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SYNTHETIC STUDIES IN THE 5-THIO-D-XYLOPYRANOSE SERIES *part 2*: COUPLING OF 5-THIO-D-XYLOPYRANOSYL DONORS WITH ELECTRON-RICH ARYL MOIETIES: ACCESS TO *C*-ARYL 5-THIO-D-XYLOPYRANOSIDES

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Abstract: Electron-rich benzene derivatives (anisole, 1,4-dimethoxybenzene) undergo electrophilic substitution by tri-*O*-acetyl-5-thio-D-xylopyranosyl oxonium ions produced at -78 °C from the corresponding α-trichloroacetimidate **1** in the presence of $BF_3.OEt_2$ complex to yield *C*-aryl 5-thio-D-xylopyranosides, and in particular, the *para*-substituted regioisomer in the case of anisole. With the corresponding acetylated 5-thio-α-D-xylopyranosyl bromide **2** and the same aromatic compounds, no reaction occurred in the presence of zinc oxide while zinc chloride at room temperature led to tetrahydrothiophene derivatives in moderate to good yields, by a sulfur transannular participation mechanism. With 1,3-diphenol and 1,3,5-triphenol, those sugar derivatives also reacted under quite different conditions (**1**: -78°C, $BF_3.OEt_2$, **2**: 50°C, ZnO) to afford the corresponding *C*-aryl 5-thio-D-xylopyranosides exclusively. Although *O*-aryl 5-thio-D-xylopyranosides could not be isolated, their formation as intermediates seemed reasonable under basic conditions only. With acidic catalysts, our observations, in accordance with other results, suggested that *C*-aryl 5-thio-D-xylopyranosides were formed essentially by electrophilic substitution of electron-rich aromatic derivatives.

Keywords: 2,3,4-Tri-*O*-acetyl-5-thio-D-xylopyranosyl donors; Electrophilic substitution; Electron-rich aromatic derivatives.; *C*-Aryl 5-thio-D-xylopyranosides; Sulfur transannular participation

As a result of investigations aimed at the chemical synthesis of 5-thio-β-D-xylopyranosides as potential antithrombotic agents,[1] we recently reported on the preparation of new *C*-hetaryl 5-thio-D-xylopyranosides,[2] obtained by the tri-*O*-acetyl-5-thio-D-xylopyranosyl oxonium-mediated electrophilic substitution of either furan, thiophene or benzothiophene. Even though the chemistry of 4- and 5-thiosugars is receiving a continuing attention,[3-5] the synthesis of *C*-glycosides of such thiosugars has been reported in the literature[6,7] only once, to the best of our knowledge.[5] Our initial observations revealed a straightforward access to some of these derivatives which could be obtained in ~70 % yield, as an anomeric mixture, when the more reactive tri-*O*-acetyl-5-thio-α-D-xylopyranosyl trichloroacetimidate **1**[8] was reacted with an heterocyclic compound in the presence of boron trifluoride etherate complex in dichloromethane at -78°C for ~30 min (Fig. 1). However, when the α-bromide **2** was used for this purpose, its transformation in the presence of $ZnCl_2$ required a higher temperature in order to proceed completely: a selective although partial conversion was observed when the experiment was carried out at -5°C whereas allowing **2** to react at room temperature resulted in decreased yields of the *C*-xylosides due to the formation of

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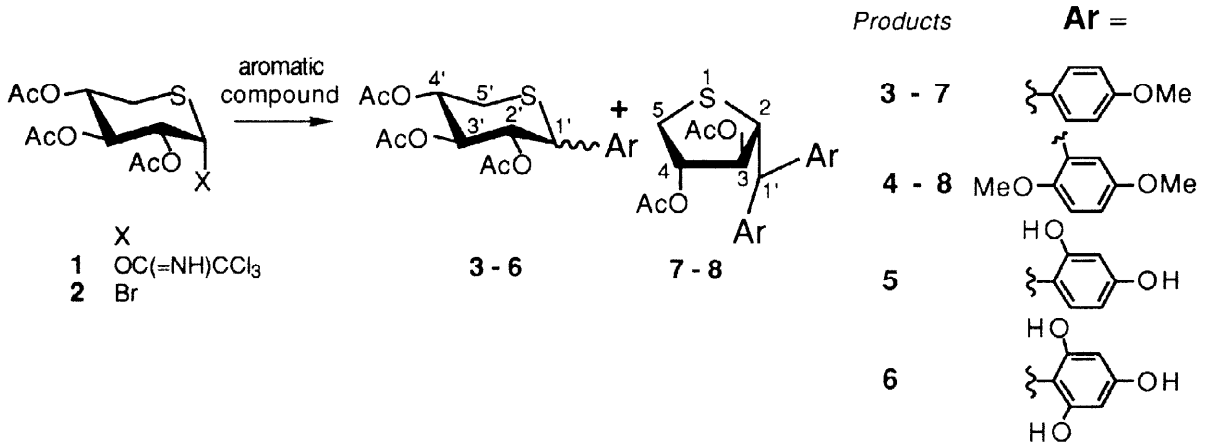
tetrahydrothiophene derivatives by a sulfur transannular participation mechanism.[2,9] This approach to an almost unknown class of sugar derivatives[2,5] was extended to a series of phenol-derived compounds in order to more precisely establish the scope and limitations of the method and to get a better insight into the various reaction pathways leading to the final products. Therefore, our initial investigations with heterocyclic compounds were pursued, using phenol derivatives bearing electron-releasing substituents and either the trichloroacetimidate **1**[8] or the bromide **2**. The observations gathered along this study are disclosed thereafter. Additional data collected when using either phenol or electron-poor phenol derivatives will be reported in following papers.

