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Note

Efficient synthesis of 5-thio-D-arabinopyranose and 5-thio-D-xylopyranose from the corresponding D-pentono-1,4-lactones

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Abstract

5-Thio-D-arabinopyranose (**5**) and 5-thio-D-xylopyranose (**10**) were synthesized from the corresponding D-pentono-1,4-lactones. After regioselective bromination at C-5, transformation into 5-*S*-acetyl-5-thio derivatives, reduction into lactols and deprotection afforded the title compounds in 49 and 42% overall yield, respectively.

Keywords: 5-Bromo-5-deoxy-D-pentono-1,4-lactone; 5-*S*-Acetyl-5-thio-D-arabinono and D-xylono-1,4-lactones; 5-*S*-Acetyl-5-thio-D-arabinofuranose and D-xylofuranose; 5-Thio-D-arabinopyranose and 5-thio-D-xylopyranose

5-Thiosugars with a sulfur atom in the ring possess interesting biological properties, that have been reviewed recently.[1] Among others, 5-thio-D-xylopyranose is an inhibitor of β-D-xylosidase.[2] Glycosides of 1,5-dithio-D-xylopyranose, in particular, have proved to be orally active venous antithrombotic agents.[3]

For these reasons, synthesis of thiosugars have been described since the 1960s. Whereas numerous different synthetic routes of 5-thioglycopyranoses are well established, in general, these syntheses require long synthetic strategies that lead to substantially moderate if not lowered yields.

Very often the synthetic strategy for 5-thiopentoses requires a primary-*O*-sulfonate displacement of the furanoside form by use of reagents containing nucleophilic sulfur.[1]

The first example of a thioaldose synthesized was 5-thio-D-xylopyranose[4] which was prepared again recently, from D-xylose, by Bellamy and co-workers.[3a] in five steps and 36.5% overall yield.

The first synthesis of 5-thio-D-arabinopyranose was reported by Hughes and co-workers.[5] More recently, another synthesis was described by Hashimoto and co-workers,[6] from D-arabinose, in six steps and 15% overall yield.

Earlier, we reported the synthesis of 5-thio-D-ribopyranose from D-ribono-1,4-lactone in 57% overall yield.[7] Herein we extend our investigations to D-arabinono and D-xylono-1,4-lactones as starting materials. Our retrosynthetic route is illustrated in Scheme 1.

The synthesis of 5-thio-D-arabinopyranose (**5**) was achieved from D-arabinono-1,4-lactone via the C-5 brominated derivative **2** (Scheme 2). Treatment of D-arabinono-1,4-lactone with thionyl bromide in *N,N*-dimethylformamide[8] followed by reaction of the resultant bromide lactone **2a** (85%) with acetic anhydride which gave 2,3-di-*O*-acetyl-5-bromo-5-deoxy-D-arabinono-1,4-lactone (**2b**) in one pot sequence and good overall yield (88%). Displacement of the bromide group in **2b** with potassium thiacetate gave the 2,3-di-*O*-acetyl-5-*S*-acetyl-5-thio-D-arabinono-1,4-lactone (**3**) in excellent yield (>95%). Compound **3** was treated with disiamylborane in tetrahydrofuran to give the lactol **4** in 82% yield. Methanolysis of **4** gave the expected pure 5-thio-D-arabinopyranose (**5**) in 71% yield.

A similar sequence of reactions was repeated with D-xylono-1,4-lactone **6** (Scheme 2). Thus a one pot bromination–acetylation of **6** afforded 2,3-di-*O*-acetyl-5-bromo-5-deoxy-D-xylono-1,4-lactone (**7b**) in 75% yield. Treatment of **7b** with potassium thioacetate followed by reduction of the lactone functionality by

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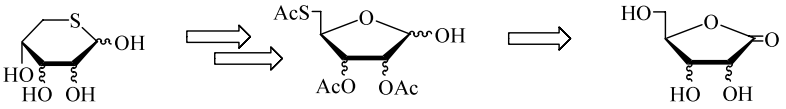


Scheme 1.

disiamylborane afforded 5-*S*-acetyl-5-thio-D-xylofuranose (**9**). Saponification of **9** with sodium methoxide in methanol gave 5-thio-D-xylopyranose (**10**) in 84% yield.

In summary, we have developed an efficient synthesis of **5** and **10**, which were obtained in 49 and 42% overall yield in five steps from D-arabinono- and D-xylono-1,4-lactones.

