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Radical-mediated bromination of peracetylated 5-thio-D-xylopyranosyl bromides: an easy access to the corresponding anomeric orthothiolactones

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Abstract

On treatment with *N*-bromosuccinimide in refluxing carbon tetrachloride under irradiation with visible light, both α and β anomers of 2,3,4-tri-*O*-acetyl-5-thio-D-xylopyranosyl bromide were converted mainly to 2,3,4-tri-*O*-acetyl-5-thio-D-xylopyranosylidene dibromide (**5**) and to 2,3,4-tri-*O*-acetyl-5(*S*)-5-bromo-5-thio-D-xylopyranosylidene dibromide (**6**). Whereas the more reactive β anomer could be transformed cleanly into the dibromide **5** after heating for 2 h, complete conversion of the α-bromide required a prolonged treatment (~ 5 h) leading to a mixture of di-, tri- and tetra-bromides. Similarly, an anomeric mixture of 2,3,4,6-tetra-*O*-acetyl-5-thio-D-glucopyranosyl bromide yielded mainly tribromide **11** after prolonged heating. The reaction rates and the structure of the products showed again the higher reactivity of axial C–H bonds at either C-1 or C-5 in pyranosyl rings towards S_H2 processes. However, activation by the sulfur atom allowed attack of equatorial bonds as well and polybromination at both C-1 and C-5. Treatment of the C-1 dibromide **5** by silver triflate in the presence of either alcohols or thiols yielded the corresponding 5-thiosugar ortholactones **12–15**. Methyl 1-methoxy-5-thio-D-xylopyranoside (**18**), obtained from **12** on deacetylation, showed no venous antithrombotic activity in rats according to a Wessler test.

Keywords: Free-radical bromination; 5-Thio-D-xylopyranosyl bromides; 5-Thio-D-glucopyranosyl bromides; Polybromides; 5-Thio sugars ortholactones

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1. Introduction

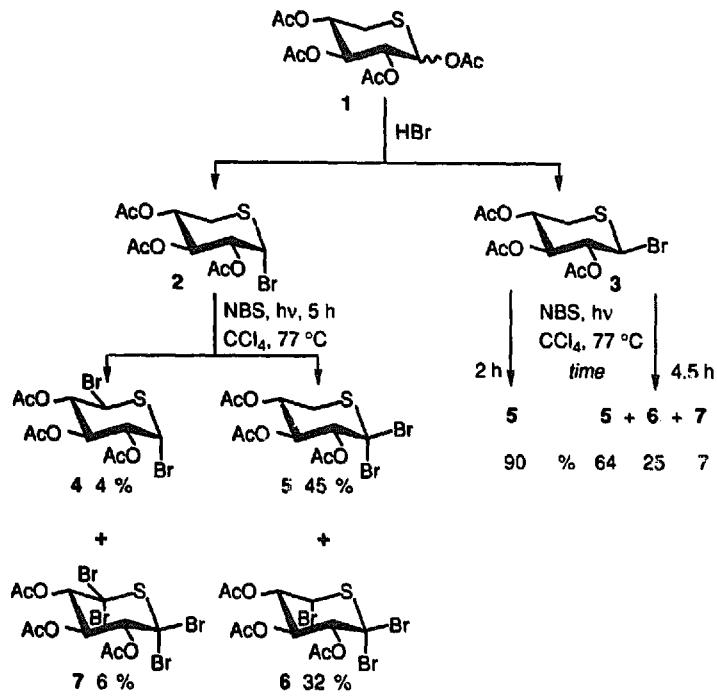
Amongst the wide class of thio sugars, sulfur-in-the-ring derivatives [1] have received limited attention, as compared to the more accessible thioglycosides for example. In fact, the methods available for the introduction of the ring sulfur atom resort to multistep syntheses which have to meet highly demanding requirements in terms of regio- and stereo-selectivity. Besides classical approaches to 4-thiofuranose [2] and 5-thiopyranose [3] derivatives, new routes to thio sugars with sulfur in the ring based on aldolases [4], modification of optically pure Diels–Alder adducts [5], or dithioacetal rearrangements [6] have also been proposed. The need for developing new and/or more potent drugs explains partially the growing interest in this domain, as shown by the recently reported synthesis of 4-thio-D-furanoses and 4'-thionucleosides [7] or the preparation of 4-cyanophenyl 1,5-dithio-β-D-xylopyranoside and analogues as antithrombotic agents [8–11]. While taking part in this research programme [12], we addressed the point whether it could be synthetically useful to take advantage of the presence of the ring sulfur atom to extend methodologies based on the radical-mediated halogenation of suitably protected sugar derivatives [13]. Such an approach opened new routes to either anomeric *gem*-dihalides [13] and diazides [14] or sugar ortholactones [15].