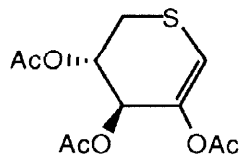


Compound	ArH	Temp., (Time) °C h		Products %[a]	β/α[b]		%[a]
1[c]	anisole	-78 (0.5)	**3**	69	57/43		
1[c]	*p*-dimethoxybenzene	-78 (1)	**4**	5–7	-		
1[c]	"	-78 (1)[d]	**4**	25	~1/1		
1[c]	"	-78 (1)[e]	**4**	56	~1/1		
1[f]	1,3-diphenol	-78 (0.25)	**5**	85	74/26		
1[f]	1,3,5-triphenol	-78 (1)	**6**	82	76/24		
2[g]	anisole[h]	-5 (40)[i]	**3**	6	90/10	**7**	22
2[g]	"	45 (2)[j]	**3**	0	-	**7**	36
2[g]	"	r.t. (2.5)[k]				**7**	67
2[g]	*p*-dimethoxybenzene	r.t. (21)[l]	**4**	m		**8**	22
2[n]	anisole	50 (12)	**3**	0		**9**	m
2[n]	*p*-dimethoxybenzene	50 (12)	**4**	0		**9**	m
2[n]	1,3-diphenol	50 (<1)	**5**	82	70/30		
2[n]	1,3,5-triphenol	50 (<1)	**6**	88	80/20		

Fig. 1. [a] Isolated yields. [b] This ratio was measured by ^1H NMR. [c] The reaction was performed at -78 °C in dry CH_2Cl_2 under argon in the presence of boron trifluoride etherate (1 / ArH / $BF_3.OEt_2$: 1 / 2 / 0.1 eq unless otherwise indicated). [d] One equivalent of $BF_3.OEt_2$ was used. [e] Four equivalents of $BF_3.OEt_2$ were used. [f] The reaction was performed in anhydrous CH_2Cl_2 in the presence of $BF_3.OEt_2$ (1 / ArH / $BF_3.OEt_2$: 1 / 2 / 0.1 molar eq). [g] With 2, the reactions were performed in dry $CHCl_3$ in the presence of anhydrous $ZnCl_2$ (2 / ArH / $ZnCl_2$: 1 / 5 / 5 eq unless otherwise indicated). [h] No transformation was observed after 5h at -30°C. [i] 40% of unchanged 2 was recovered. [j] A smaller amount of $ZnCl_2$ (1.1 eq) was used. [k] The ratio 2 / anisole / $ZnCl_2$ was: 1 / 9 / 10 eq. [l] 2eq of $ZnCl_2$ were used. [m] The yield was not determined. [n] The reaction was performed in anhydrous CH_3CN under nitrogen in the presence of ZnO and 13 X molecular sieves.

Reaction of trichloroacetimidate **1** occurred at -78°C, as already observed,[2] in the presence of $BF_3.OEt_2$ to afford selectively, by reaction with either anisole or 1,4-dimethoxybenzene, the corresponding *C*-aryl 5-thio-D-xylopyranosides **3** and **4** respectively. Similar electrophilic substitutions of fully *O*-protected polyphenols have been shown to occur with dihydropyran[10] and natural sugar derivatives,[11-14] usually around room temperature.[11,12,14] The high efficiency of sulfur atoms in stabilizing a nearby positive charge most probably accounted for the lower reaction temperatures and milder conditions observed along this study. Whereas the stereoselectivity of the studied $BF_3.OEt_2$-catalyzed electrophilic substitutions was low under the applied conditions, it is worth to note that only the less hindered, *para*-substituted *C*-xylosides were formed on reaction with anisole. Other groups reported that similar treatments applied to natural sugar derivatives also led to the *C*-*p*-methoxyphenyl glucopyranosides.[14-16] However, in the case of 1,4-dimethoxybenzene, use of a catalytic amount of $BF_3.OEt_2$ (0.1 eq) led to the corresponding *C*-xyloside in low yield. An excess of Lewis acid increased significantly the reaction yield to 25% (1 eq) and 56% (4 eq). It was assumed that boron trifluoride might give a tighter complex with 1,4-dimethoxybenzene as a result of the enhanced basicity of the oxygen atoms in this compound, as compared to anisole and diethyl ether. This is reasonable on the basis of the extended electron delocalization possible in 1,4-dimethoxybenzene, in analogy with proposals put forward to account for the different reaction rates observed for the Lewis acid-catalyzed debenzylation of *p*-substituted benzyloxybenzene derivatives.[17] Even though the lability of electron-rich benzene derivatives under acidic conditions has been mentioned in the literature,[12] the decomposition of the aromatic compound seemed a less probable hypothesis since this process should be even more favoured when larger amounts of $BF_3.OEt_2$ were used, thus resulting in decreased yields, in contradiction with our results.