1. Experimental

1.1. General methods

Melting points were determined on a Buchi 535 apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-370 digital polarimeter, using a sodium lamp ($\lambda = 589$ nm) at 20 °C. ^{1}H and ^{13}C NMR spectra were recorded in D_2O or $CDCl_3$. Me_4Si was used as an internal standard on a Bruker 300 MHz spectrometer. Thin-layer chromatography (TLC) was performed on E. Merck glass plates silica gel sheets (Silica Gel F_{254}) and visualised under UV light or stained with phosphomolybdic acid-aqueous H_2SO_4 solution. Column chromatography was performed on Kieselgel (E. Merck 230–400 mesh). All solvents were distilled before use (Tables 1 and 2).

1.2. 2,3-Di-*O*-acetyl-5-bromo-5-deoxy-D-arabinono-1,4-lactone (2b)

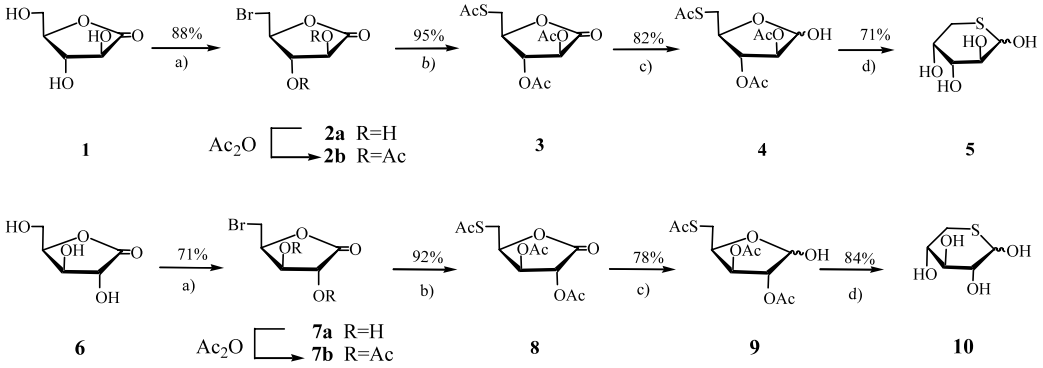
D-Arabinono-1,4-lactone (**1**) (0.5 g, 3.4 mmol) was stirred in *N,N*-dimethylformamide (5 mL) under an inert atmosphere. Freshly distilled $SOBr_2$ (0.445 mL, 1.7 equiv) was added dropwise at 0 °C. The mixture was stirred at room temperature (rt) for 30 min, then MeOH was added and the solution was kept for 10 min at rt and concentrated under diminished pressure. The crude material was treated with Ac_2O (10 mL). After 15 min at 60 °C under an inert atmosphere, the solution was concentrated and the residue was added to water and extracted with CH_2Cl_2. the extracts were dried ($MgSO_4$), filtered and concentrated under diminished pressure. Column chromatography (4:1 then 3:2, hexanes–EtOAc) of the residue afforded **2b** (0.817 g, 88%) as a colourless syrup: R_f 0.62 (3:2 hexanes–EtOAc); $[\alpha]_D$ + 22° (*c* 1.69, CH_2Cl_2). Anal. Calcd for $C_9H_{11}BrO_6$: C, 36.63; H, 3.76; Br, 27.08. Found: C, 36.71; H, 3.85; Br, 27.82.

1.3. 2,3-Di-*O*-acetyl-5-*S*-acetyl-5-thio-D-arabinono-1,4-lactone (3)

To a solution of **2b** (0.5 g, 1.7 mmol) in *N,N*-dimethylformamide (5 mL) was added potassium thioacetate (0.23 g, 2 mmol). The mixture was stirred under an inert atmosphere at rt for 10 min. The mixture was filtered and concentrated under diminished pressure to yield a crude product, which was partitioned between CH_2Cl_2 and water. The CH_2Cl_2 extracts were dried ($MgSO_4$), filtered and concentrated. Column chromatography (4:1, hexanes–EtOAc) of the residue afforded **3** (0.467 g, 95%) as a colourless syrup: R_f 0.54 (3:2 hexanes–EtOAc); $[\alpha]_D$ +26° (*c* 1.09, CH_2Cl_2). Anal. Calcd for $C_{11}H_{14}O_7S$: C, 45.51; H, 4.86. Found: C, 45.61; H, 4.92.

1.4. 2,3-Di-*O*-acetyl-5-*S*-acetyl-5-thio-D-arabinofuranose (4)

To 2,3-di-*O*-acetyl-5-*S*-acetyl-D-ribono-1,4-lactone (**3**) (0.5 g, 1.72 mmol) at 0 °C was added disiamylborane[9] freshly prepared (8 equiv) in THF. The mixture was



Scheme 2.

