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SYNTHETIC STUDIES IN THE 5-THIO-D-XYLOPYRANOSE SERIES *part 1*: A READY ACCESS TO *C*-HETARYL 5-THIO-D-XYLOPYRANOSIDES BY ELECTROPHILIC SUBSTITUTION

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Abstract: Reaction of *O*-(2,3,4-tri-*O*-acetyl-5-thio-α-D-xylopyranosyl) trichloroacetimidate **3** with heterocyclic compounds such as furan, thiophene and benzothiophene in the presence of boron trifluoride etherate at -78 °C for ~0.5 h leads to the corresponding *C*-hetaryl 5-thio-D-xylopyranosides as anomeric mixtures obtained in 73, 79 and 64 % yield, respectively. Use of the 2,3,4-tri-*O*-acetyl-5-thio-α-D-xylopyranosyl bromide **4** led also to these previously unknown compounds, the yields being either comparable (furan) or lower (thiophene) due to the formation of tetrahydrothiophene derivatives. A mechanism based on the acid-catalyzed cleavage of the 2'-acetoxy group and/or a sulfur transannular participation is proposed to account for the observed ring-restricted tetrahydrothiophene derivatives which were unambiguously assigned based on crystal analysis of the 3(*S*),4(*S*)-diacetoxy-2(*R*)-[bis-(2-furanyl)methyl]tetrahydrothiophene **8**. Therefore, these model reactions shed light on possible routes to unprecedented *C*-hetaryl 5-thio-D-xylopyranosides by an electrophilic coupling, the selectivity of which being controlled by a proper tuning of the reaction parameters, in particular temperature and reaction time. Under kinetic conditions, *C*-hetaryl 5-thio-α-D-xylopyranosides can be formed predominantly, in particular from the bromide **4**, on treatment with zinc chloride. Otherwise, anomerization occurred as well as ring-restriction to produce, particularly when using thiophene, more complex reaction mixtures. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: 2,3,4-Tri-*O*-acetyl-5-thio-D-xylopyranosyl donors; Electrophilic substitution; Furan; Thiophene; *C*-Hetaryl 5-thio-D-xylopyranosides; Sulfur transannular participation

The need for improved treatments of thrombosis and related diseases explains the continuing search for more potent molecules, of either synthetic[1-8] or natural[9-11] origin, with less associated side-effects. Along this quest for new drugs, a more detailed picture of the biochemical events leading to thrombus formation has been gained and the role at the molecular level of exogenous species showing anticoagulant properties is receiving more light. In particular, recent studies[6] have demonstrated that *O*- and *S*-aryl β-D-xylopyranosides and also their 5-thio analogues were good antithrombotic agents in a rat model of venous thrombosis. In addition to the fact that the 5-thio-β-D-xylopyranosides, having as the aglycone diverse aryl moieties substituted by an electron withdrawing group, were more potent as compared to their oxygenated counterparts, they also proved to be better substrates for the galactosyl transferase I (*GT I*) responsible for the attachment of a β-D-galactopyranose residue to a serine-linked xylopyranoside at the earlier stage of the glycosaminoglycan biosynthesis.[6] Together with earlier studies,[12] these observations suggested that 5-thioxylosides might act as exogenous primers for glycosaminoglycan formation. However, among the desired features an ideal drug should comply with, oral administration is highly desirable. Although some 5-thioxylopyranosides meet this requirement,[4,6] *C*-xylosides with a higher stability

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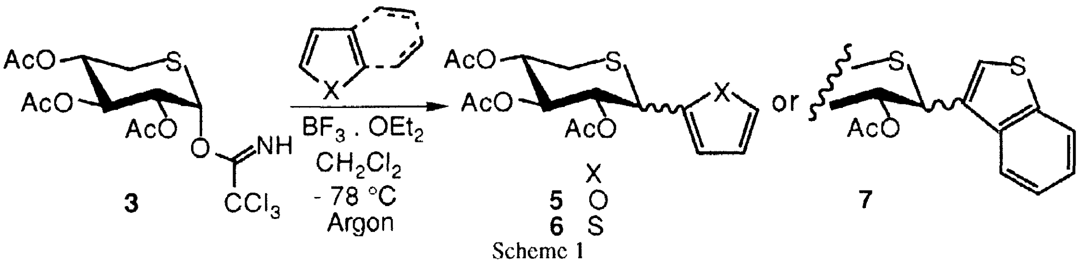
towards hydrolysis,[13] in particular as regard to cleavage due to sugar-processing enzymes, could be advantageous. Since the synthesis of *C*-5-thioglycosides was not documented in the literature at the outset of our work,[13d] we wanted to explore in more details the reactivity of 5-thio-D-xylopyranosyl derivatives, in order to open, hopefully, a route applicable for the preparation of more stable *C*-5-thioxylosides, analogous to the known active *O*-5-thioxylopyranosides. Along this line, we investigated the access to *C*-aryl and *C*-hetaryl 5-thioxylopyranosides from 5-thio-D-xylopyranosyl donors by electrophilic substitution.[14] We report herein on the more selective synthesis of *C*-hetaryl 5-thio-D-xylopyranosides obtained from heterocyclic compounds such as furan, thiophene, benzothiophene and either tri-*O*-acetyl-5-thio-α-D-xylopyranosyl trichloroacetimidate **3**[1,14] or the corresponding bromide **4**.[1,14,15]

Regioselective *O*-1 deacetylation of 5-thio-D-xylopyranose tetraacetate was efficiently achieved with hydrazine acetate[16] to afford 2,3,4-tri-*O*-acetyl-5-thio-α-D-xylopyranose **1**[1] in a 76% yield and 1,3,4-tri-*O*-acetyl-5-thio-α-D-xylopyranose **2** (5% yield) which could be easily separated by crystallisation. This procedure was found to be more selective than that resorting to ammoniac[17] with either acetonitrile or 7:3 THF–methanol as the solvent. Reaction of **1** with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) led to the *O*-(2,3,4-tri-*O*-acetyl-5-thio-α-D-xylopyranosyl) trichloroacetimidate **3**[1] in high yield. Not surprisingly, **3** was found to be fairly reactive since its transformation occurred at - 78 °C in dry dichloromethane in the presence of catalytic amounts of boron trifluoride etherate. With two molar equivalents of either furan, thiophene or benzothiophene, these conditions led within 30 min and in high yield to anomeric mixtures of the corresponding *C*-hetaryl 5-thioxylopyranosides **5**, **6**, **7** respectively. Under these conditions, the β-anomers predominated (β/α = ~ 60 / 40), except in the case of furan (β/α = 44 / 56). Experiments carried out at room temperature, as it is usual with acetyl-[18] or benzyl-protected[19] trichloroacetimidates of natural sugars, led to multicomponent mixtures whatever the heterocyclic compound used, showing that controlled temperatures are needed for achieving selective electrophilic substitutions with **3**.

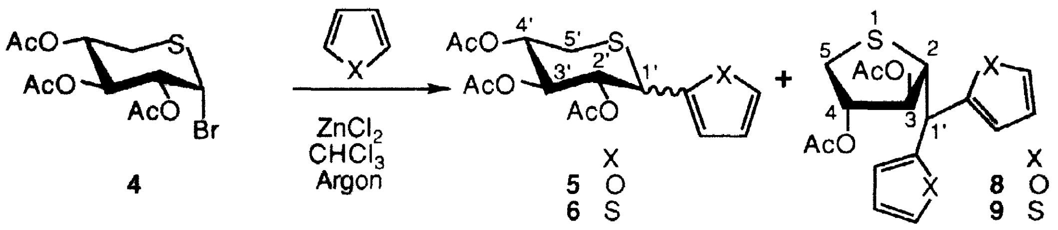


Scheme 1

Table 1: *C*-Hetaryl 5-thio-D-xylopyranosides obtained from the reaction of the trichloroacetimidate **3** with either furan, thiophene or benzothiophene

ArH	3 / ArH / BF_3-OEt_2 eq	Time min	Products	%	β / α
Furan	1 / 2 / 0.1	30	**5**	73	44 / 56
Thiophene	1 / 2 / 0.1	20	**6**	79	58 / 42
Benzothiophene	1 / 2 / 0.1	30	**7**	64	63 / 37

By analogy with published procedures,[13] the α-bromide **4** was transformed in dry chloroform at room temperature in the presence of anhydrous zinc chloride with the aforementioned heterocyclic compounds. The best results were obtained with a 5-fold excess of both the heterocycle and zinc chloride whereas cooling either slowed down (- 5 °C) or stopped (< - 10 °C) the reaction. In the case of furan, these conditions led essentially to the expected *C*-(2-furanyl) 5-thio-D-xylopyranosides **5**, obtained in good yield as an anomeric mixture in which the β-anomer predominated. However, when this procedure was applied to a larger amount of **4**, the [bis-(2-furanyl)methyl]tetrahydrothiophene derivative **8** was produced in a 5 % yield. When using thiophene instead, the electrophilic substitution proceeded cleanly, although partially, at - 5 °C to afford an anomeric mixture of the corresponding *C*-5-thioxylopyranosides **6**. Whereas the α-anomer was found more abundant at this temperature, the β-anomer predominated when applying a higher temperature which, however, had a detrimental effect on the selectivity: each of the corresponding *C*-xylosides **6** and the [bis-(2-thienyl)methyl]tetrahydrothiophene derivative **9** amounted to 28 %. This compound was obtained in a 35 % yield when thiophene was used in large excess without any solvent added.



