% methanolic ammonia (7 mL) was stirred at 23°C for 18 hr, then the reaction mixture was evaporated to dryness. The residue was partitioned between water (10 mL) and ether (3 × 10 mL), and the aqueous layer was evaporated to dryness. The residue was coevaporated with ethanol (4 × 10 mL), then recrystallized from ethanol to give **25** (143 mg, 84%) as a solid, m.p. 136–140°C. ^{1}H NMR (DMSO-d_6/D_2O): δ 7.57 (s, 1H, H-6), 4.47 (d, 1H, $J_{1',2'} = 3.9$ Hz, H-1′), 4.32 (dd, 1H, $J_{2',3'} = 5.0$ Hz, H-2′), 3.96 (dd, 1H, $J_{4',5'} = 9.5$ Hz, H-4′), 3.90 (dd, 1H, $J_{5',6'a} = 4.3$ Hz, H-6′a), 3.80 (dd, 1H, $J_{3',4'} = 3.3$ Hz, H-3′), 3.75 (dd, 1H, $J_{6'a,6'b} = 12.0$ Hz, H-6′b), 3.34 (ddd, 1H, $J_{5',6'b} = 5.7$ Hz, H-5′). Anal. Calcd for $C_{11}H_{17}N_5O_6S$ (347.37): C, 38.04; H, 4.93; N, 20.16. Found: C, 37.86; H, 4.78; N, 19.89. MS: m/z (FAB) 370 ($M + Na^+$).

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