In keeping with our previous observations,[2] the bromide **2** only reacted partially at -5°C in the presence of anhydrous zinc chloride and anisole to afford **3** in low yield and the tetrahydrothiophene derivative **7** (22% yield). Similar rearranged products, explained by a sulfur transannular participation mechanism, were also obtained by electrophilic substitution of heterocyclic compounds.[2] When the reaction was carried out at 45°C, **7** could be isolated in a somewhat higher yield (36 %). However, use of anisole and $ZnCl_2$ in larger excess allowed an efficient preparation of **7** (67 % yield). When **2** was reacted with 1,4-dimethoxybenzene for 21 h, the ring-restricted compound **8** was isolated in a 22 % yield from the complex reaction mixture. Attempts were made in order to react the bromide with anisole and 1,4-dimethoxybenzene in the presence of ZnO and molecular sieves. This oxide, mentioned in the literature[18] as an efficient activator for glycosidation, is advantageous in terms of price, handling and environmental concern, as compared to more conventional activating systems. The 5-thio-D-xylal **9**[19] was the only product observed under these conditions, produced in small amounts by dehydrobromination while heating for 12h at 50 °C.



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The reactivity of polyphenols was also investigated. Whereas the product distribution observed with phenol was complex, as disclosed in a following paper, **1** and **2** could be selectively coupled to either 1,3-diphenol (resorcinol) or 1,3,5-triphenol (phloroglucinol). With such electron-rich polyphenols and with both glycosyl donors, the reaction led exclusively to the corresponding *C*-aryl 5-thioxylosides in high isolated yields (~85%), the β-anomer being predominant (α/β:~3/1). None of the products arising from either *O*-5-thioxylosylation or ring-restriction were observed. The unsaturated compound **9** was not detected either. With these polyphenols, the coupling reaction also proceeded when **2** was treated in the presence of zinc oxide and molecular sieves to give **5** and **6** in yield and α/β ratio comparable to those observed with **1**.

These observations shed some light on the possible pathways leading to the reaction products. The activation of the phenyl ring by one or two methoxy groups reasonably accounts for its enhanced reactivity towards electrophilic substitution, thus allowing efficient preparations of **3** and **4** from **1**, at -78°C. In the case of unprotected polyphenols, the initial formation of *O*-aryl 5-thioxylopyranosides followed by a fast *O*—>*C*-glycoside rearrangement (Fries-type rearrangement) is a possibility to be considered on the basis of various reported precedents.[20-28] It is known from the literature that this rearrangement occurs easily near or below room temperature for *O*-aryl glycosides of natural sugars, depending on the reactivity of the aglycon moiety.[22] This pathway which was investigated in more details when our study was extended to phenols, can explain the success of the ZnO-induced transformation of **2** in the presence of polyphenols which could also result from the electrophilic substitution of phenate species.[5] It is reasonable to assume that the zinc oxide acted as a base, producing phenolate ions involved in the bromide displacement, as proposed for a long-known base-catalyzed preparation of *O*-aryl glycosides of natural sugars.[29-31] Such a nucleophilic displacement was, of course, not feasible with anisole and 1,4-dimethoxybenzene, thus explaining the formation of the 5-thio-D-xylal **9** as a byproduct. However, under the acidic conditions applied to transform the trichloroacetimidate **1** and also the bromide **2**, this pathway might play a minor role, if no role at all, since electrophilic substitution was observed to occur, with anisole and 1,4-dimethoxybenzene, at temperatures as low as -78 °C, thus proving that electrophilic substitution can take place directly through a single reaction step.The reason why sulfur transannular participation did not occur in the case of polyphenols is questionable. This might be due to a possible *H*-bonding between a hydrogen atom from a hydroxyl group and the endocyclic sulfur atom, favourably arranged in a 6-membered ring. The occurrence of such intramolecular *H*-bondings has been demonstrated by NMR[32] and X-ray analysis[33] for either heterocyclic[32] or sugar analogs[33] displaying a primary carbinol. Since hydroxyl groups are more acidic in phenols than in alcohols, compounds **7** and **8** should favour even more such a *H*-bonding, thereby decreasing the nucleophilicity of the ring sulfur atom and its aptitude to trigger further reactions through transannular participation.

The obtained products could be identified readily by ^1H and ^{13}C NMR spectroscopy. Assignment of the anomeric configuration of the *C*-aryl 5-thio-D-xylopyranosides was straightforward on the basis of the observed $J_{1',2'}$ couplings found smaller (4 - 6 Hz) for α-anomers as compared to their β-counterparts (~10.5 Hz).[34] Comparison of the other vicinal couplings showed that β-*C*-xylosides existed under a typical $^4C_1$-D chair conformation. Due to the bulkiness of their aglycon moiety, the corresponding α-anomers exhibited $^4C_1$-D chair conformations more or less distorted depending on the magnitude of unfavourable steric interactions. Hence, structure **4** was more distorted than **3** in $CDCl_3$ solution. However, in MeOH, **5** was found unexpectedly to be more distorted than **6**. Depending on the anomeric configuration, the proton resonances in the ^1H NMR spectra appeared following the same sequence, from low to high fields:

β-anomers: δ H2' > H4' > H3' > H1' > H5e' > H5a'

α-anomers: δ H3' > H2' > H4' > H1' > H5e' > H5a'

For compound **6**α in which both H-3' and H-5a' were deshielded by ~0.5 ppm, H-5a' appeared however at lower field as compared to H-5e'. This deshielding was most probably induced by the proximity of a phenolic hydroxyl group which could also account for the low field resonance of H-2' in **6**β. In the case of **5**β, we observed sharper signals for the H-1' and H-2' resonances when the ^1H NMR spectrum was recorded at 50 and 80°C. The broadening of the signals observed at room temperature suggested the existence of conformers in solution due to a restricted rotation around the *C*-glycosidic bond. It is worth to note that the 2-acetoxy resonance was shielded in each of these *C*-aryl 5-thio-D-xylopyranosides, this effect being more pronounced for β-anomers.