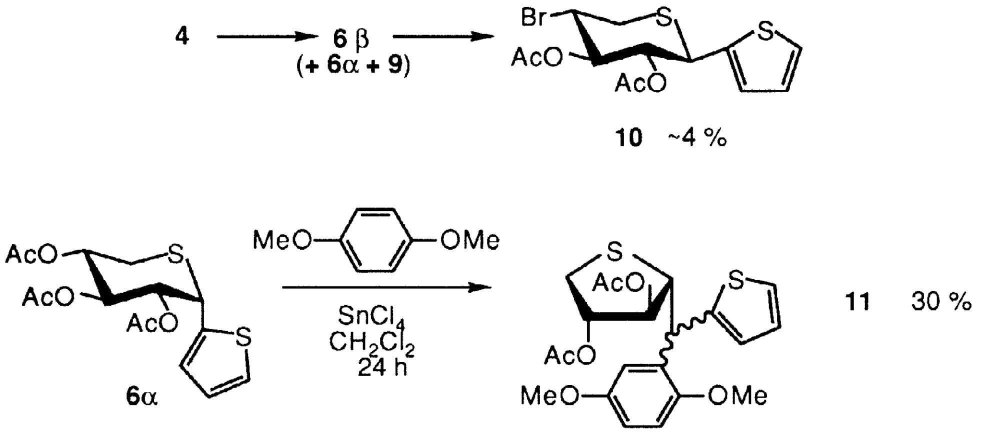
Scheme 2

Table 2: *C*-Hetaryl 5-thio-D-xylopyranosides and tetrahydrothiophene derivatives obtained from the reaction of the bromide **4** with either furan or thiophene

ArH	4 / ArH / $ZnCl_2$	T °C	Time			Products		
	eq				%	β / α		%
Furan	1 / 5 / 1.1	r.t.	18 h	**5**	57	87 / 13		
"	1 / 5 / 5	-10	7 h	**5**	traces			
"	1 / 5 / 5	r.t.	17 h	**5**	76	80 / 20		
"[a]	1 / 5 / 5	r.t.	1 h 45	**5**	58	-	**8**	5
Thiophene[b]	1 / 5 / 5	-5	7 h	**6**	55[c]	35 / 65	**9**	2
"	1 / 5 / 2	r.t.	7 h	**6**	28	61 / 39	**9**	28
"	1 / solvent / 10	r.t.	2 h 30	**6**			**9**	35

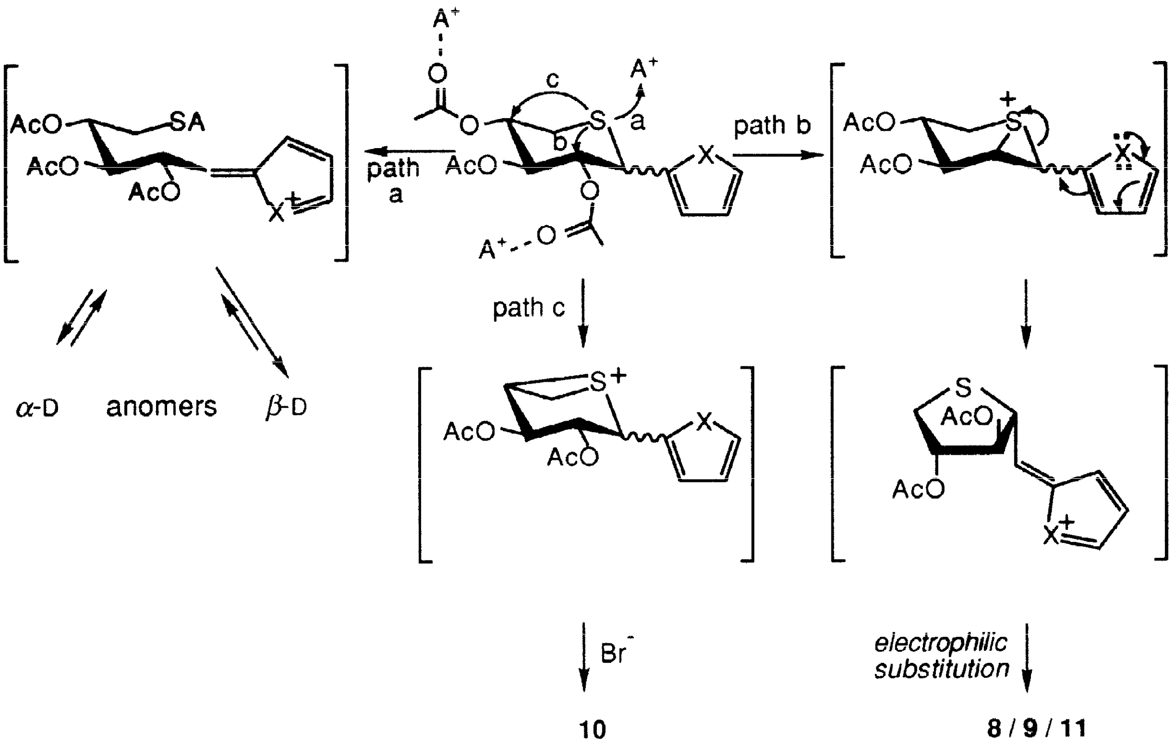
[a] carried out on a larger quantity (starting material: 3.55 g instead of 0.5 - 1 g in the other cases); [b] no significant transformation could be detected after 5 h at -30 °C with a 1 / 5 / 5 ratio of reactants; [c] 15 % of the starting material **4** was not transformed.

When the bromide **4** was reacted with thiophene, the 4-bromo derivative **10** produced (~4 %) could be isolated by column chromatography in small amount (~1 % isolated yield). In order to better explain the presence of the byproducts observed along these studies, compound **6α** was allowed to react with 1,4-dimethoxybenzene for 24 h in dichloromethane in the presence of tin (IV) tetrachloride. This led mainly to the mixed tetrahydrothiophene derivative **11**, (30 % yield, ~1 : 1 diastereoisomeric mixture), as a result of the ring-restriction process which also accounts for the formation of **8** and **9**.



Scheme 3

It is clear from these results that the selective preparation of *C*-hetaryl 5-thioxylopyranosides required carefully controlled conditions (temperature and reaction time, mainly). As shown by the anomeric ratio of the *C*-xylosides obtained when **4** was reacted with thiophene at -5 °C, kinetic conditions favored the α-anomers[19] from which their β-counterparts can be produced at higher temperatures or when the reaction was allowed to proceed over extented time. Such an anomerization is best explained by the cleavage of the endocyclic C—S bond (path a) which has been invoked to explain earlier observations.[20,21] Both electronic and steric factors account for the higher thermodynamic stability of β-anomers.[21-23] Although compound **10** is structurally different from compounds **8**, **9** and **11**, their formation can be explained similarly by sulfur transannular participation mechanisms[24] which assist the acid-catalyzed cleavage of the acetoxy group at either C-2 (path b)[25] or C-4 (path c).[26,27] Attack at C-4 of the episulfonium ion from the less hindered side led to **10** with retention of configuration, as shown by the observed ${}^3J$ coupling between the H-3', H-4' and H-5a' hydrogen atoms (numbered as usual for *C*-hetaryl glycosides[19]) corresponding to a *trans* diaxial arrangement ($J_{3',4'} = 10.2$, $J_{4',5a'} = 11.7$ Hz). The episulfonium ions resulting from loss of the 2-acetoxy group could also react with bromide ions. However, the corresponding benzylic bromides, if formed, were not isolated, probably as a result of a high reactivity. Under the prevailing conditions, it is reasonable to assume that they can react further to afford either **8** or **9** by electrophilic attack of the heterocycle present in the medium. Although ring restrictions are known for some derivatives of natural sugars,[28] sulfur transannular participation which reflects the high nucleophilicity of this element contributes to the rich palette of 5-thiosugar chemistry[29] and explains the difficulties for achieving selective transformations in this series.