2. Results and discussion

Whereas glycopyranosyl bromides of natural aldoses adopt preferentially the α-anomeric configuration, both α and β anomers are known for either 2,3,4,6-tetra-*O*-acetyl-5-thio-D-glucopyranosyl bromide [16,17] or 2,3,4-tri-*O*-acetyl-5-thio-D-xylopyranosyl bromide [18]. These latter compounds were readily obtained from the corresponding peracetates **1** on treatment with either hydrogen bromide in acetic acid, hydrogen bromide gas, or trimethylsilyl bromide [12]. Crystallisation from diethyl ether–isopropyl ether afforded first the less stable β-anomer **3** [19], while the α anomer separated from the mother liquors on cooling, as a fairly stable solid.

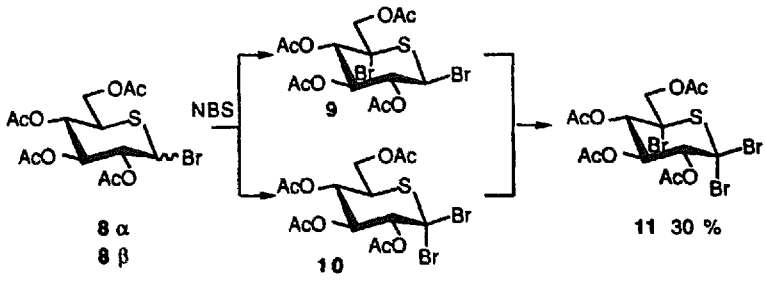
Previous studies showed that free-radical bromination of acetylated glycopyranosyl β-halides occurred at the anomeric carbon with a substituent-controlled regioselectivity which, for β-halides, follows the sequence: F ≪ Cl. In fact, whereas peracetylated β-D-glucopyranosyl fluoride led, besides a major 5-bromo isomer, to the corresponding C-1 brominated derivative in a 4% yield only, a ~65% yield was observed for the preparation of the C-1 chlorobromo sugars from the β-chlorides in both the *manno* and *gluco* series [13].

This trend suggested an even more favourable influence of a β-oriented bromine atom towards bromination at C-1. Hence, the β-bromide **3** appeared to be a favourable candidate to check this hypothesis. In turn, its α anomer could be used to investigate the sulfur atom influence on *N*-bromosuccinimide-mediated bromination since α-halides were previously found to be poorly reactive under these reaction conditions [13].



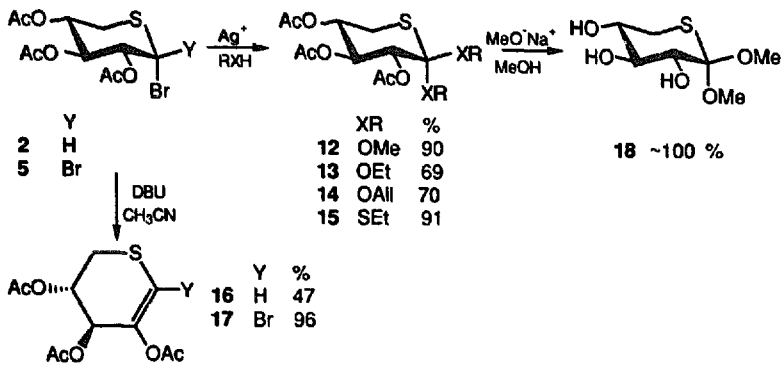
Boiling for 5 h a mixture of **2** and an excess of *N*-bromosuccinimide in carbon tetrachloride under illumination with a 250 W tungsten lamp resulted in complete conversion of the substrate to a multicomponent mixture, as shown by either TLC or ^{1}H NMR. In sharp contrast to the previously observed low reactivity of α-halides, **2** was converted not only to regio-isomeric dibromides such as **4** and **5** but also to the tribromide **6** and the tetrabromide **7**. The mixture composition, deduced from both the ^{1}H NMR spectrum of the crude material (**4**: 3%, **5**: 45%, **6**: 35%, **7**: 8%) and isolated yields (4, 25, 32, 6%, respectively), showed that the dibromide **5** and the tribromide **6** predominated. Treatment of the β-anomer **3** for 2 h under similar conditions led essentially to the dibromide **5** as shown by the ^{1}H NMR spectrum of the crude material (90% yield). However, heating for ~ 5 h led again to a mixture of **5** (64%), **6** (25%), and **7** (7%), as shown by ^{1}H NMR spectroscopy. These observations showed that, except for the minor dibromide **4**, the conversion of either **2** or **3** to polybrominated compounds followed the sequence: **2**/**3** → **5** → **6** → **7** with a higher reactivity for the β-bromide **3** as compared to its α-anomer **2**. Formation of the 5-epimer of **4**, as a minor undetected compound which, on further bromination, could be partially converted into **6** and **7**, cannot be excluded.