Compounds **10** and **11**, obtained from **7** and **5** upon deacetylation were assayed in a Wessler test[35] performed on rats.* They showed no activity at a 20 mg/kg dose, the product being administered by oral route 4 h before examination of thrombus formation, induced by factor Xa as the thrombogenous agent.

In summary, this study showed that tri-*O*-acetyl-5-thio-D-xylopyranosyl oxonium ions produced from the corresponding trichloroacetimidate reacted at -78 °C with electron-rich benzene derivatives (anisole, 1,4-dimethoxybenzene) to afford by electrophilic substitution *C*-aryl 5-thio-D-xylopyranosides in good yields, and in particular, the *para*-substituted regioisomer in the case of anisole. With the corresponding 5-thioxylosyl bromide and the same aromatic compounds, no reaction occurred in the presence of zinc oxide while zinc chloride at room temperature led to tetrahydrothiophene derivatives in moderate to good yields, by a sulfur transannular participation mechanism. With 1,3-diphenol and 1,3,5-triphenol, the sugar derivatives also reacted under quite different conditions (**1**: -78°C, $BF_3.OEt_2$, **2**: 50°C, ZnO) to afford the corresponding *C*-aryl 5-thio-D-xylopyranosides, exclusively. Although *O*-aryl 5-thio-D-xylopyranosides could not be isolated, their formation as intermediates seemed reasonable under basic conditions only. With acidic catalysts, our observations suggested that *C*-aryl 5-thio-D-xylopyranosides were formed essentially by electrophilic substitution of electron-rich aromatic derivatives.

* The assays were performed by Fournier Laboratories (Daix, France).

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EXPERIMENTAL

General methods. Acetonitrile, chloroform and dichloromethane were freshly distilled over CaH_2 and kept under an inert atmosphere. The indicated yields were calculated from the weight of purified anomeric mixtures, the ratio of which was determined by ^1H NMR. Proton coupling constants (J) are given in Hz. For further details, see the preceding papers[2,19] in this series.

*1-(2,3,4-Tri-*O*-acetyl-5-thio-*D*-xylopyranosyl)-4-methoxybenzene* **3**. Boron trifluoride etherate (25 µL, ~0.2 mmol) was added with a seringe to a cooled (-78°C) and magnetically stirred solution of **1** (0.786 g, 1.8 mmol) and anisole (0.39 g, 3.6 mmol) in dry dichloromethane (~12 mL), with exclusion of moisture (argon atmosphere). When TLC monitoring showed the complete transformation of the glycosyl donor **1** (~35 min), the medium was quenched by adding triethylamine (~3.6 mmol). The residue obtained upon concentration under reduced pressure was applied to a silica gel column eluted with ethyl acetate-petroleum ether 1:2 (v/v) to afford **3** (0.473 g, 1.24 mmol, 69% yield, β/α=57/43). Pure **3**β was obtained by crystallisation from diethyl ether. Concentration of the enriched mother liquors led to **3**α in admixture with small amounts of the β-anomer which could not be removed by chromatography due to identical mobilities in different solvent systems.

3β : white crystals; mp 168-169°C (diethyl ether); $[\alpha]_D$ -15° (c 0.6, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 7.23 (d, 2H, J 8.7, H-*arom.*), 6.83 (d, 2H, J 8.7, H-*arom.*), 5.47 (dd, 1H, $J_{2',3'}$ 9.1, H-2'), 5.20 (m, 1H, $J_{4',5'e}$ 4.4, H-4'), 5.12 (t, 1H, $J_{3',4'}$ 9.7, H-3'), 3.91 (d, 1H, $J_{1',2'}$ 10.6, H-1'), 3.78 (s, 3H, OMe), 2.92 (dd, 1H, $J_{5'a,5'e}$ 13.3, H-5'e), 2.80 (dd, 1H, $J_{4',5'a}$ 10.5, H-5'a), 2.05, 2.02, 1.72 (3s, 9H, acetyl). ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.9, 169.8, 169.1 (acetyl), 159.6 (C-*arom.*: C-1), 129.4, 129.4 (C-H-*arom.*: C-3, C-5), 127.2 (C-*arom.*: C-4), 114.1, 114.1 (C-H-*arom.*: C-2, C-6), 75.1, 74.6, 72.9 (C-2', C-3', C-4'), 55.2 (OMe), 49.1 (C-1'), 31.3 (C-5'), 20.9, 20.6, 20.3 (acetyl).

Anal.: Calcd for $C_{18}H_{22}O_7S$ (382.43): C, 56.53; H, 5.80; S, 8.38; found: C, 56.33; H, 5.82; S, 8.21.

3α : colourless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 7.47 (d, 2H, J 8.7, H-*arom.*), 6.88 (d, 2H, J 8.7, H-*arom.*), 5.55 (t, 1H, $J_{3',4'}$ 8.5, H-3'), 5.37 (dd, 1H, $J_{2',3'}$ 8.7, H-2'), 5.09 (ddd, 1H, $J_{4',5'e}$ 4.7, H-4'), 4.40 (d, 1H, $J_{1',2'}$ 4.5, H-1'), 3.81 (s, 1H, OMe), 2.88 (dd, 1H, $J_{5'a,5'e}$ 13.8, H-5'e), 2.69 (dd, 1H, $J_{4',5'a}$ 9.2, H-5'a), 2.09, 2.05, 2.00 (3s, 9H, acetyl). ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.8, 169.7, 169.6 (acetyl), 158.9 (C-*arom.*: C-1), 130.0, 130.0 (C-H-*arom.*: C-3, C-5), 129.0 (C-*arom.*: C-4), 113.9, 113.9 (C-H-*arom.*: C-2, C-6), 73.3, 71.4, 69.6 (C-2', C-3', C-4'), 55.3 (OMe), 43.9 (C-1'), 27.5 (C-5'), 20.9, 20.8, 20.7 (acetyl).