Scheme 4

Structure assignment of the *C*-5-thio-D-xylopyranosides **5**, **6** and **7** was based on NMR spectroscopy which, whatever their anomeric configuration, showed a $^4C_1$-D chair conformation for the 5-thiopyranose ring. Compounds **12**, **13**, **14** and **15** obtained in high yields from **5**β, **6**β, **7**β and **9** upon deacetylation were also found to exist under the $^4C_1$-D chair conformation, except for **15**. The anomeric proton in **5**, **6** and **7** were deshielded (~ 0.3 ppm) for α-anomers, as compared to their β-counterparts. This effect which corresponds to that observed for hydrogen atoms attached to the cyclohexane ring,[30] depending on their axial/equatorial orientation, is lower as compared to that recorded for anomers of *O*-glycosides[31] and *C*-hetaryl D-glucopyranosides.[19] Not surprisingly, in the studied *C*-hetaryl 5-thio-D-xylopyranosides, the resonances of the H-4' proton and also to a lesser extent of the H-5e' nucleus did not differ markedly depending on the anomeric configuration. This latter was deduced from the $^3J_{1',2'}$ couplings (α-anomers: ~5 Hz, β-anomers: ~10.5 Hz). Whereas the H-2' resonance was shifted to low fields for the β-anomers, the axial orientation of the aromatic ring in their α-counterparts was responsible of the deshielding of the proximal axially oriented H-3' and H-5a' protons. The resonances of the acetyl groups at C-2 were found shielded, as compared to the others, due to the anisotropy induced by the aromatic ring, this effect being more pronounced in the case of the β-anomers. Finally, the structure of compound **8** was established unambiguously by crystal analysis, thus providing a firm support for assigning the structure of **9** and **11**. This also proved that electrophilic substitution occurred at the 2-position of furan.

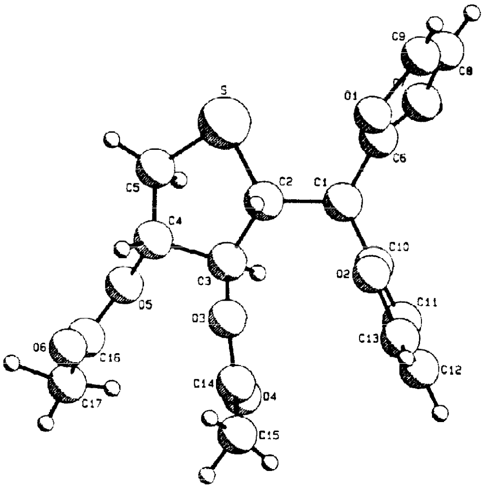
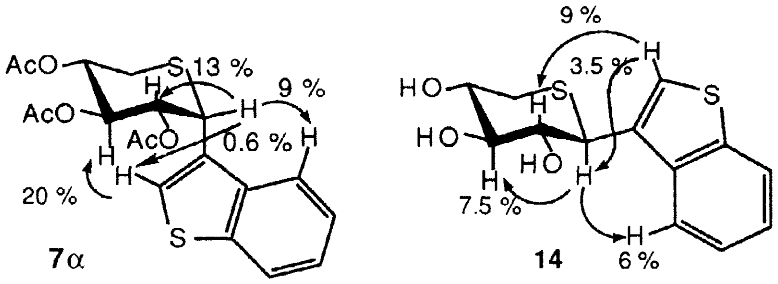


Fig. 1. PLUTO[32] drawing of compound **8**

Since benzothiophene leads by electrophilic substitution to 3-substituted derivatives preferentially,[33,34] more informations were needed in order to properly assign the structure of compounds **7**. To this end, n.O.e. difference spectra were obtained for compound **7α** and its deacetylated *β*-analogue **14**, in $CDCl_3$ and MeOH, respectively, upon irradiation of the proton attached to the thiophene ring. It was assumed that, in the case of a 3-substituted benzothiophene derivative, no n.O.e. enhancement would be possible for the remote aromatic protons whereas, in 2-substituted derivatives, the shorter interatomic distance between the isolated proton and that at the *ortho* position on the phenyl ring, would result in an appreciable n.O.e. enhancement for the latter. In fact, in the case of **7α**, a strong n.O.e. (20 %) was observed for H-3' (5.89 ppm) only, whereas, with **14**, enhancements were visible for H-1' (3.5 %) and H-2' (9 %) (see Scheme 5). These observations suggested that the substitution occurred, as expected, at the 3-position of the thiophene ring. This conclusion was confirmed by the enhancements observed upon irradiation of the proton H-1' in **7α** and **14**, in particular for the nucleus attached to the aromatic moiety, more informative, for structure elucidation, than the effects observed for H-2', H-3' and H-5'a. Albeit proton chemical shifts appeared useless in this context,[35] an additional supporting evidence for this substitution pattern was found, based on comparison of the chemical shifts reported for carbon atoms in *2*- and *3*-methyl-benzothiophene.[36] Since the C-3a and C-7a in **7α**, **7β** and **14** should appear near 140 ppm,[36] the aromatic carbon bonded to the thiopyranose ring was observed at 129.1, 130.0 and 134.2 ppm, respectively. These values, compared with the chemical shifts reported for the substituted carbon atom in *2*- and *3*-methyl-benzothiophene (140.6 and 131.8 ppm, respectively), are also in agreement with the structures proposed for **7α**, **7β** and **14**.



Scheme 5. Structure of the 5-thio-D-xylopyranosides 7α and 14, with the observed n.O.e.

The deprotected compounds **12**, **13**, and **15** were assayed in a Wessler test[37] 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 conclusion, reaction of 5-thio-D-xylopyranosyl donors with heterocyclic compounds by electrophilic substitution opens a practical access to the corresponding *C*-hetaryl 5-thio-D-xylopyranosides in particular when the reaction was allowed to proceed at low temperature with the more reactive trichloroacetimidate **3**. Use of the corresponding bromide **4** led to these previously unknown compounds in either comparable (furan) or decreased (thiophene) yields, due to the formation of tetrahydrothiophene derivatives by a sulfur transannular participation mechanism. Therefore, these model reactions shed light on possible routes to unprecedented *C*-hetaryl 5-thioxylopyranosides. In particular, it was found that the coupling selectivity can be controlled by a proper tuning of the reaction conditions which allow to overcome problems arising mainly from sulfur transannular participation. Other examples of ring-restricted products formed from 5-thio-D-xylopyranose derivatives are included in our following papers and in recent literature reports.[38]

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

Table 3
Relative atomic coordinates and isotropic thermal parameters ($B_{eq} = 4/3\ \Sigma_i\Sigma_j\beta_{ij}a_ia_j$) for compound **8**