The same treatment was also applied to an anomeric mixture (α/β ratio: ~ 2/1) of peracetylated 5-thio-D-glucopyranosyl bromides **8** [16,17]. Prolonged heating time (> 7 h) brought about its complete conversion to give essentially the tribromide **11** (30% isolated yield) via the non-isolated dibromo intermediates **9** and **10**. The observed reactivity of α-bromides in both the 5-thio-D-*xylo* and 5-thio-D-*gluco* series suggested that homolysis of C–H equatorial bonds is due to sulfur activation [20,21] rather than conformational lability which is precluded for hexopyranoses. Formation of tri- and tetra-bromides is also the consequence of such an activation.



Identification of the reaction products was straightforward on the basis of chemical transformations and NMR data. From both ^{1}H and ^{13}C NMR spectroscopy (DEPT sequence), *gem* dibromination at C-1 in **5** was established based on the absence of an anomeric proton while the multiplicity of the H-4 proton (ddd) showed that the C-5 methylene carbon atom was not substituted. The formation of **6** from either **2** or **3** supported the proposed structure which also accounted for the small coupling (4.3 Hz) observed between H-4 and H-5e (*axial–equatorial* arrangement in a $^{4}C_{1}$ pyranosyl ring). The symmetry of structure **7** explained the absence of optical rotation as well as its NMR spectra (A_2B proton spin system, seven carbon resonances only). Finally, the structure of compound **4**, which was not produced from **3**, was in agreement with the ^{1}H NMR data ($J_{1,2}$ 3.5, $J_{4,5a}$ 10.2 Hz) and its measured optical rotation (+192°) close to that of **2** (+230°). As a matter of fact, comparison of the optical rotations of **6** (+2°) and **7** (0°) showed that replacement of an equatorial hydrogen atom by a bromine atom at C-5 resulted in a very small change. Whereas it was evident from the ^{1}H NMR spectrum of **11** that bromination occurred at both C-1 and C-5, the proposed configuration at this latter carbon atom was based on the comparison of the δ values (ppm, $CDCl_3$) measured for H-2, H-3 and H-4 in **11** (5.59, 5.72, 5.49), **8*α*** (4.91, 5.53, 5.32) and **8*β*** (5.35, 5.02, 5.33) [22]. Whereas the H-3 signal in **11** exhibited a marked deshielding induced by two axially oriented bromine atoms, the resonances of H-4 appeared at similar chemical shifts, indicating an identical environment for this nucleus in the investigated series.

Conversion of the easily accessible dibromide **5** into the corresponding thioortholactones [15] was also investigated using simple alcohols or thiols and silver triflate as the activator. The corresponding thio- or trithio-ortholactones were produced in high yields, provided appropriate precautions to prevent basic conditions had been taken. To this end, *sym*-collidine was the latter added reagent. When it was introduced first or used in excess, the decreased observed yields of compounds **12–15** were explained by the occurrence of dehydrobromination reactions [13]. In fact, treatment of bromides **2** and **5** by DBU in acetonitrile led in good yields to either 2,3,4-tri-*O*-acetyl-1,5-anhydro-5-thio-D-*threo*-pent-1-enitol **16** or its 1-bromo analogue **17**. The measured $J_{3,4}$ homonuclear couplings (~ 4 Hz) suggested that compounds **16** and **17** existed in solution mainly in the $^{5}H_{4}$ conformation [23].



Compound **12** was deprotected under Zemplén conditions to give **18** as a crystalline material which was assayed in a Wessler test [24] performed on rats [1]. Contrary to expectations based on the fact that thioxylosides might act as exogenous primers for glycosaminoglycan biosynthesis [9], compound **18** showed no venous antithrombotic activity.

3. Experimental

General methods.—Melting points were determined with a Büchi capillary apparatus and were not corrected. Optical rotations were determined with a Perkin–Elmer 241 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded with Bruker AC 200/AM 300 instruments for solutions in $CDCl_3$, with Me_4Si as the internal reference. Reactions were monitored by TLC on Silica Gel 60 F_{254} (E. Merck) plates exposed to H_2SO_4 spray followed by charring. Spraying successively a fluorescein solution in absolute EtOH (0.1% w/v), then a mixture made of H_2O_2 (30% in water) and AcOH (1/1, v/v) followed by charring was used to detect bromine-containing compounds which appeared as pink-coloured spots. Column chromatography was performed using Silica Gel Geduran Si 60 (E. Merck). On charring the TLC plates, both **2** ($R_f \sim 0.13$) and **3** ($R_f \sim 0.10$) gave a green-yellowish coloured spot.