Anal.: Calcd for $C_{18}H_{22}O_7S$ (382.43): C, 56.53; H, 5.80; S, 8.38; found: C, 56.67; H, 5.87; S, 8.29.

*2-(2,3,4-Tri-*O*-acetyl-5-thio-*D*-xylopyranosyl)-1,4-dimethoxybenzene* **4**. Boron trifluoride etherate (345 µL, ~2.75 mmol) was added to **1** (0.30 g, 0.69 mmol) and 1,4-dimethoxybenzene (0.19 g, 1.37 mmol) dissolved in anhydrous dichloromethane (~4 mL), with stirring at -78°C under an argon atmosphere. After completion of the reaction, triethylamine (~1.4 mmol) was added before removal of the low-boiling compounds under reduced pressure. The obtained residue was resolved by column chromatography with ethyl acetate-petroleum ether 1:1 (v/v) as the mobile

phase to afford **4** (0.157 g, 0.38 mmol, 56% yield, β/α=1/1). Analytical samples of pure anomers were obtained by "flash" chromatography with ethyl acetate-hexane 1:1.5 (v/v) as the mobile phase. **4β** : clear yellowish oil; $[\alpha]_D$ -6° (c 1.2, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 6.87 (d, 1H, ^3J 1.5, H-3), 6.78 (m, 2H, H-5, H-6), 5.60 (dd, 1H, $J_{2',3'}$ 9.5, H-2'), 5.18 (m, 1H, $J_{4',5'e}$ 5.4, H-4'), 5.15 (t, 1H, $J_{3',4'}$ 9.5, H-3), 4.56 (d, 1H, $J_{1',2'}$ 9.5, H-1'), 3.81 (s, 3H, OMe), 3.75 (s, 3H, OMe), 2.94-2.78 (m, 2H, H-5'a, H-5'e), 2.05, 2.02, 1.72 (3s, 9H, acetyl). ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.9, 169.8, 169.2 (acetyl), 153.7, 151.4 (C-*arom.*: C-1, C-4), 129.0 (C-*arom.*: C-2), 124.2, 115.0, 112.4 (C-H-*arom.*: C-3, C-5, C-6), 74.9, 74.3, 73.1 (C-2', C-3', C-4'), 56.5, 55.7 (OMe), 31.5 (C-1'), 25.3 (C-5'), 20.9, 20.6, 20.3 (acetyl). M.S. (c.i.) *m/z* (intensity %): 412.30 (M^+, 10), 411.80 (12), 292.00 (27), 250.00 (32), 233.00 (12), 84.95 (30), 82.85 (21), 71.05 (16), 57.05 (21), 54.95 (18), 43.05 (100).
4α : clear yellowish oil; ^1H NMR (200 MHz, $CDCl_3$) δ 7.08 (d, 1H, H-3), 6.78 (m, 2H, H-5, H-6), 5.46 (t, 1H, $J_{3',4'}$ 6.9, H-3'), 5.28 (dd, 1H, $J_{2',3'}$ 7.1, H-2'), 5.06 (ddd, 1H, $J_{4',5'e}$ 3.6, H-4'), 4.87 (d, 1H, $J_{1',2'}$ 4.2, H-1'), 3.79 (s, 1H, OMe), 3.78 (s, 1H, OMe), 3.06 (dd, 1H, $J_{5'a,5'e}$ 14.1, H-5'e), 2.86 (dd, 1H, $J_{4',5'a}$ 7.5, H-5'a), 2.11, 2.10, 1.95 (3s, 9H, acetyl). ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.8, 169.7, 169.6 (acetyl), 153.2, 150.9 (C-*arom.*: C-1, C-4), 127.1 (C-*arom.*: C-2), 115.7, 112.7, 111.4 (C-H-*arom.*: C-3, C-5, C-6), 70.5, 69.4, 69.3 (C-2', C-3', C-4'), 56.1, 55.8 (OMe), 37.6 (C-1'), 28.4 (C-5'), 21.0, 20.8, 20.8 (acetyl). M.S. (c.i.) *m/z* (intensity %): 412.70 (M^+, 7), 412.00 (13), 292.00 (28), 250.00 (31), 233.00 (10), 84.95 (27), 82.95 (26), 71.05 (17), 57.05 (25), 54.95 (19), 42.95 (100).