Atom	x	y	z	B_{eq}(Å^2)	Atom	x	y	z	B_{eq}(Å^2)
S	0.0303(2)	0.6516(2)	0.21131(3)	6.68(2)	C6	0.3244(5)	0.3923(5)	0.1736(1)	4.91(8)
O1	0.2536(6)	0.2285(6)	0.1845(1)	12.2(1)	C7	0.4850(5)	0.4207(5)	0.1887(1)	6.54(9)
O2	0.1504(4)	0.2957(3)	0.09245(7)	5.24(6)	C8	0.5237(8)	0.2727(9)	0.2125(2)	14.2(22)
O3	-0.1319(3)	0.6270(3)	0.09524(6)	3.86(4)	C9	0.4057(9)	0.1599(7)	0.2105(1)	14.0(2)
O4	-0.0522(4)	0.8547(4)	0.05282(7)	5.62(6)	C10	0.2354(5)	0.4544(4)	0.1004(1)	4.02(7)
O5	-0.2266(3)	0.9828(3)	0.13824(7)	4.60(5)	C11	0.2988(5)	0.5228(5)	0.0650(1)	4.47(7)
O6	-0.4785(4)	0.8819(4)	0.1077(1)	8.86(9)	C12	0.2549(5)	0.4052(6)	0.0321(1)	5.36(9)
C1	0.2323(5)	0.5194(5)	0.14420(9)	4.01(7)	C13	0.1647(6)	0.2681(6)	0.0498(1)	5.88(9)
C2	0.0380(5)	0.5657(4)	0.15767(9)	4.14(7)	C14	-0.1240(5)	0.7121(5)	0.05776(9)	4.31(7)
C3	-0.0471(5)	0.7127(4)	0.13066(9)	3.65(6)	C15	-0.2127(6)	0.6003(6)	0.0247(1)	5.9(1)
C4	-0.1887(5)	0.8099(5)	0.1567(1)	4.32(7)	C16	-0.3696(5)	0.9964(5)	0.1135(1)	5.26(8)
C5	-0.1079(6)	0.8464(6)	0.1994(1)	6.1(1)	C17	-0.3744(6)	1.1798(6)	0.0935(1)	7.0(1)

Table 4
Bond distances in Angströms in compound **8**

S—C2	1.830(3)	O5—C4	1.448(4)	C6—C7	1.290(6)
S—C5	1.814(5)	O5—C16	1.317(5)	C7—C8	1.371(8)
O1—C6	1.375(6)	O6—C16	1.185(5)	C8—C9	1.210(9)
O1—C9	1.483(7)	C1—C2	1.528(5)	C10—C11	1.325(5)
O2—C10	1.364(4)	C1—C6	1.497(5)	C11—C12	1.406(5)
O2—C13	1.383(4)	C1—C10	1.482(4)	C12—C13	1.344(6)
O3—C3	1.441(4)	C2—C3	1.530(4)	C14—C15	1.495(5)
O3—C14	1.357(4)	C3—C4	1.516(5)	C16—C17	1.513(6)
O4—C14	1.199(4)	C4—C5	1.512(5)		

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, unless otherwise indicated. 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).

*2,3,4-Tri-*O*-acetyl-5-thio-α-*D*-xylopyranose* **1**. A solution of 1,2,3,4-tetra-*O*-acetyl-5-thio-D-xylopyranose (3.0 g, 8.98 mmol, α/β = 81/19) in DMF (12 mL) was heated to 50 °C before adding hydrazine acetate[16] (0.99 g, 10.7 mmol). After the crystals of hydrazine acetate were dissolved, the reaction mixture was stirred for 15 min without heating. Then, EtOAc (40 mL) was added and the obtained organic phase was extracted with satd brine (3 x 30 mL). The combined aqueous phases were extracted with EtOAc (20 mL). The organic phases were combined, dryed ($MgSO_4$), filtered through a bed of celite and evaporated under reduced pressure. The obtained residue, dissolved in the minimum volume of Et_2O, was allowed to crystallize overnight at room temperature to yield **2** (0.131 g, 5%). After the mother liquors were concentrated under reduced pressure, the residue was stored at +4 °C to yield **1** (1.99 g, two crops, 76%); white crystals; mp 116-117 °C (Et_2O); $[\alpha]_D$ +157° (*c* 0.8, $CHCl_3$). ^{1}H NMR (200 MHz): δ 5.55 (t, 1 H, $J_{2,3}$ 9.9 Hz, $J_{3,4}$ 9.9 Hz, H-3), 5.14 (d, 1 H, $J_{1,2}$ 4.4 Hz, H-1), [5.15–5.02] (m, 1 H, H-2), 5.09 (ddd, 1 H, $J_{4,5a}$ 11.4 Hz, H-4), 3.12 (dd, 1 H, $J_{5e,5a}$ 13.0 Hz, H-5a), 3.11 (s, 1 H, OH), 2.73 (dd, 1 H, $J_{4,5e}$ 4.5 Hz, H-5e), 2.08, 2.04, 2.03 (3s, 9 H, acetyl). ^{13}C NMR (50 MHz): δ 170.2, 170.1, 170.0 ($CH_3\mathit{C}(O)O$), 75.3, 73.1, 71.6, 69.9 (C-1 to C-4), 24.9 (C-5), 20.9, 20.8, 20.7 ($\mathit{C}H_3C(O)O$).

Anal.: Calcd for $C_{11}H_{16}O_7S$ (292.30): C, 45.20; H, 5.52; S, 10.94. Found: C, 45.33; H, 5.40; S, 10.94.

*1,3,4-Tri-*O*-acetyl-5-thio-α-*D*-xylopyranose* **2**. white crystals; mp 155-156 °C (Et_2O); $[\alpha]_D$ +282° (*c* 0.5, $CHCl_3$). ^{1}H NMR (200 MHz): δ 5.92 (d, 1 H, $J_{1,2}$ 2.9 Hz, H-1), 5.23 (t, 1 H, $J_{3,4}$ 9.6 Hz, H-3), 5.09 (ddd, 1 H, $J_{4,5a}$ 10.4 Hz, H-4), 4.01 (dd, 1 H, $J_{2,3}$ 9.6 Hz, H-2), 2.91 (dd, 1 H, $J_{5e,5a}$ 13.3 Hz, H-5a), 2.73 (dd, 1 H, $J_{4,5e}$ 4.5 Hz, H-5e) 2.19, 2.11, 2.05 (3s, 9 H, acetyl), 2.06–2.03 (s, 1 H, OH). ^{13}C NMR (50 MHz): δ 171.4, 169.9, 169.5 ($CH_3\mathit{C}(O)O$), 73.9, 73.7, 73.3, 72.1 (C-1 to C-4), 26.1 (C-5), 21.0, 20.8, 20.8 ($\mathit{C}H_3C(O)O$).

Anal.: Calcd for $C_{11}H_{16}O_7S$ (292.30): C, 45.20; H, 5.52; S, 10.94. Found: C, 45.40; H, 5.56; S, 11.00.

*1-*O*-(2,3,4-Tri-*O*-acetyl-5-thio-α-*D*-xylopyranosyl) trichloroacetimidate* **3**. To a solution of 2,3,4-tri-*O*-acetyl-5-thio-α-D-xylopyranose **1** (0.10 g, 0.34 mmol) and trichloroacetonitrile (344 µL, 3.43 mmol) in anhydrous CH_2Cl_2 (2 mL) under argon, DBU (20 µL, ~0.13 mmol) was added, after the mixture was cooled down to 0 °C (ice water). After stirring for 1 h, the reaction mixture was concentrated under reduced pressure and the residue was applied to a column of silica gel irrigated with EtOAc-hexane 2:3 (v/v) to afford **3** (0.141 g, 95% yield) which crystallized readily at room temperature from Et_2O-petroleum ether (one crop, 87%); colourless crystals; mp 110-111 °C; $[\alpha]_D$ +214° (*c* 1.3, $CHCl_3$). ^1H NMR (200 MHz): δ 8.71 (s, 1 H, H-N=), 6.29 (dd, 1 H, $J_{1,2}$ 2.7 Hz, $J_{1,5e}$ 0.8 Hz, H-1), 5.58 (t, 1 H, $J_{3,4}$ 10.0 Hz, H-3), 5.28 (dd, 1 H, $J_{2,3}$ 10.0 Hz, H-2), 5.16 (ddd, 1 H, $J_{4,5a}$ 11.3 Hz, H-4), 3.07 (dd, 1 H, $J_{5e,5a}$ 13.2 Hz, H-5a), 2.82 (ddd, 1 H, $J_{4,5e}$ 4.7 Hz, H-5e), 2.06, 2.05, 2.00 (3s, 9 H, acetyl). ^{13}C NMR (50MHz): δ 169.8, 169.8, 169.5 ($CH_3\mathit{C}(O)O$), 160.7 (*C*=N), 76.0 (C-1), 73.7, 72.4, 69.9 (C-2 to C-4), 26.2 (C-5), 20.8, 20.6, 20.5 ($\mathit{C}H_3C(O)O$).

Anal.: Calcd for $C_{13}H_{16}O_7NCl_3S$ (436.69): C, 35.76; H, 3.69; O, 25.65; N, 3.21; S, 7.34. Found: C, 35.80; H, 3.70; O, 25.47; N, 3.24; S, 7.52.