Free-radical bromination of **2**.—A suspension of 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide **2** (1.065 g, 3 mmol) and *N*-bromosuccinimide (2.142 g, 12 mmol) in CCl_4 (108 mL) was introduced into a 500 mL Erlenmeyer flask equipped with a cooling device. A 250 W tungsten lamp, placed below the reaction vessel, was used to boil the mixture for 5 h, whereupon TLC monitoring (4:1 CH_2Cl_2–petroleum ether) showed the complete transformation of **2** to more mobile compounds. After cooling down the liquid phase to room temperature, the insoluble materials were removed by filtration and washed. The organic phase was washed successively with a saturated sodium thiosulfate solution (40 mL), then with water (4 × 30 mL). After drying (Na_2SO_4), the solvent was removed under diminished pressure, then the residue (1.63 g) was allowed to crystallise from diethyl ether–petroleum ether, to give **5** (319 mg, 2 crops, 25% yield). Concentration of the mother liquors led to a residue which was

[1] The assays were performed by Fournier Laboratories (Daix, France).

resolved by column chromatography, using CH_2Cl_2–petroleum ether mixtures as the eluant (800 mL, 2:1; then 400 mL, 3:1). This procedure, applied again to the impure fractions, led, after crystallisation and following a decreasing order of mobility, to **7** (104 mg, 0.176 mmol, 6% yield), **6** (485 mg, 0.946 mmol, 32% yield) and **4** (52 mg, 0.119 mmol, 4% yield). These figures compared well with the composition of the crude reaction mixture, calculated by comparison of the area of the acetyl resonances in the ^1H NMR spectrum: 45, 8.5, 35 and 3%, respectively. The moderate stability of **5** which was not recovered from the column, can account for its diminished isolated yield. The bromides **2**, **4**, **5**, **6**, and **7**, visible on TLC plates under UV light, showed the following R_f (4:1 CH_2Cl_2–petroleum ether): 0.13, 0.23, 0.20, 0.27, and 0.32. After H_2SO_4 spray and charring the TLC plates, the polybromides showed differently coloured spots: **2**: green/yellowish; **4**: black; **5**: pale brown; **6** and **7**: brown.

*2,3,4-Tri-*O*-acetyl-5(*R*)-5-bromo-5-thio-α-*D*-xylopyranosyl bromide* (**4**).—White crystals, mp 120–121 °C (diethyl ether–petroleum ether); $[\alpha]_D$ +192° (*c* 1.2, $CHCl_3$). ^1H NMR (300.13 MHz): δ 5.53 (t, 1 H, $J_{3,4}$ 9.6 Hz, H-3), 5.39 (t, 1 H, $J_{4,5a}$ 10.2 Hz, H-4), 5.37 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 5.06 (d, 1 H, H-5a), 4.97 (dd, 1 H, $J_{2,3}$ 9.8 Hz, H-2), 2.11, 2.09, 2.04 (3 s, 3 × 3 H, acetyl). ^{13}C NMR (75.47 MHz): δ 75.78, 73.95, 70.34 (C-2 to C-4), 53.05 (C-1), 42.18 (C-5), 20.65, 20.50, 20.44 (CH_3), 169.71, 169.21, 169.12 (C=O). CIMS [NH_3]: *m/z* 450, 452, 454 (ratio: 1/2/1): $[M + 18]^+$.

*2,3,4-Tri-*O*-acetyl-5(*S*)-5-bromo-5-thio-*D*-xylopyranosylidene dibromide* (**6**).—White crystals, mp 130–131 °C (diethyl ether–petroleum ether); $[\alpha]_D$ +2° (*c* 0.85, $CHCl_3$). ^1H NMR (200.13 MHz): δ 5.75 (t, 1 H, $J_{3,4}$ 10.1 Hz, H-3), 5.54 (d, 1 H, H-5e), 5.51 (d, 1 H, $J_{2,3}$ 9.6 Hz, H-2), 5.08 (dd, 1 H, $J_{4,5e}$ 4.3 Hz, H-4), 2.21, 2.11, 2.065 (3 s, 3 × 3 H, acetyl). ^{13}C NMR (50.32 MHz): δ 79.35, 68.17, 73.27 (C-2 to C-4), 54.47 (C-1), 51.63 (C-5), 20.58, 20.49, 20.36 (CH_3), 169.58, 168.85, 168.71 (C=O). Anal. Calcd for $C_{11}H_{13}Br_3O_6S$: C, 25.76; H, 2.55; Br, 46.73; O, 18.71; S, 6.25. Found: C, 25.90; H, 2.60; Br, 46.60; O, 18.77; S, 5.72.