*2-(2,3,4-Tri-*O*-acetyl-5-thio-*D*-xylopyranosyl)-1,5-dihydroxybenzene* **5** . from **1** : To a dichloromethane-acetonitrile 1:1 (v/v) mixture (4 mL) containing **1** (0.258 g, 0.59 mmol) and resorcinol (0.13 g, 1.18 mmol), boron trifluoride etherate was added (8 µL, ~0.063 mmol) at -78°C under an inert atmosphere. After 15 min, when TLC showed the disappearance of the starting material, the reaction medium was quenched with triethylamine (1.8 mmol). After the volatiles were removed under reduced pressure, the reaction mixture was taken up in chloroform. Washings of the organic phase with a 5% aq NaOH solution, then water followed by drying ($MgSO_4$), filtration through a bed of celite and concentration, led to a crude reaction mixture which was resolved by column chromatography on silica gel with ethyl acetate-hexane 3:2 (v/v). **5** was obtained as an anomeric mixture (0.202 g, 0.5 mmol, 85% yield, β/α=74/26). When using a smaller amount of resorcinol (0.078 g, 0.71 mmol), this procedure led to comparable results.
from **2**: Zinc oxide (459 mg, 5.64 mmol) and 13X molecular sieves (3.15 g) were introduced into a round bottomed flask connected to a vacuum pump. After heating at ~80 °C for ~30 min under reduced pressure, the solids were allowed to cool down to room temperature under an inert atmosphere. Dry acetonitrile (25 mL) was then poured into the flask and heated to 50 °C for ~30 min. Addition of resorcinol (1,3-dihydroxybenzene) (1.55 g, 14.1 mmol) was followed by heating for ~30 min at the same temperature under stirring. The bromide **2** (1 g, 2.82 mmol) was then added and the reaction was allowed to proceed at 50 °C under nitrogen. After complete transformation of **2**, the reaction mixture was centrifugated. The separated solids were rinsed with ethyl acetate before centrifugation. The combined organic phases were evaporated under reduced pressure to afford a residue which was taken up in chloroform. The organic phase was washed twice with a 10 % NaOH aq solution, then with water. After drying ($MgSO_4$), filtration of the liquid phase through a bed of

celite and concentration, the obtained residue was resolved by column chromatography on silica gel with ethyl acetate-hexane 1:1.5 (v/v) as eluent to give an anomeric mixture of the *C*-5-thio-D-xyloside **5** (0.93 g, 2.31 mmol, 82% yield, β/α=70/30). Pure **5β** was obtained first by crystallisation. **5α** was also obtained by crystallisation from enriched mother liquors.

5β : white crystals; mp 163-165°C (diethyl ether); $[\alpha]_D$ -2° (c 0.6, AcOEt). ^{1}H NMR (300 MHz, MeOD) δ 6.91 (d, 1H, $J_{arom.}$8.5, H-*arom.*), 6.25 (d, 1H, $J_{arom.}$2.3, H-*arom.*), 6.14 (dd, 1H, $J_{arom.}$2.3, $J_{arom.}$8.5, H-*arom.*), 5.36 (dd, 1H, $J_{2',3'}$ 9.2, H-2'), 5.07 (t, 1H, $J_{3',4'}$ 9.2, H-3'), 5.04 (ddd, 1H, $J_{4',5'a}$ 8.4, H-4'), 4.88 (s, 2H, OH), 4.49 (d, 1H, $J_{1',2'}$ 10.8, H-1'), 2.92 (m, 1H, $J_{5'a,5'e}$ 13.1, H-5'a), 2.80 (dd, 1H, $J_{4',5'e}$ 3.5, H-5'a), 1.99, 1.94, 1.67 (3s, 9H, acetyl). ^{13}C NMR (75 MHz, MeOD) δ 171.5, 171.4, 171.1 (acetyl), 159.1, 157.6 (C-*arom.*), 131.2 (C-H-*arom.*), 114.0 (C-*arom.*), 107.8, 103.3 (C-H-*arom.*), 76.4, 76.4, 74.6 (C-2', C-3', C-4'), 56.0 (C-1'), 31.9 (C-5'), 20.8, 20.6, 20.4 (acetyl).

Anal.: Calcd for $C_{17}H_{20}O_8S.1H_2O$: C, 50.74; H, 5.51; S, 7.97; found: C, 50.99; H, 5.18; S, 7.70.

5α : colourless oil; $[\alpha]_D$ +173° (c 0.2, MeOH). ^{1}H NMR (200 MHz, MeOD) δ 7.17 (d, 1H, $J_{arom.}$9.1, H-*arom.*), 6.28 (dd, 1H, $J_{arom.}$2.5, $J_{arom.}$9.1, H-*arom.*), 6.28 (d, 1H, $J_{arom.}$2.5, H-*arom.*), 5.36 (t, 1H, $J_{3',4'}$ 6.9, H-3'), 5.20 (dd, 1H, $J_{2',3'}$ 4.2, H-2'), 5.00 (ddd, 1H, $J_{4',5'a}$ 7.5, H-4'), 4.84 (s, 2H, OH), 4.77 (d, 1H, $J_{1',2'}$ 4.1, H-1'), 3.08 (dd, 1H, $J_{4',5'e}$ 3.8, H-5'e), 2.91 (dd, 1H, $J_{5'a,5'e}$ 14.2, H-5'a), 2.07, 2.06, 1.91 (3s, 9H, acetyl). ^{13}C NMR (50 MHz, MeOD) δ 171.5, 171.5, 171.1 (acetyl), 158.9, 157.0 (C-*arom.*), 130.5 (C-H-*arom.*), 117.0 (C-*arom.*), 107.2, 103.3 (C-H-*arom.*), 72.3, 70.8, 70.5 (C-2', C-3', C-4'), 38.2 (C-1'), 29.3 (C-5'), 20.9, 20.7, 20.7 (acetyl).

Anal.: Calcd for $C_{17}H_{20}O_8S.1H_2O$: C, 50.74; H, 5.51; S, 7.97; found: C, 50.85; H, 5.31; S, 7.74.