*2-(2',3',4'-Tri-*O*-acetyl-5'-thio-*D*-xylopyranosyl)furan* **5**. The trichloroacetimidate **3** (0.215 g, 0.492 mmol) and furan (67 µL, 0.916 mmol), dissolved by stirring in anhydrous CH_2Cl_2 (~3 mL) under an argon atmosphere, were treated at -78°C with boron trifluoride etherate (6 µL, ~0.05 mmol). After stirring for 30 min, triethylamine was added and the medium was allowed to warm up before concentration under reduced pressure. The obtained mixture was applied to a column of silica gel irrigated with EtOAc-petroleum ether 1:2 (v/v). This afforded an anomeric mixture of compound **5** contaminated with trichloroacetamide (0.182 g) which is poorly soluble in halogenated solvents. After the mixture was taken up in the minimum volume of CH_2Cl_2 cooled to 0°C, the impurity was discarded by filtration. Concentration of the liquid phase led to **5** (0.123 g, 0.36 mmol, 73% yield, β/α = 44/56) whose anomers were resolved by column chromatography with the same eluent.

5β : white crystals; mp 152 °C (diethyl ether); $[\alpha]_D$ -43° (*c* 0.6, $CHCl_3$). ^1H NMR (200 MHz): δ 7.35 (dd, 1 H, $J_{0.9}$, $J_{1.8}$ Hz, H-3), 6.29 (m, 2 H, H-4, H-5), 5.48 (dd, 1 H, $J_{2',3'}$ 9.3 Hz, H-2'), 5.14 (m, 1 H, $J_{4',5'e}$ 4.3 Hz, H-4'), 5.11 (t, 1 H, $J_{3',4'}$ 9.3 Hz, H-3'), 4.15 (d, 1 H, $J_{1',2'}$ 10.7 Hz, H-1'), 2.93 (dd, 1 H, $J_{5'a,5'e}$ 13.2 Hz, H-5'e), 2.79 (dd, 1 H, $J_{4',5'a}$ 10.2 Hz, H-5'a), 2.04, 2.03, 1.84 (3s, 9 H, acetyl). ^{13}C NMR (50 MHz): δ 169.8, 169.7, 169.0 ($CH_3\mathit{C}(O)O$), 148.5 (C-2), 142.8 (C-5), 110.6, 108.5 (C-3, C-4), 74.2, 73.6, 72.7 (C-2' to C-4'), 42.8 (C-1'), 30.5 (C-5'), 20.8, 20.6, 20.3 ($\mathit{C}H_3C(O)O$).

Anal.: Calcd for $C_{15}H_{18}O_7S$ (342.36): C, 52.62; H, 5.30; S, 9.37. Found: C, 52.34; H, 5.31; S, 9.15.

5α : colourless oil; $[\alpha]_D$ +172° (*c* 0.2, $CHCl_3$). ^1H NMR (200 MHz): δ 7.47 (dd, 1 H, *J* 0.8 Hz, *J* 1.9 Hz, H-3), 6.36 (dd, 1 H, *J* 3.2 Hz, *J* 1.9 Hz, H-4), 6.30 (d, 1 H, *J* 3.2 Hz, H-5), 5.68 (t, 1 H, $J_{3',4'}$ 10.2 Hz, H-3'), 5.25 (dd, 1 H, $J_{2',3'}$ 10.2 Hz, H-2'), 5.13 (ddd, 1 H, $J_{4',5'e}$ 4.6 Hz, H-4'), 4.39 (dd, 1 H, $J_{1',2'}$ 5.6 Hz, $J_{1',5'e}$ 0.7 Hz, H-1'), 3.10 (dd, 1 H, $J_{4',5'a}$ 11.1 Hz, H-5'a), 2.77 (ddd, 1 H, $J_{5'a,5'e}$ 13.3 Hz, H-5'e), 2.05, 2.04, 1.94 (3s, 9 H, acetyl). ^{13}C NMR (50 MHz): δ 170.0, 169.9, 169.8 ($CH_3\mathit{C}(O)O$), 150.9 (C-2), 143.0 (C-5), 110.3, 109.2 (C-3, C-4), 73.8, 73.3, 70.7 (C-2' to C-4'), 38.2 (C-1'), 27.8 (C-5'), 20.9, 20.7, 20.6 ($\mathit{C}H_3C(O)O$).

Anal.: Calcd for $C_{15}H_{18}O_7S$ (342.36): C, 52.62; H, 5.30; S, 9.37. Found: C, 52.41; H, 5.34; S, 9.13.

*2-(2',3',4'-Tri-O-acetyl-5'-thio-*D*-xylopyranosyl)thiophene* **6**. Trichloroacetimidate **3** (2 g, 4.58 mmol) and thiophene (700 µL, ~9.16 mmol), dissolved in anhydrous CH_2Cl_2 (~20 mL) at -78°C were treated with boron trifluoride etherate (58 µL, ~0.46 mmol) under argon. After stirring for 20 min, triethylamine was added and the medium was allowed to warm up before concentration under reduced pressure. The obtained mixture was applied to a column of silica gel irrigated with EtOAc-petroleum ether 1:2 (v/v) to yield **6** in admixture with trichloroacetamide (1.71 g). After this fraction was taken up in the minimum volume of chilled $CHCl_3$ (0 °C), trichloroacetamide was filtered off and concentration of the liquid phase afforded **6** (1.3 g, 3.62 mmol, 79% yield, $\beta/\alpha = 58/42$). Pure **6β** could be obtained by crystallization from Et_2O-petroleum ether while column chromatography of the mother liquors using EtOAc-petroleum ether 1:2 (v/v) as the mobile phase yielded pure **6α**.

6β : white crystals; mp 179-180 °C (diethyl ether); $[\alpha]_D$ +6° (*c* 0.6, $CHCl_3$). ^1H NMR (200MHz): δ 7.23 (dd, 1 H, *J* 1.1 Hz, *J* 5.0 Hz, H-*thiophene*), 7.02 (dd, 1 H, *J* 3.5 Hz, *J* 0.8 Hz, H-*thiophene*), 6.93 (dd, 1 H, *J* 3.5 Hz, *J* 5.0 Hz, H-*thiophene*), 5.40 (dd, 1 H, $J_{2',3'}$ 9.3 Hz, H-2'), 5.20 (m, 1 H, $J_{4',5'e}$ 4.5 Hz, H-4'), 5.11 (t, 1 H, $J_{3',4'}$ 9.3 Hz, H-3'), 4.27 (d, 1 H, $J_{1',2'}$ 10.4 Hz, H-1'), 2.93 (dd, 1 H, $J_{5'a,5'e}$ 13.2 Hz, H-5'e), 2.81 (dd, 1 H, $J_{4',5'a}$ 10.1 Hz, H-5'a), 2.05, 2.02, 1.81 (3s, 9 H, acetyl). ^{13}C NMR (50 MHz): δ 169.9, 169.7, 169.0 ($CH_3C(O)O$), 137.7 (C-2), 126.8, 126.6, 125.6 (C-3 to C-5), 75.9, 74.3, 72.6 (C-2' to C-4'), 44.5 (C-1'), 31.4 (C-5'), 20.8, 20.6, 20.3 ($CH_3C(O)O$).

Anal.: Calcd for $C_{15}H_{18}O_6S_2$ (358.42): C, 50.27; H, 5.06; S, 17.89. Found: C, 50.16; H, 5.10; S, 17.79.

6α : colourless oil; $[\alpha]_D$ +169° (*c* 0.5, CH_2Cl_2). ^1H NMR (200 MHz): δ [7.35–7.28] (m, 2 H, H-*thiophene*), 7.01 (dd, 1 H, *J* 3.6 Hz, *J* 5.2 Hz, H-*thiophene*), 5.53 (dd, 1 H, $J_{3',4'}$ 9.0 Hz, H-3'), 5.41 (dd, 1 H, $J_{2',3'}$ 10.1 Hz, H-2'), 5.12 (m, 1 H, H-4'), 4.60 (d, 1 H, $J_{1',2'}$ 4.4 Hz, H-1'), [2.85–2.80] (m, 2 H, H-5'a, H-5'e), 2.08, 2.06, 2.01 (3s, 9 H, acetyl). ^{13}C NMR (50 MHz): δ 169.8, 169.7, 169.7 ($CH_3C(O)O$), 140.0 (C-2), 127.6, 126.9, 126.0 (C-3 to C-5), 74.4, 72.9, 69.9 (C-2' to C-4'), 41.2 (C-1'), 27.5 (C-5'), 20.9, 20.8, 20.6 ($CH_3C(O)O$).

