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Note

Cyclization of dialkyl dithioacetals of L-arabinose through the 5-tosylates

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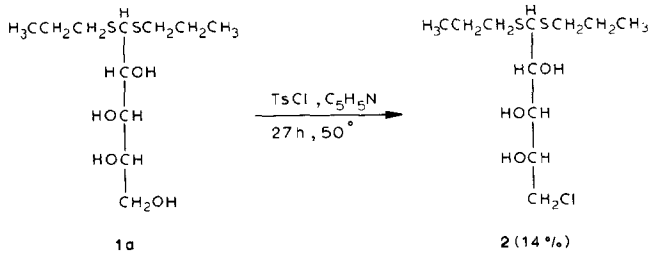
Defaye and Horton[1] reported that dialkyl dithioacetals of arabinose are not cyclized to 2,5-anhydro derivatives when stirred with tosyl chloride in pyridine for 24 h at ambient temperature. We now report conditions that give 2,5-anhydro derivatives.

We desired a 2,5-anhydro-L-arabinose derivative such as **5** as a synthetic intermediate. The only 2,5-anhydro derivative we found in the literature[2] was derived from a methyl acetal in seemingly nonpractical yield. The only other method we considered was that by Defaye and Horton[1], wherein dialkyl dithioacetals of pentoses were treated with tosyl chloride in pyridine for 24 h at room temperature. Derivatives of ribose, xylose, and lyxose, analogous to **5**, were formed in good yield, but the arabinose derivative did not cyclize. Instead, the tosylate **3b** was isolated.

Horton and Wander[3] had studied the conformations of the reactants (or their peracetylated derivatives) by n.m.r. spectroscopy. They found that arabinose derivatives favor an extended, zigzag conformation. When the transition states that would lead to 2,5-anhydro derivatives are compared, it is seen that the *arabino* starting-material has the most-crowded transition state (see Scheme 1, structure **3**),



1a 2 (14 %)

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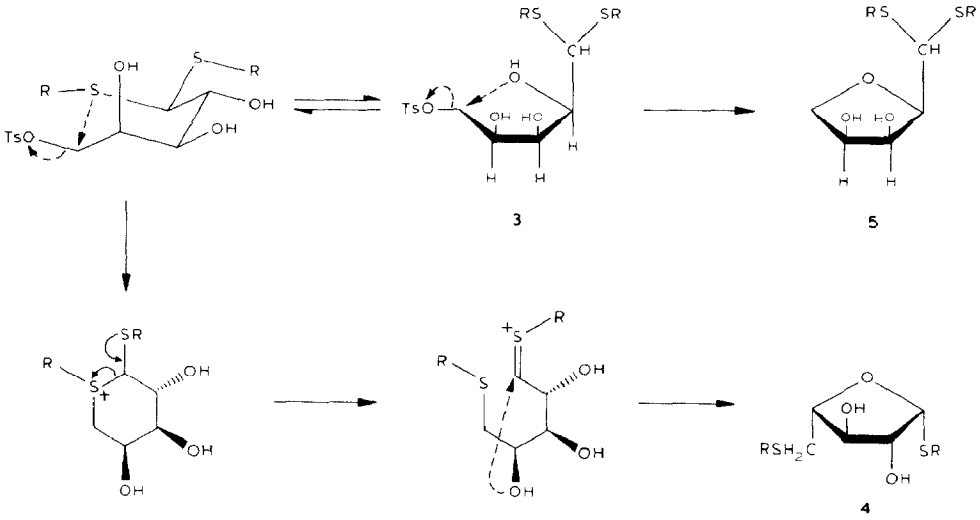
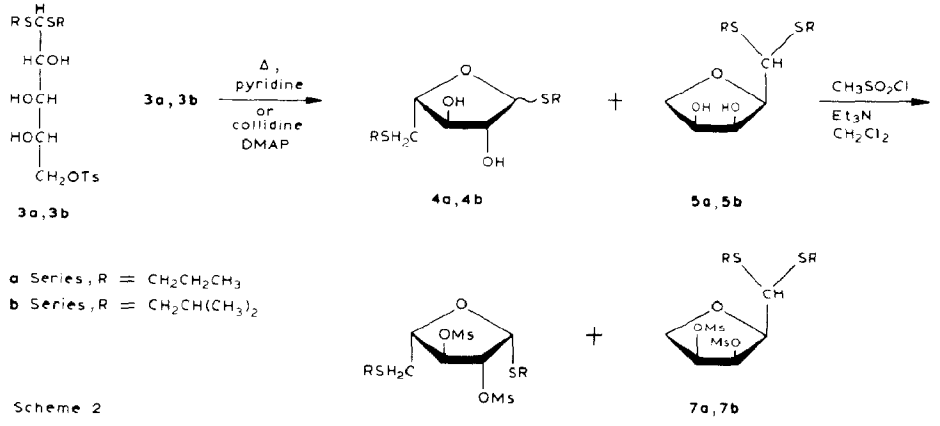


Scheme 1

a product having all three substituents on the same side of the ring being formed.