*2,3,4-Tri-*O*-acetyl-5,5-dibromo-5-thio-*D*-xylopyranosylidene dibromide* (**7**).—Colourless needles, mp 173–174 °C (diethyl ether–petroleum ether); $[\alpha]_D$ 0° (*c* 1.2, $CHCl_3$). ^1H NMR (300.13 MHz): δ 5.65 (2 H, H-2, H-4), 5.52 (1 H, H-3), 2.19 (s, 6 H, acetyl), 2.03 (s, 3 H, acetyl). ^{13}C NMR (75.47 MHz): δ 79.34 (C-2, C-4), 69.36 (C-3), 56.85 (C-1, C-5), 20.46, 20.46, 20.22 (CH_3), 168.60, 168.60, 168.53 (C=O). Anal. Calcd for $C_{11}H_{12}Br_4O_6S$: C, 22.32; H, 2.04; Br, 53.00; O, 16.22; S, 5.42. Found: C, 22.39; H, 2.06; Br, 52.47; O, 16.22; S, 5.46.

Free-radical bromination of **3**.—As described above for **2**, a mixture of the β-bromide **3** (0.5 g, 1.4 mmol) and NBS (1 g, 5.6 mmol) in CCl_4 (50 mL) was boiled for 2 h. This resulted in complete transformation of the starting material as shown by the presence of a slightly more mobile spot on TLC Application of the aforementioned workup led to crude **5** (0.563 g, 93% yield) as an almost pure solid as shown by ^1H NMR. A pure sample (0.367 g, 60%) was obtained on crystallisation from Et_2O; white crystals, mp 152–153 °C; $[\alpha]_D$ +102° (*c* 0.7, $CHCl_3$). ^1H NMR (200.13 MHz, $CDCl_3$): δ 5.39 (t, 1 H, $J_{3,4}$ 9.4 Hz, H-3), 5.32 (d, 1 H, $J_{2,3}$ 9.4 Hz, H-2), 5.16 (ddd, 1 H, $J_{4,5e}$ 5.0 Hz, H-4), 3.02 (dd, 1 H, $J_{4,5a}$ 10.8 Hz, H-5a), 2.86 (dd, 1 H, $J_{5a,5e}$ 13.8 Hz, H-5e), 2.17, 2.05, 2.03 (3 s, 9 H, acetyl). ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 169.6, 169.2, 168.9 (C=O), 79.4, 72.1, 72.0 (C-2 to C-4), 60.7 (C-1), 33.7 (C-5), 20.7, 20.5,

20.4 (CH_3). Anal. Calcd for $C_{11}H_{14}Br_2O_6S$: C, 30.44; H, 3.25; Br, 36.81; O, 22.11; S, 7.39. Found: C, 30.40; H, 3.26; Br, 36.67; O, 22.28; S, 7.39.

Prolonged bromination of **3**.—An Erlenmeyer flask containing **3** (100 mg, 0.28 mmol) and NBS (200 mg, 1.12 mmol) in CCl_4 (10 mL) was irradiated and heated for 4.5 h with a 60 W tungsten lamp. After workup, ^{1}H NMR spectroscopy showed the crude reaction mixture (111 mg) to contain **5** (64%), **6** (25%), and **7** (7%).

*2,3,4,6-Tetra-*O*-acetyl-5-thio-*D*-glucopyranosyl bromides* (**8**).—The anomeric mixture (α/β: ~2/1) of 2,3,4,6-tetra-*O*-acetyl-5-thio-D-glucopyranosyl bromides was prepared in 83% yield from the acetates as described [17]. These latter compounds were prepared following a known procedure [16], except for the last step. Hydrolysis of 3,6-di-*O*-acetyl-5(*S*)-acetyl-1,2-*O*-isopropylidene-5-thio-α-D-glucofuranose (0.5 g) in water (8 mL) occurred within 2 h on heating to 80 °C in the presence of an acidic resin (0.5 g, Dowex 50 W X 4, Fluka) [5,25]. Filtration and water removal under diminished pressure followed by acetylation (Ac_2O–pyridine) under standard conditions led to the desired 1,2,3,4,6-penta-*O*-acetyl-5-thio-D-glucopyranose (0.54 g) as an anomeric mixture (α/β: ~9/1) containing no impurities visible by ^{1}H NMR.