*3-(2',3',4'-Tri-O-acetyl-5'-thio-*D*-xylopyranosyl)benzothiophene* **7**. Trichloroacetimidate **3** (1.3 g, 2.98 mmol) and benzothiophene (0.8 g, 5.95 mmol) in anhydrous CH_2Cl_2 (~12 mL) were treated at -78°C with boron trifluoride etherate (37 µL, ~0.297 mmol) for 30 min under argon. The procedure described previously led to a mixture (1.137 g) made of **7** and trichloroacetamide which was separated by filtration after the osides were dissolved in a few mL of $CHCl_3$ cooled down to 0 °C. The anomeric mixture (0.78 g, 1.9 mmol, 64% yield, $\beta/\alpha = 63/37$) obtained upon concentration was resolved by column chromatography, with EtOAc-petroleum ether 1:2 (v/v) as the mobile phase (R_f: **7α**: 0.5; **7β**: 0.43 in EtOAc-petroleum ether 3:7).

7β : white crystals; mp 235-237 °C (EtOAc-hexane); $[\alpha]_D$ +10° (*c* 0.4, $CHCl_3$). ^1H NMR (200 MHz): δ 7.91 (d, 1 H, *J* 7.3 Hz, H-*arom.*), 7.85 (d, 1 H, *J* 7.2 Hz, H-*arom.*), 7.47 (s, 1 H, H-*arom.*), [7.44–7.33] (m, 2 H, H-*arom.*), 5.66 (dd, 1 H, $J_{2',3'}$ 9.5 Hz, H-2'), [5.26–5.17] (m, 2 H, H-3', H-4'), 4.46 (d, 1 H, $J_{1',2'}$ 10.7 Hz, H-1'), [3.00–2.90] (m, 2 H, H-5'a, H-5'e), 2.07, 2.03, 1.61 (3s, 9 H, acetyl). ^{13}C NMR (50 MHz): δ 169.9, 169.8, 169.3 ($CH_3C(O)O$), 140.2, 137.7, 130.0 (C-arom.), 125.0, 124.7, 124.2, 122.9, 121.8 (C-H-*arom.*), 75.0, 74.7, 72.9 (C-2' to C-4'), 42.6 (C-1'), 31.3 (C-5'), 20.9, 20.6, 20.2 (CH$_3$C(O)O).

Anal.: Calcd for $C_{19}H_{20}O_6S_2$ (408.48): C, 55.87; H, 4.93; S, 15.70. Found: C, 55.60; H, 4.98; S, 15.59.

7α : white crystals; mp 166-167 °C (EtOAc-hexane); $[\alpha]_D$ +330° (*c* 0.5, CHCl$_3$). ^{1}H NMR (300 MHz): δ 7.87 (m, 1 H, H-*arom.*), 7.79 (m, 1 H, H-*arom.*), 7.69 (d, 1 H, J 1.2 Hz, H-*arom.*), [7.45–7.35] (m, 2 H, H-*arom.*), 5.89 (dd, 1 H, $J_{3',4'}$ 9.2 Hz, H-3'), 5.52 (dd, 1 H, $J_{2',3'}$ 10.0 Hz, H-2'), 5.13 (ddd, 1 H, $J_{4',5'e}$ 4.2 Hz, H-4'), 4.81 (ddd, 1 H, $J_{1',2'}$ 5.3 Hz, $J_{1',5e'}$ 1.1 Hz, H-1'), 2.73 (dq, 1 H, $J_{5'a,5'e}$ 13.7 Hz, H-5'e), 2.55 (dd, 1 H, $J_{4',5'a}$ 10.6 Hz, H-5'a), 2.12, 2.05, 1.93 (3s, 9 H, acetyl). Upon selective irradiation of H-1', the signals visible at 2.73, 5.52 and 7.69 ppm (H-5'e, H-2' and the isolated aromatic proton, respectively) were simplified. Upon selective irradiation of the proton visible at 7.69 ppm, n.O.e. difference spectra revealed a strong enhancement (20 %) of the signal at 5.89 ppm (H-3'). Selective irradiation of the anomeric proton resulted in n.O.e. enhancements for H-2' (13 %) and for protons in the aromatic region (δ, intensity): 7.80, 9 %; 7.69, 0.6 %. ^{13}C NMR (50 MHz): δ 170.1, 169.8, 169.8 (CH$_3$$C$(O)O), 139.9, 138.3, 129.1 (C-*arom.*), 124.8, 124.7, 124.1, 122.8, 122.5 (C-H-*arom.*), 73.5, 72.8, 70.6 (C-2' to C-4'), 39.4 (C-1'), 27.1 (C-5'), 20.9, 20.7, 20.7 (CH$_3$C(O)O).

Anal.: Calcd for $C_{19}H_{20}O_6S_2$ (408.48): C, 55.87; H, 4.93; S, 15.70. Found: C, 55.72; H, 4.95; S, 15.47.

Reaction of **4** *with furan*. A solution of the bromide **4** (3.56 g, 10 mmol) and furan (3.2 mL, 50 mmol) in anhydrous CHCl$_3$ was introduced into a Schlenk tube containing anhydrous zinc chloride (6.8 g, 50 mmol) protected from moisture by an argon atmosphere. The mixture was stirred at room temperature for 1.5 h. After fitration through a bed of celite, addition of triethylamine and concentration under reduced pressure, the residue was applied to a column of silica gel irrigated with EtOAc-petroleum ether 1:2 (v/v). In addition to pure **5** (2 g, 5.84 mmol, 58% yield), another fraction was obtained from which **8** (0.17 g, 0.48 mmol, 5% yield) was extracted after a new chromatography with EtOAc-petroleum ether 1:3 (v/v) as the mobile phase. Other results gathered from smaller scale experiments are indicated in Table 2.

3(S),4(S)-Diacetoxy-2(R)-[bis-(2-furanyl)methyl]tetrahydrothiophene **8**. colourless single crystals; mp 68-69 °C (diethyl ether-petroleum ether); $[\alpha]_D$ -23° (*c* 0.5, CHCl$_3$). ^{1}H NMR (200 MHz): δ [7.37–7.35] (m, 2 H, H-*furan*), [6.35–6.31] (m, 2 H, H-*furan*), 6.26 (d, 1 H, J 3.1 Hz, H-*furan*), 6.17 (d, 1 H, J 3.1 Hz, H-*furan*), [5.39–5.27] (m, 2 H, H-3, H-4), 4.44 (d, 1 H, $J_{1',2}$ 10.2 Hz, H-1'), 4.01 (dd, 1 H, $J_{2,3}$ 3.9 Hz, H-2), 3.20 (dd, 1 H, $J_{4,5a}$ 5.1 Hz, $J_{5a,5b}$ 12.0 Hz, H-5a), 2.89 (dd, 1 H, $J_{4,5b}$ 4.6 Hz, H-5b), 2.12, 1.95 (2s, 6 H, acetyl). ^{13}C NMR (50 MHz): δ 169.9, 169.4 (CH$_3$$C$(O)O), 152.8, 152.5 (C-*furan*), 142.1, 142.0, 110.5, 110.4, 107.5, 107.5 (C-H-*furan*), 79.1, 78.1 (C-3, C-4), 52.1 (C-2), 44.1 (C-1'), 32.5 (C-5), 21.1, 20.8 (CH$_3$C(O)O).

Anal.: Calcd for $C_{17}H_{18}O_6S$ (350.38): C, 58.28; H, 5.18; S, 9.14. Found: C, 58.42; H, 5.25; S, 9.03.

Reaction of **4** *with thiophene*. Anhydrous zinc chloride (1.2 g, 8.8 mmol) was obtained by fusion in a Schlenk tube which was subsequently allowed to cool down to room temperature under vacuum. While the tube was flushed with argon, a solution of **2** (1 g, 2.82 mmol) and thiophene (1.115 mL, 14.1 mmol) in anhydrous $CHCl_3$ (10 mL) was introduced into the tube. After stirring at room temperature for 24 h, the mixture was filtered through a bed of celite. Addition of triethylamine and concentration under reduced pressure led to a residue which was applied to a column of silica gel eluted with EtOAc-petroleum ether 1:3 (v/v) to afford **6** (0.155 g, 0.43 mmol, 15% yield) and **9** (0.26 g, 0.68 mmol, 24% yield). When this procedure was applied to larger quantities of **4** (4.0 g) and thiophene (1.72 mL), a byproduct identified as **10** (0.05 g, 0.13 mmol, ~1% yield) was recovered by chromatography using EtOAc-hexanes 1:5 (v/v).