*2-(2,3,4-Tri-*O*-acetyl-5-thio-*D*-xylopyranosyl)-1,3,5-trihydroxybenzene* **6**. from **1**, following the procedure described above for compound **5**: Boron trifluoride etherate (12 µL, ~0.096 mmol) was added at -78°C to a dry dichloromethane-acetonitrile 1:1 (v/v) mixture (6 mL) containing **1** (0.416 g, 0.95 mmol) and phloroglucinol (0.31 g, 1.91 mmol). Workup and two chromatographic purifications on silica gel with first dichloromethane-methanol 9:1, then chloroform-methanol 9:1 (v/v) led to **6** (0.328 g, 0.78 mmol, 82% yield, β/α=76/24).

from **2**, following the procedure described above for compound **5**: The treatment of **2** (1 g, 2.82 mmol) and 1,3,5-trihydroxybenzene (phloroglucinol) (1.776 g, 14.1 mmol) with ZnO (459 mg, 5.64 mmol) and 13X molecular sieves (3.15 g) led, after workup and silica gel chromatography with dichloromethane-hexane 9:1 (v/v), to an anomeric mixture of the *C*-5-thio-D-xyloside **6** (1.04 g, 2.48 mmol, 88% yield, β/α=80/20). Analytical samples of each anomers could be obtained by chromatography using chloroform-methanol 9:1 (v/v) as the mobile phase.

6β : beige solid; mp~201-203°C (darken before melting); $[\alpha]_D$ -6° (c 0.7, MeOH). ^{1}H NMR (200 MHz, MeOD) δ 6.04 (dd, 1H, $J_{2',3'}$ 9.2, H-2'), 5.82 (d, 1H, $J_{arom.}$2.3, H-*arom.*), 5.75 (d, 1H, $J_{arom.}$2.3, H-*arom.*), 5.11 (m, 1H, H-4'), 5.02 (t, 1H, $J_{3',4'}$ 9.2, H-3'), 4.84 (s, 3H, OH), 4.60 (d, 1H, $J_{1',2'}$ 10.8, H-1'), 2.82 (m, 2H, H-5'a, H-5'e), 2.01, 1.97, 1.70 (3s, 9H, acetyl). ^{13}C NMR (50 MHz, MeOD) δ 171.7, 171.6, 171.1 (acetyl), 159.7, 159.3, 158.6 (C-*arom.*), 100.9 (C-*arom.*), 95.9, 95.0 (C-H-*arom.*), 77.2, 74.9, 74.8 (C-2', C-3', C-4'), 41.2 (C-1'), 32.2 (C-5'), 20.8, 20.7, 20.5 (acetyl).

Anal.: Calcd for $C_{17}H_{20}O_9S.1H_2O$: C, 48.80; H, 5.30; S, 7.66; found: C, 48.82; H, 5.00; S, 7.53.

6α : clear beige oil; $[\alpha]_D$ +139° (c 0.6, MeOH). ^{1}H NMR (200 MHz, MeOD) δ 5.86 (t, 1H, $J_{3,4}$ 8.9, H-3), 5.83 (s, 2H, H-*arom.*), 5.26 (dd, 1H, $J_{2',3'}$ 8.9, H-2'), 5.06 (ddd, 1H, $J_{4',5'a}$ 9.8, H-4'), 5.03 (d,

1H, $J_{1',2'}$ 6.6, H-1'), 4.87 (s, 3H, OH), 3.57 (dd, 1H, $J_{5'a,5'e}$ 12.7, H-5'a), 2.77 (dd, 1H, $J_{4',5'e}$ 4.8, H-5'e), 2.02, 2.00, 1.84 (3s, 9H, acetyl). ^{13}C NMR (50 MHz, MeOD) δ 171.8, 171.7, 171.6 (acetyl), 158.7, 152.5, 152.5 (C-*arom.*), 104.7 (C-*arom.*), 95.6, 95.6 (C-H-*arom.*), 74.6, 73.7, 72.1 (C-2', C-3', C-4'), 35.4 (C-1'), 30.2 (C-5'), 20.9, 20.8, 20.7 (acetyl).

Anal.: Calcd for $C_{17}H_{20}O_9S.1H_2O$: C, 48.80; H, 5.30; S, 7.66; found: C, 48.72; H, 5.13; S, 7.70.

3(S),4(S)-Diacetoxy-2(R)-[bis-(4-methoxyphenyl)methyl]tetrahydrothiophene **7**. Zinc chloride (0.122 g, 0.9 mmol) introduced into a Schlenk tube was heated to the melting point whereupon vacuum was applied. While cooling down to room temperature, argon was introduced into the tube which was fitted with a septum. **2** (0.3 g, 0.84 mmol) and anisole (0.457 g, 4.22 mmol) dissolved in anhydrous chloroform (10 mL) were introduced into the tube with a seringe. After stirring for 2h at 45°C, the mixture was filtered through a bed of celite before adding triethylamine. Concentration of the reaction mixture led to a residue which was applied to a silica gel column eluted with ethyl acetate-petroleum ether 1:2 (v/v) to afford **7** (0.132 g, 0.31 mmol, 36% yield). colourless oil; $[\alpha]_D$ -31° (c 0.6, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.21 (d, 2H, *J* 8.7, H-*arom.*), 7.16 (d, 2H, *J* 8.7, H-*arom.*), 6.83 (d, 2H, *J* 8.7, H-*arom.*), 6.79 (d, 2H, *J* 8.7, H-*arom.*), 5.34-5.25 (m, 2H, H-3, H-4), 4.16 (dd, 1H, $J_{2,3}$ 5.1, H-2), 4.07 (d, 1H, $J_{1',2}$ 11.2, H-1'), 3.75 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.15 (dd, 1H, $J_{4,5a}$ 5.4, $J_{5a,5b}$ 11.6, H-5a), 2.84 (dd, 1H, $J_{4,5b}$ 6.2, H-5b), 2.08, 1.71 (2s, 6H, acetyl). ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.9, 169.3 (acetyl), 158.4, 158.3 (C-*arom.*), 135.2, 134.7 (C-*arom.*), 128.9, 128.9, 128.8, 128.8, 114.0, 114.0, 113.9, 113.9 (C-*arom.*), 79.6, 77.9 (C-3, C-4), 55.8 (C-2), 55.2, 55.1 (OMe), 52.0 (C-1'), 31.5 (C-5), 20.9, 20.4 (acetyl).