Table 1
^{13}C NMR data

Compound	Chemical shifts δ (ppm)					
	C-1	C-2	C-3	C-4	C-5	Other signals
2b [a]	170.4	72.8	75.0	78.4	31.8	169.9 ($COCH_3$); 20.9–20.6 ($COCH_3$)
3 [a]	170.1	72.9	74.9	78.2	31	170.0; 168.0 ($COCH_3$); 20.8–20.5 ($COCH_3$); 194.6 ($SCOCH_3$); 30.8 ($SCOCH_3$)
4α [a]	95.2	77.2	78.1	79.4	33.7	170.5; 170.3 ($COCH_3$); 21.2, 20.8 ($COCH_3$); 195.3 ($SCOCH_3$); 30.6 ($SCOCH_3$)
4β [a]	100.6	823	79.1	81.0	31.4	170.5; 170.3.0 ($COCH_3$); 21.9–20.8 ($COCH_3$); 195.3 ($SCOCH_3$); 30.6 ($SCOCH_3$)
5α [b]	78.8	74.2	74.2	68.4	29.8	-
5β [b]	74.0	71.5	70.0	69.8	29.1	-
7b [a]	173.8	72.6	71.5	77.6	29.6	170.1, 169.8 ($COCH_3$); 21.8; 20.9 ($COCH_3$)
8 [a]	170.1	71.4	72.8	77.3	28.5	169.7, 168.9 ($COCH_3$); 20.9, 20.7 ($COCH_3$); 194.0 ($SCOCH_3$); 30.8 ($SCOCH_3$)
9α [a]	94.4	77.8	75.3	79.6	29.3	170.2; 170.0 ($COCH_3$); 21.3–21 ($COCH_3$); 195.7 ($SCOCH_3$); 30.7 ($SCOCH_3$)
9β [a]	101.0	81.7	75.8	75.3	28.3	170.6; 170.5 ($COCH_3$); 21.3, 21.0 ($COCH_3$); 195.3 ($SCOCH_3$); 30.7 ($SCOCH_3$)
10α [b]	74.6	78.0	76.9	73.5	30.0	-
10β [b]	73.5	75.8	74.0	73.5	27.4	-

[a] In $CDCl_3$.
[b] In D_2O.

stirred, under an inert atmosphere, at rt for 24 h. Then MeOH was added and the solution was kept for 30 min and concentrated. The crude material was diluted with CH_2Cl_2 and washed with water. The CH_2Cl_2 extracts were dried ($MgSO_4$), filtered and concentrated. Column chromatography (4:1, hexanes–EtOAc) of the residue afforded **4** (0.413 g, 82%) as a colourless syrup: R_f 0.34 (3:2 hexanes–EtOAc); $[\alpha]_D$ +32° (α/β 7:3, NMR) (*c* 1.83, CH_2Cl_2). Anal. Calcd for $C_{11}H_{16}O_7S$: C, 45.20; H, 5.52. Found: C, 45.23; H, 5.60.

1.5. 5-Thio-D-arabinopyranose (5)

To a soln of the thioacetate (**4**) (0.5 g, 1.71 mmol) in MeOH (5 mL) was added NaOMe (0.092 g, 6 equiv). The mixture was stirred for 3 h at rt. The solution was passed through an ion exchange resin column (Dowex 50 × 8-100) filtered and concentrated. Column chromatography (9:1, CH_2Cl_2–MeOH) of the residue afforded **5** (0.20 g, 71%) as a colourless syrup: R_f 0.61 (4:1 CH_2Cl_2–MeOH); $[\alpha]_D$ +45° (α/β 3:7, NMR) (*c* 1.02, water), lit.: for β form $[\alpha]_D$ −250° (*c* 0.6, water),[5] mp 173–175 °C.[6] Anal. Calcd for $C_5H_{10}O_4S$: C, 36.13; H, 6.06. Found: C, 36.18; H, 6.14.

1.6. 2,3-Di-*O*-acetyl-5-bromo-5-deoxy-D-xylono-1,4-lactone (7b)

Reaction of D-xylono-1,4-lactone (**6**) (0.5 g, 3.4 mmol) with thionyl bromide in *N,N*-dimethylformamide as for **1**, followed by acetylation with acetic anhydride gave **7b** (0.496 g, 71%) as a thick liquid; R_f 0.60 (3:2 hexanes–EtOAc); $[\alpha]_D$ +62° (*c* 4.8, CH_2Cl_2). Anal. Calcd for $C_9H_{11}BrO_6$: C, 36.63; H, 3.76; Br, 27.08. Found: C, 36.67; H, 3.81; Br, 27.32.