*3(*S*),4(*S*)-Diacetoxy-2(*R*)-[bis-(2-thienyl)methyl]tetrahydrothiophene* **9**. colourless oil; $[\alpha]_D$ -25° (*c* 0.5, $CHCl_3$). ^1H NMR (200 MHz): δ 7.22 (dd, 1 H, *J* 1.2 Hz, *J* 5.1 Hz, H-*thiophene*), 7.18 (dd, 1 H, *J* 1.4 Hz, *J* 4.9 Hz, H-*thiophene*), 7.06 (dd, 1 H, *J* 0.7 Hz, *J* 3.4 Hz, H-*thiophene*), [7.02–6.89] (m, 3 H, H-*thiophene*), [5.37–5.27] (m, 2 H, H-3, H-4), 4.83 (d, 1 H, $J_{1',2}$ 9.3 Hz, H-1'), 4.04 (dd, 1 H, $J_{2,3}$ 5.00 Hz, H-2), 3.16 (dd, 1 H, $J_{4,5a}$ 5.0 Hz, $J_{5a,5b}$ 11.5 Hz, H-5a), 2.85 (dd, 1 H, $J_{4,5b}$ 5.3 Hz, H-5b), 2.08, 1.92 (2s, 6 H, acetyl). ^{13}C NMR (50 MHz): δ 169.7, 169.4 ($CH_3\mathit{C}(O)O$), 145.3, 144.6 (C-*thiophene*), 126.8, 126.4, 125.9, 125.1, 125.0, 124.7 (C-H-*thiophene*), 79.0, 77.7 (C-3, C-4), 55.1 (C-2), 46.8 (C-1'), 32.3 (C-5), 20.9, 20.6 ($\mathit{C}H_3C(O)O$). *Anal.*: Calcd for $C_{17}H_{18}O_4S_3$ (382.51): C, 53.38; H, 4.74; S, 25.15. Found: C, 52.92; H, 4.71; S, 25.19.

*2-(2',3'-Di-*O*-acetyl-4'-bromo-4'-deoxy-5'-thio-β-*D*-xylopyranosyl)thiophene* **10**. white crystals; mp 163-164 °C (EtOAc-petroleum ether); $[\alpha]_D$ -26° (*c* 0.8, CH_2Cl_2). ^1H NMR (200 MHz): δ 7.23 (d, 1 H, *J* 3.6 Hz, H-*thiophene*), 7.01 (d, 1 H, *J* 2.6 Hz, H-*thiophene*), 6.93 (dd, 1 H, *J* 3.6 Hz, *J* 2.6 Hz, H-*thiophene*), 5.35 (t, 1 H, $J_{3',4'}$ 10.2 Hz, H-3'), 5.16 (t, 1 H, $J_{2',3'}$ 10.2 Hz, H-2'), 4.37 (d, 1 H, $J_{1',2'}$ 10.4 Hz, H-1'), 4.36 (ddd, 1 H, $J_{4',5'e}$ 4.7 Hz, H-4'), 3.28 (dd, 1 H, $J_{4',5'a}$ 11.7 Hz, H-5'a), 3.12 (dd, 1 H, $J_{5'a,5'e}$ 13.9 Hz, H-5'e), 2.09, 1.81 (2s, 6 H, acetyl). The assignments of H-2' and H-3' may be reversed. ^{13}C NMR (50 MHz): δ 169.6, 169.1 ($CH_3\mathit{C}(O)O$), 137.6 (C-2), 126.9, 126.6, 125.7 (C-3 to C-5), 76.6, 76.5 (C-2', C-3'), 49.1 (C-4'), 45.0 (C-1'), 36.1 (C-5'), 20.6, 20.3 ($\mathit{C}H_3C(O)O$).
Anal.: Calcd for $C_{13}H_{15}O_4S_2Br$ (379.28): C, 41.17; H, 3.99; S, 16.91; Br, 21.06. Found: C, 41.49; H, 4.04; S, 16.94; Br, 20.68.

*3(*S*),4(*S*)-Diacetoxy-2(*R*)-[(*R,S*)(2-*p*-dimethoxyphenyl)(2-thienyl)methyl]tetrahydrothiophene* **11**. A solution of **6α** (0.10 g, 0.28 mmol) and 1,4-dimethoxybenzene (0.077 g, 0.56 mmol) in anhydrous CH_2Cl_2 (2 mL) was stirred at room temperature for 12 h in the presence of tin (IV) tetrachloride (0.010 g, 0.038 mmol). Triethylamine (0.2 mL) was added to the reaction medium which was concentrated under reduced pressure.The residue, applied to a column of silica gel eluted with EtOAc-hexane 1:2 (v/v) led to **11** (0.037 g, 0.084 mmol, 30% yield) as a ~1/1 diastereoisomeric mixture. Chromatography under the same conditions provided analytical samples of each diastereoisomer which were not completely characterized.

11a : ^1H NMR (200 MHz): δ 7.15 (d, 1 H, *J* 5.1 Hz, H-*thiophene*), 7.01 (d, 1 H, *J* 3.1 Hz, H-*thiophene*), 6.91 (dd, 1 H, H-*thiophene*), 6.87 (d, 1 H, ^4J 2.8 Hz, H-*aryl*), 6.77 (d, 1 H, *J* 8.9 Hz, H-*aryl*), 6.69 (dd, 1 H, H-*aryl*), [5.32–5.23] (m, 2 H, H-3, H-4), 4.98 (d, 1 H, $J_{1',2}$ 10.9 Hz, H-1'), 4.19 (dd, 1 H, $J_{2,3}$ 5.0 Hz, H-2), 3.80 (s, 3 H, OMe), 3.73 (s, 3 H, OMe), 3.16 (dd, 1 H,

$J_{4,5a}$ 5.0 Hz, $J_{5a,5b}$ 11.7 Hz, H-5a), 2.91 (dd, 1 H, $J_{4,5b}$ 5.5 Hz, H-5b), 2.07, 1.78 (2s, 6 H, acetyl).

11b : ^{1}H NMR (200 MHz): δ 7.12 (d, 1 H, J 5.0 Hz, H-*thiophene*), 6.92 (d, 1 H, J 3.4 Hz, H-*thiophene*), 6.89 (d, 1 H, ^4J 2.5 Hz, H-*aryl*), 6.86 (dd, 1 H, H-*thiophene*), 6.80 (d, 1 H, J 8.8 Hz, H-*aryl*), 6.72 (dd, 1 H, H-*aryl*), 5.37 (t, 1 H, $J_{3,4}$ 4.5 Hz, H-3), 5.31 (m, 1 H, $J_{4,5a}$ 5.1 Hz, H-4), 4.97 (d, 1 H, $J_{1',2}$ 10.6 Hz, H-1'), 4.25 (dd, 1 H, $J_{2,3}$ 4.5 Hz, H-2), 3.80 (s, 3 H, OMe), 3.77 (s, 3 H, OMe), 3.16 (dd, 1 H, $J_{5a,5b}$ 11.3 Hz, H-5a), 2.98 (dd, 1 H, $J_{4,5b}$ 4.0 Hz, H-5b), 2.12, 1.86 (2s, 6 H, acetyl).

General procedure for deacetylation of 5β, 6β *and* 7β. A catalytic amount of sodium methoxide in anhydrous MeOH (1-2 drops, ~1M solution) was added to a methanolic solution of the *C*-hetaryl tri-*O*-acetyl-5-thio-D-xylopyranoside. Stirring at room temperature was maintained until complete deacetylation was indicated by TLC, whereupon the solvent was removed under reduced pressure prior to purification by column chromatography with $CHCl_3$-MeOH 9:1 (v/v).