*2,3,4,6-Tetra-*O*-acetyl-5-bromo-5(*S*)-5-thio-*D*-glucopyranosylidene dibromide* (**11**).—The obtained mixture of 2,3,4,6-tetra-*O*-acetyl-5-thio-D-glucopyranosyl bromides (**8**) (0.37 g, 0.87 mmol) was boiled for 36 h in dry CCl_4 (20 mL) in the presence of NBS (0.74 g) using a 60 W tungsten lamp (completion of the reaction occurred within 7 h for smaller scale experiments). After workup, the obtained crude residue (0.23 g) was shown by ^{1}H NMR to contain ~75% of 2,3,4,6-tetra-*O*-acetyl-5-bromo-5(*S*)-thio-D-glucopyranosylidene dibromide. Column chromatography (1:3 EtOAc–petroleum ether) led to the pure compound (0.15 g, 30%) as a gum; $[\alpha]_D$ +114° (*c* 1, $CHCl_3$). ^{1}H NMR (200.13 MHz, $CDCl_3$): δ 5.59 (d, 1 H, $J_{2,3}$ 9.6 Hz, H-2), 5.72 (t, 1 H, $J_{3,4}$ 9.6 Hz, H-3), 5.49 (d, 1 H, H-4), 4.45 (d, 1 H, $J_{6,6'}$ 12.5 Hz, H-6), 4.27 (d, 1 H, H-6'), 2.21, 2.15, 2.08, 2.02 (4 s, 12 H, acetyl). ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 169.63, 168.89, 168.83, 168.71 (C=O), 70.10, 54.86 (C-1, C-5), 79.27, 71.53, 69.90 (C-2 to C-4), 20.58, 20.53, 20.34, 20.26 (CH_3). Anal. Calcd for $C_{14}H_{17}Br_3O_8S$: C, 28.74; H, 2.93; O, 21.88. Found: C, 28.65; H, 2.84; O, 20.99.

*General procedure for the synthesis of 5-thio sugar ortholactones from 2,3,4-tri-*O*-acetyl-5-thio-*D*-xylopyranosylidene dibromide* (**5**).—A solution containing 2,3,4-tri-*O*-acetyl-5-thio-D-xylopyranosylidene dibromide (1 mmol) and a glycosyl acceptor (methyl-, ethyl-, allyl-alcohol, or ethanethiol, 10 mmol) in dry CH_2Cl_2 (3 mL) was stirred at 0 °C. Silver triflate (2 mmol) was added at once under stirring. After 10 min, while temperature was allowed to raise gradually to ~20 °C, *sym*-collidine (1.8 mmol) was added dropwise to the reaction mixture. When TLC monitoring showed complete conversion of the dibromide, the insoluble silver bromide was separated by filtration or preferably centrifugation. The solids were rinsed with $CHCl_3$ (2 × 10 mL). The liquid phases were concentrated under diminished pressure and the residue was purified by column chromatography on silica gel using mixtures of 1:2 EtOAc–petroleum ether (compounds **12**, **13**) or 1:3 (compounds **14**, **15**).

*Methyl 2,3,4-tri-*O*-acetyl-1-methoxy-5-thio-*D*-xylopyranoside* (**12**).—This compound was obtained in a 90% yield with MeOH following the general procedure (12 h stirring); mp 130–131 °C; $[\alpha]_D$ +134° (*c* 0.4, CH_2Cl_2). ^{1}H NMR (200.13 MHz, $CDCl_3$): δ 5.54

(d, 1 H, $J_{2,3}$ 9.7 Hz, H-2), 5.38 (t, 1 H, $J_{3,4}$ 9.5 Hz, H-3), 5.04 (ddd, 1 H, $J_{4,5e}$ 5.1 Hz, H-4), 3.46 (s, 3 H, OMe), 3.40 (s, 3 H, OMe), 2.76 (dd, 1 H, $J_{5a,5e}$ 13.1 Hz, H-5e), 2.64 (dd, 1 H, $J_{4,5a}$ 10.8 Hz, H-5a), 2.08, 2.02, 2.01 (3 s, 9 H, acetyl). ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 169.9, 169.7, 168.6 (C=O), 110.2 (C-1), 73.0, 72.8, 72.4 (C-2 to C-4), 53.3 (OMe), 50.3 (OMe), 26.8 (C-5), 20.8, 20.8, 20.6 (CH_3). Anal. Calcd for $C_{13}H_{20}O_8S$ (336.36): C, 46.42; H, 6.00; S, 9.53. Found: C, 46.52; H, 5.99; S, 9.61.