1.7. 2,3-Di-*O*-acetyl-5-*S*-acetyl-5-thio-D-xylono-1,4-lactone (8)

To a soln of **7b** (0.5 g, 1.7 mmol) in *N,N*-dimethylformamide was added potassium thioacetate (0.23 g, 2 mmol) and the reaction was treated as for **2b** to give **8** (0.452 g, 92%) as a colourless syrup: R_f 0.54 (3:2 hexanes–EtOAc); $[\alpha]_D$ +83° (*c* 1.69, CH_2Cl_2). Anal. Calcd for $C_{11}H_{14}O_7S$: C, 45.51; H, 4.86. Found: C, 45.55; H, 4.90.

1.8. 2,3-Di-*O*-acetyl-5-*S*-acetyl-5-thio-D-xylopyranose (9)

2,3-di-*O*-acetyl-5-*S*-acetyl-D-xylono-1,4-lactone (**8**) (0.5 g, 1.72 mmol) was reduced by disiamylborane as described for **3** to give **9** (0.391 g, 78%) as a colourless syrup: R_f 0.35 (3:2 hexanes–EtOAc); $[\alpha]_D$ +75° (α/β 2:3, NMR) (*c* 0.7, CH_2Cl_2). Anal. Calcd for $C_{11}H_{16}O_7S$: C, 45.20; H, 5.52. Found: C, 45.26; H, 5.57.

1.9. 5-Thio-D-xylopyranose (10)

The lactol (0.5 g, 1.71 mmol) was treated by NaOMe in MeOH as described for **4** to give **10** (0.239 g, 84%) as a colourless syrup: R_f 0.61 (4:1 CH_2Cl_2–MeOH), $[\alpha]_D$ + 120° (α/β 1:4, NMR) (*c* 2.7, water), lit.: mp 122–123 °C, $[\alpha]_D$ +202 → +178° (*c* 2, water);[4a] $[\alpha]_D$ +202 → +173° (*c* 1.6, water).[4b] Anal. Calcd for $C_5H_{10}O_4S$: C, 36.13; H, 6.06. Found: C, 36.21; H, 6.11.

Table 2
^{1}H NMR data

Compound	^{1}H Chemical shifts δ (ppm) and ^{1}H coupling constants J (Hz)						
	H-1 $J_{1,2}$	H-2 $J_{2,3}$	H-3 $J_{3,4}$	H-4 $J_{4,5}$	H-5 $J_{4,5'}$	H-5′ $J_{5,5'}$	Others signals
2b [a]	-	5.48 dd 7.12	5.35 t 7.12	4.53 ddd 4.10	3.66 dd 5.05	3.58 dd 11.63	COCH_3 2.06, 2.00 s
3 [a]	-	5.47 d 7.27	5.30 t 7.27	4.48 m 4.75	3.40 dd 6.46	3.22 dd 14.58	(SCOCH_3) 2.34 s (COCH_3) 2.10, 2.14 s
4α [a]	5.17 s -	4.86 d 5.83	4.75 dd 5.08	4.18 ddd 5.16	3.20 dd 6.74	3.00 dd 13.96	(SCOCH_3) 2.21 s (COCH_3) 1.97, 1.90 s
4β [a]	5.34 d 4.40	4.89 dd 5.95	5.14 dd 5.12	3.78 m 5.10	3.27 dd 9.80	3.05 dd 13.96	(SCOCH_3) 2.20 s (COCH_3) 1.97, 1.95 s
5α [b]	4.58 d 7.85	3.74 m 8.30	3.43 dd 2.94	4.07 m 2.27	2.76 dd 5.58	2.36 dd 14.36	-
5β [b]	4.85 d 3.12	3.86 dd 3.86	3.68 m 3.04	4.18 m 1.70	3.08 dd 4.11	2.48 dd 14.46	-
7b [a]	-	5.65–5.58 m	5.10 m	3.64 dd 5.48	3.51 dd 6.20	COCH_3 2.17, 2.09 s 11.40	
8 [a]	-	5.53–5.46 m	4.89 m	3.27 dd 4.66	3.14 dd 6.76	(SCOCH) 2.33 s (COCH_3) 2.12, 2.11 s 14.48	
9α [a]	5.13–4.88 m	5.13 m	4.22 m	2.99–2.91 m	(SCOCH) 2.22 s (COCH_3) 2.00, 1.90 s		
9β [a]	5.45 s	5.30–4.88 m	4.35 m	2.99 dd 6.09	2.91 dd 6.74	(SCOCH_3) 2.22 s (COCH_3) 2.00, 1.90 s 13.82	
10α [b]	4.56 d 9.15	3.40–3.10 m	3.66 m	2.56–2.52 m	-		
10β [b]	4.80 d 2.26	3.63 m 9.3	3.48 t 9.30	3.63 m 11.21	2.75 dd 4.29	2.47 dd 13.00 s	-

[a] In $CDCl_3$.
[b] In D_2O.

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