*2-(5'-thio-β-*D*-xylopyranosyl)furan* **12**. 5β (0.57 g, 1.67 mmol) was deacetylated according to the general procedure to afford **12** (0.355 g, 1.64 mmol, 98% yield). white solid; mp 148-149 °C; $[\alpha]_D$ -26° (*c* 0.5, MeOH). ^{1}H NMR (200 MHz, MeOD): δ 7.41 (dd, 1 H, J 1.8 Hz, J 0.8 Hz, H-*furane*), 6.35 (dd, 1 H, J 1.8 Hz, J 3.2 Hz, H-*furane*), 6.28 (d, 1 H, J 3.2 Hz, H-3), 4.89 (s, 3 H, OH), 3.94 (d, 1 H, $J_{1',2'}$ 10.3 Hz, H-1'), 3.79 (dd, 1 H, $J_{2',3'}$ 8.7 Hz, H-2'), 3.68 (ddd, 1 H, $J_{4',5'e}$ 5.2 Hz, H-4'), 3.16 (t, 1 H, $J_{3',4'}$ 8.8 Hz, H-3'), 2.72 (dd, 1 H, $J_{4',5'a}$ 10.2 Hz, H-5'a), 2.61 (dd, 1 H, $J_{5'a,5'e}$ 13.4 Hz, H-5'e). ^{13}C NMR (50 MHz, MeOD): δ 152.9 (C-2), 143.2 (C-5), 111.4, 108.8 (C-3, C-4), 80.7, 77.1, 74.7 (C-2' to C-4'), 45.6 (C-1'), 34.4 (C-5'). *Anal.*: Calcd for $C_9H_{12}O_4S$ (216.25): C, 49.99; H, 5.59; S, 14.83. Found: C, 49.72; H, 5.58; S, 14.96.

*2-(5'-thio-β-*D*-xylopyranosyl)thiophene* **13**. 6β (0.304 g, 0.85 mmol) was deacetylated (1.5 h treatment) according to the general procedure to afford **13** (0.195 g, 0.84 mmol, 99% yield). white solid; mp 168-169 °C; $[\alpha]_D$ +54° (*c* 0.5, MeOH). ^{1}H NMR (200 MHz, MeOD): δ 7.29 (d, 1 H, J 5.1 Hz, H-*thiophene*), 7.03 (d, 1 H, J 3.5 Hz, H-*thiophene*), 6.94 (dd, 1 H, H-*thiophene*), 4.89 (s, 3 H, OH), 4.08 (d, 1 H, $J_{1',2'}$ 10.3 Hz, H-1'), 3.72 (ddd, 1 H, $J_{4',5'e}$ 4.9 Hz, H-4'), 3.64 (dd, 1 H, $J_{2',3'}$ 8.9 Hz, H-2'), 3.18 (t, 1 H, $J_{3',4'}$ 8.9 Hz, H-3'), 2.76 (dd, 1 H, $J_{4',5'a}$ 10.5 Hz, H-5'a), 2.62 (dd, 1 H, $J_{5'a,5'e}$ 13.4 Hz, H-5'e). ^{13}C NMR (50 MHz, MeOD): δ 142.6 (C-2), 127.5, 127.3, 125.7 (C-3 to C-5), 80.6, 79.8, 74.7 (C-2' to C-4'), 47.5 (C-1'), 34.9 (C-5'). *Anal.*: Calcd for $C_9H_{12}O_3S_2$ (232.31): C, 46.43; H, 5.21; S, 27.60. Found: C, 46.27; H, 5.24; S, 27.92.

*3-(5'-thio-β-*D*-xylopyranosyl)benzothiophene* **14**. 7β (0.113 g, 0.267 mmol) was treated for 24 h according to the general deacetylation procedure to yield **14** (0.075 g, 0.26 mmol, 96% yield). colourless needles; mp 187 °C (MeOH); $[\alpha]_D$ +7° (*c* 0.5, MeOH). ^{1}H NMR (200 MHz, MeOD): δ 8.02 (d, 1 H, J 7.0 Hz, H-*arom.*), 7.86 (d, 1 H, J 7.0 Hz, H-*arom.*), 7.53 (s, 1 H, H-*arom.*), 7.36 (m, 2 H, H-*arom.*), 4.28 (d, 1 H, $J_{1',2'}$ 10.3 Hz, H-1'), 4.03 (dd, 1 H, $J_{2',3'}$ 8.8 Hz, H-2'), 3.80 (ddd, 1 H, $J_{4',5'e}$ 4.6 Hz, H-4'), 3.30 (t, 1 H, $J_{3',4'}$ 8.8 Hz, H-3'), 2.84 (dd, 1 H, $J_{4',5'a}$ 10.7 Hz, H-5'a), 2.68 (dd, 1 H, $J_{5'a,5'e}$ 13.3 Hz, H-5'e).Upon selective irradiation of the proton at 7.53 ppm, the following n.O.e. enhancements were observed (nucleus, intensity %): H-

1', 3.5; H-2', 9. Selective irradiation of H-1' resulted in n.O.e.enhancements for signals in the aromatic region (ppm, intensity): 8.02, 6 %; 7.53, 2.5 %, as well as for H-3' (7.5 %) and H-5a (4 %). ^{13}C NMR (50 MHz, MeOD): δ 141.7, 139.8, 134.2 (C-*arom.*), 125.5, 125.3, 124.9, 123.6, 123.5 (C-H-*arom.*), 81.0, 78.0, 74.9 (C-2' to C-4'), 45.6 (C-1'), 34.8 (C-5').
Anal.: Calcd for $C_{13}H_{14}O_3S_2$ (282.37): C, 55.30; H, 5.00; S, 22.70. Found: C, 55.23; H, 4.93; S, 22.50.

3(S),4(S)-Dihydroxy-2(R)-[bis-(2-thienyl)methyl]tetrahydrothiophene **15**. Compound **9** (0.574 g, 1.5 mmol) in anhydrous MeOH was treated with a catalytic amount of sodium methoxide for 72 h. The deacetylated compound **15** (0.35 g, 1.16 mmol, 77% yield) was purified by chromatography, using $CHCl_3$-MeOH 14:1 (v/v) as the mobile phase; colourless oil; $[\alpha]_D$ +20° (*c* 0.8, $CH_3C(O)CH_3$). ^{1}H NMR (200 MHz, $CD_3C(O)CD_3$): δ 7.36 (d, 1 H, *J* 5.2 Hz, H-*thiophene*), 7.30 (d, 1 H, *J* 5.2 Hz, H-*thiophene*), 7.12 (d, 1 H, *J* 3.5 Hz, H-*thiophene*), [7.02–6.93] (m, 3 H, H-*thiophene*), 5.13 (d, 1 H, $J_{1',2}$ 7.8 Hz, H-1'), 4.23 (m, 1 H, $J_{4,5a}$ 5.3 Hz, H-4), 3.91 (dd, 1 H, $J_{2,3}$ 4.6 Hz, H-2), 3.81 (t, 1 H, $J_{3,4}$ 5.3 Hz, H-3), 3.02 (dd, 1 H, $J_{5a,5b}$ 10.7 Hz, H-5a), 2.67 (dd, 1 H, $J_{4,5b}$ 6.0 Hz, H-5b). ^{13}C NMR (50 MHz, $CD_3C(O)CD_3$): δ 148.4, 146.2 (C-*thiophene*), 127.4, 126.8, 126.8, 125.7, 125.5, 125.0 (C-H-*thiophene*), 80.6, 79.2 (C-3, C-4), 59.0 (C-2), 46.4 (C-1'), 35.6 (C-5).
Anal.: Calcd for $C_{13}H_{14}O_2S_3$ (298.43): C, 52.32; H, 4.73; S, 32.23. Found: C, 52.58; H, 4.63; S, 32.27.

X-ray structure determination of compound **8**. $C_{17}H_{18}O_6S$, M = 350.4, orthorhombic, space group $P2_12_12_1$, a = 7.3324(5), b = 7.4742(7), c = 31.941(3) Å, V = 1750.5(4) Å^3, Z = 4, D_c = 1.330 g.cm^{-3}. Data were collected on a Nonius CAD4 diffractometer. Of 3484 unique reflections measured ($2\theta_{max}$ = 146°, μ(CuKα) = 18.6 cm^{-1}, T = 295 K), 3101 had $I > 3\sigma(I)$ and were used for all calculations with the Structure Diffraction Package.[39] The six hydrogen atoms of the two furanyl groups were introduced at the theoretical positions and were not refined. All the other hydrogen atoms were located from ΔF syntheses and their positional parameters were refined. The final refinement gave R = 0.057. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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