*Ethyl 2,3,4-tri-*O*-acetyl-1-ethoxy-5-thio-*D*-xylopyranoside* (**13**).—Reaction of EtOH with dibromide **5**, following the general procedure, led to ortholactone **13** in 69% yield (12 h stirring); mp 72–73 °C; $[\alpha]_D$ +152° (*c* 0.2, CH_2Cl_2). ^{1}H NMR (200.13 MHz, $CDCl_3$): δ 5.50 (d, 1 H, $J_{2,3}$ 9.6 Hz, H-2), 5.39 (t, 1 H, $J_{3,4}$ 9.6 Hz, H-3), 5.04 (ddd, 1 H, $J_{4,5e}$ 5.7 Hz, H-4), 3.92–3.51 (m, 4 H, OCH_2CH_3), 2.76 (dd, 1 H, $J_{5a,5e}$ 13.1 Hz, H-5e), 2.65 (dd, 1 H, $J_{4,5a}$ 10.1 Hz, H-5a), 2.07, 2.03, 2.01 (3 s, 9 H, acetyl), 1.28 (t, 3 H, OCH_2CH_3), 1.14 (t, 3 H, OCH_2CH_3). ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 169.8, 169.7, 168.5 (C=O), 109.3 (C-1), 73.3, 73.0, 72.8 (C-2 to C-4), 61.2 (OCH_2CH_3), 58.7 (OCH_2CH_3), 27.0 (C-5), 20.7, 20.6, 20.5 (CH_3), 15.1 (OCH_2CH_3), 15.1 (OCH_2CH_3). Anal. Calcd for $C_{15}H_{24}O_8S$ (364.41): C, 49.44; H, 6.64; S, 8.80. Found: C, 49.39; H, 6.64; S, 8.66.

*Allyl 2,3,4-tri-*O*-acetyl-1-allyloxy-5-thio-*D*-xylopyranoside* (**14**).—Reaction of allylalcohol with dibromide **5**, following the general procedure, led to the ortholactone **14** in 70% yield (14 h stirring); colourless oil; $[\alpha]_D$ +122° (*c* 0.2, $CHCl_3$). ^{1}H NMR (200.13 MHz, $CDCl_3$): δ 5.98–5.80 (m, 2 H, allyl), 5.54 (d, 1 H, $J_{2,3}$ 9.7 Hz, H-2), 5.42 (t, 1 H, $J_{3,4}$ 9.7 Hz, H-3), 5.47–5.12 (m, 4 H, allyl), 5.06 (m, 1 H, $J_{4,5e}$ 6.1, $J_{4,5a}$ 9.3 Hz, H-4), 4.30 (m, 2 H, allyl), 4.14 (m, 2 H, allyl), 2.76–2.72 (m, 2 H, H-5a, H-5e), 2.07, 2.03, 2.01 (3 s, 9 H, acetyl). ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 169.9, 169.7, 168.5 (C=O), 133.8, 133.2 ($CH_2CH=CH_2$), 117.0, 116.9 ($CH_2CH=CH_2$), 109.5 (C-1), 73.6, 72.9, 72.4 (C-2 to C-4), 66.3, 64.4 ($CH_2CH=CH_2$), 27.2 (C-5), 20.8, 20.7, 20.6 (CH_3). Anal. Calcd for $C_{17}H_{24}O_8S$ (388.43): C, 52.57; H, 6.23; O, 32.95. Found: C, 52.20; H, 6.16; O, 32.90.

*Ethyl 2,3,4-tri-*O*-acetyl-1-ethylthio-1,5-dithio-*D*-xylopyranoside* (**15**).—Reaction of ethanethiol with dibromide **5**, following the general procedure, led to the trithioortholactone **15** in 91% yield (12 h stirring); colourless oil; $[\alpha]_D$ +78° (*c* 0.4, CH_2Cl_2). ^{1}H NMR (200.13 MHz, $CDCl_3$): δ 5.58 (t, 1 H, $J_{3,4}$ 9.5 Hz, H-3), 5.48 (d, 1 H, $J_{2,3}$ 9.5 Hz, H-2), 5.05 (m, 1 H, $J_{4,5e}$ 4.8 Hz, H-4), 3.12 (dd, 1 H, $J_{4,5a}$ 11.2 Hz, H-5a), 2.85 (m, 2 H, SCH_2CH_3), 2.76 (SCH_2CH_3), 2.73 (dd, 1 H, $J_{5a,5e}$ 13.2 Hz, H-5e), 2.09, 2.03, 2.00 (3 s, 9 H, acetyl), 1.30 (t, 3 H, SCH_2CH_3), 1.17 (t, 3 H, SCH_2CH_3). ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 169.8, 169.4, 168.3 (C=O), 75.3, 72.9, 71.6 (C-2 to C-4), 67.6 (C-1), 28.8 (C-5), 24.8, 24.7 (SCH_2CH_3), 20.7, 20.5, 20.4 (CH_3), 13.9, 13.5 (SCH_2CH_3). Anal. Calcd for $C_{15}H_{24}O_6S_3$ (396.53): C, 45.44; H, 6.10. Found: C, 45.56; H, 6.07.