Anal.: Calcd for $C_{23}H_{26}O_6S$ (430.51): C, 64.17; H, 6.08; S, 7.45; found: C, 64.11; H, 6.14; S, 7.54.

3(S),4(S)-Diacetoxy-2(R)-[bis-(2,5-dimethoxyphenyl)methyl]tetrahydrothiophene **8**. Anhydrous zinc chloride (0.384 g, 2.82 mmol) placed under inert atmosphere in a Schlenk tube secured with a septum, was obtained as before. After cooling down to room temperature, a dry chloroform (8 mL) solution containing **2** (0.5 g, 1.41 mmol) and 1,4-dimethoxybenzene (0.97g, 7.04 mmol) was added into the tube. The heterogeneous medium was stirred at room temperature for 21 h, before filtration through a bed of celite and triethylamine addition. Removal of the volatiles under reduced pressure followed by silica gel chromatography with ethyl acetate-petroleum ether 1:2 (v/v) led to **8** (0.134 g, 0.31 mmol, 22% yield). colourless oil; $[\alpha]_D$ -22° (c 0.3, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.98 (d, 1H, *J* 2.4, H-*arom.*), 6.90 (d, 1H, *J* 2.4, H-*arom.*), 6.76-6.62 (m, 4H, H-*arom.*), 5.35 (t, 1H, $J_{3,4}$ 5.5, H-3), 5.30 (m, 1H, $J_{4,5a}$ 5.7, H-4), 4.99 (d, 1H, $J_{1',2}$ 11.8, H-1'), 4.37 (dd, 1H, $J_{2,3}$ 5.0, H-2), 3.78 (s, 6H, OMe), 3.72 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.11 (dd, 1H, $J_{5a,5b}$ 11.7, H-5a), 2.88 (dd, 1H, $J_{4,5b}$ 5.8, H-5b), 2.09, 1.69 (2s, 6H, acetyl). ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.1, 169.0 (acetyl), 153.4, 153.3, 151.8, 151.6, 132.0, 131.0 (C-*arom.*), 116.5, 115.6, 112.3, 111.8, 111.8, 111.7 (C-*arom.*), 79.6, 78.1 (C-3, C-4), 56.3, 56.0, 55.7, 55.6 (OMe), 50.4 (C-2), 44.6 (C-1'), 31.5 (C-5), 21.0, 20.4 (acetyl). M.S. (c.i.) *m/z* (intensity %): 490.80 (M^+, 12), 490.20 (24), 287 (100), 151.05 (79), 120.85 (23), 100.95 (20), 84.85 (24), 82.85 (31), 57.05 (19), 43.05 (59).

3(S),4(S)-Dihydroxy-2(R)-[bis-(4-methoxyphenyl)methyl]tetrahydrothiophene **10**. A MeOH solution of **7** (1.33 g, 3.1 mmol) was stirred for 72 h after addition of 2 drops of a sodium methoxide solution (~1 M) in anhydrous methanol. Concentration under reduced pressure followed by column chromatography on silica gel with chloroform-methanol 9:1 (v/v) led to **10** (1.07 g, 3.1

mmol, 100% yield). colourless oil; $[\alpha]_D$ +28° (c 0.6, $CHCl_3$). ^1H NMR (200 MHz, $CD_3C(O)CD_3$) δ 7.28 (d, 2H, *J* 8.7, H-*arom.*), 7.26 (d, 2H, *J* 8.7, H-*arom.*), 6.83 (d, 2H, *J* 8.7, H-*arom.*), 6.82 (d, 2H, *J* 8.7, H-*arom.*), 4.36 (d, 1H, $J_{1',2}$ 10.6, H-1'), 4.25 (m, 1H, $J_{4,5a}$ 4.7, H-4), 4.05 (dd, 1H, $J_{2,3}$ 3.1, H-2), 3.92 (t, 1H, $J_{3,4}$ 3.5, H-3), 3.75 (s, 6H, OMe), 3.09 (dd, 1H, $J_{5a,5b}$ 11.0, H-5a), 2.70 (dd, 1H, $J_{4,5b}$ 3.9, H-5b). ^{13}C NMR (50 MHz, $CD_3C(O)CD_3$) δ 159.0, 158.9 (C-*arom.*), 137.7, 137.4 (C-*arom.*), 130.1, 130.1, 129.9, 129.9, 114.5, 114.5, 114.2, 114.2 (C-H-*arom.*), 81.4, 80.0 (C-3, C-4), 58.3, 55.6 (C-2, C-1), 55.4, 55.4 (OMe), 36.6 (C-5).

Anal.: Calcd for $C_{19}H_{22}O_4S$ (346.44): C, 65.87; H, 6.40; S, 9.25; found: C, 65.20; H, 6.33; S, 9.24.

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