*2,3,4-Tri-*O*-acetyl-1,5-anhydro-5-thio-*D*-threo-pent-1-enitol* (**16**).—1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 100 μL) was added under stirring to a solution of bromide **2** (0.23 g, 0.647 mmol) in dry MeCN (4 mL) maintained at room temperature. After 20 h, the solvent was removed under diminished pressure and the residue was applied to a silica gel column (1:1 diethyl ether–petroleum ether) to give **16** (0.084 g, 0.305 mmol, 47% yield) as a colourless oil; $[\alpha]_D$ −311° (*c* 0.7, $CHCl_3$). ^{1}H

NMR (200.13 MHz, $CDCl_3$): δ 6.19 (d, 1 H, $J_{1,5}$ 0.7 Hz, H-1), 5.42 (d, 1 H, $J_{3,4}$ 4.0 Hz, H-3), 5.17 (ddd, 1 H, $J_{4,5e}$ 2.7, $J_{4,5a}$ 6.9 Hz, H-4), 3.17–2.99 (m, 2 H, H-5e, H-5a), 2.12, 2.11, 2.09 (3 s, 9 H, acetyl). ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 169.8, 169.6, 168.4 (C=O), 136.2 (C-2), 115.9 (C-1), 67.3, 65.9 (C-3 and C-4), 25.7 (C-5), 20.8, 20.8, 20.6 (CH_3). Anal. Calcd for $C_{11}H_{14}O_6S$ (274.29): C, 48.17; H, 5.14; S, 11.69. Found: C, 48.04; H, 4.97; S, 11.50.

2,3,4-Tri-O-*acetyl-1,5-anhydro-1-bromo-5-thio*-D-threo-*pent-1-enitol* (**17**).—A solution of the *gem*-dibromide **5** (0.035 g, 0.08 mmol) in MeCN (2 mL) was cooled down to 0 °C before addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 37 μL, 0.24 mmol). The solution was heated to 60 °C with stirring. After completion of the transformation (~ 8 h) and cooling, the reaction mixture was concentrated under diminished pressure and the resulting residue was applied to a silica gel column (1:1 diethyl ether–petroleum ether) to give **17** (27 mg, 0.0765 mmol, 96% yield) as a colourless oil; $[\alpha]_D$ −277° (*c* 1.0, $CHCl_3$). ^{1}H NMR (200.13 MHz, $CDCl_3$): δ 5.50 (d, 1 H, $J_{3,4}$ 3.9 Hz, H-3), 5.19 (m, 1 H, $J_{4,5e}$ 2.0 Hz, H-4), 3.36 (dd, 1 H, $J_{5e,5a}$ 13.6 Hz, H-5e), 3.15 (dd, 1 H, $J_{4,5a}$ 5.5 Hz, H-5a), 2.16, 2.15, 2.09 (3 s, 9 H, acetyl). ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 169.9, 169.5, 168.0 (C=O), 135.3 (C-2), 111.7 (C-1), 67.6, 67.1 (C-3 and C-4), 30.6 (C-5), 20.8, 20.8, 20.4 (CH_3). Anal. Calcd for $C_{11}H_{13}O_6SBr$ (355.18): C, 37.41; H, 3.71; S, 9.08. Found: C, 37.54; H, 3.72; S, 8.94.

Methyl 1-methoxy-5-thio-D-*xylopyranoside* (**18**).—Compound **12** (1.072 g, 3.187 mmol) in dry MeOH (15 mL) was deacetylated by addition of 2 drops of a ~ 1 M solution of NaOMe in dry MeOH. After stirring for 3 weeks at room temperature, deacetylation was complete. The solution was filtered through a pad of silica gel and concentrated. The residue (0.663 g, 3.155 mmol, quantitative) was crystallised from a MeOH solution to which was added successively small amounts of EtOAc, diethyl ether, and hexane (0.414 g, 1.969 mmol, 62% yield); white crystals, mp 120–123 °C; $[\alpha]_D$ +178° (*c* 0.5, MeOH). ^{1}H NMR (200.13 MHz, D_2O): δ 3.98 (d, 1 H, $J_{2,3}$ 9.0 Hz, H-2), 3.74 (m, 1 H, $J_{4,5e}$ 5.4 Hz, H-4), 3.49 (t, 1 H, $J_{3,4}$ 9.3 Hz, H-3), 3.47 (s, 3 H, OMe), 3.45 (s, 3 H, OMe), 2.66 (dd, 1 H, $J_{5e,5a}$ 13.3 Hz, H-5e), 2.57 (dd, 1 H, $J_{4,5a}$ 10.0 Hz, H-5a). ^{13}C NMR (50.32 MHz, D_2O): δ 110.7 (C-1), 75.7, 74.9, 72.5 (C-2, C-3 or C-4), 52.5, 49.6 (OMe), 28.6 (C-5).

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