We therefore decided to apply Defaye and Horton's method[1] under more-forcing conditions. In the first attempt, dithioacetal **1a** was heated with tosyl chloride in pyridine for 27 h at 50°. Only chloride **2**, identified by n.m.r. and mass spectra, was isolated, in only 14% yield; this is a known procedure for synthesizing chlorides[4].

Consequently, in order to avoid the formation of **2**, the tosylate **3a** was isolated and subjected to pyridine for 6 d at 60° (see Scheme 2). A small amount of starting material was separated from the more-polar product. Examination of the ^{1}H-n.m.r. spectrum of the product revealed that it contained more than one compound. The n.m.r. spectrum was consistent with that of a mixture of the expected anhydride **5a** and the thioglycoside derivative **4a** (see Scheme 2).



Scheme 2

TABLE I

YIELDS FOR REACTIONS IN SCHEME 2

Reactant	*Solvent*	*Products*[a]	*Mesylates*		
			Compound	*Yield from* **4**+**5** *(%)*	*Yield from* **3** *(%)*
3a	2,4,6-collidine	**4a, 5a** 3:2 58	**6a**	55	32
			7a	39	22
3a	pyridine	**4a, 5a** 5:14 26	**6a**	not determined (low)	
			7a	55	14
3b	2,4,6-collidine	**4b, 5b** 1:1 82	**6b**	35	29
			7b	30	24

[a]Products, ratio (estimated from n.m.r. data), combined yield (%).

From the n.m.r. spectra, the ratios of the two products were estimated. The area of the H-1 signal of **4a** at δ 5.30 was compared with that of the CH_3 signal at δ 1.00, which was assigned a value of 6 H. Thus, the percentage values in Table I were obtained.

Several articles were found in the literature[5–7] describing the mechanism (see Scheme 1) that gives rise to product **4**. In our case, only the β anomer of **4** was found (see Experimental section for assignment).

Our intended use for **5a** required its conversion into the dimesylate **7a**. Thus, the inseparable mixture of **4a** and **5a** was mesylated, giving dimesylates **6a** and **7a**, which were readily separated by flash chromatography.

From Scheme 1, it may be seen that both reaction paths must begin by attack on the tosylate, either by oxygen or sulfur. It is not clear how ratios of products could be affected, but, presumably, yields of both **4** and **5** could be improved. We decided to investigate how the nature of the group R, the solvent (base), or added *p*-(dimethylamino)pyridine (DMAP) would affect the reaction. Pyridine has been known to react with 3-chloro-1,2-propanediol[8], with a D-glucose-derived 6-triflate[9], and with a tosylate[10], to give pyridinium salts. It is possible that pyridine reacts with intermediates along the path from **3** to **4** (see Scheme 1), giving water-soluble products.

The results are given in Table I. It was found that added DMAP speeds up the reaction only slightly and does not change the ratio of the products. The R group makes little difference in the ratio of products, but it was demonstrated that the isobutyl derivative **3b** of Defaye and Horton[1] also reacts. Its cyclization (no experimental details given) was carried out exactly like that of **3a**. The effect of 2,4,6-collidine was noticeable. It increased the yields of thioglycoside **4a** or **4b** isolated, but had much less effect on the yields of **5a** or **5b**; however, the overall yield of **7a** (**3a** → **5a** → **7a**) was improved from 14 to 22%.

The results suggest that pyridine *is* involved in a side reaction along the **3** → **4** transformation, and that this may not happen as easily with the more-hindered 2,4,6-collidine.

The experiments summarized in Table I were conducted under conditions described in the Experimental section for **3a** in collidine. Because there are two chromatographic separations, each run had slightly different workup procedures, and yields of the dimesylates are not the best basis for comparison; the initial, n.m.r.-based, product ratios are more accurate.

Tosylate **3b** was also cyclized in DMF with 1.1 equiv. of DMAP present, affording **4b** and **5b** in the ratio of 1:1, and a yield much lower than those given in Table I.

The dimesylate **7a** was converted into 4-amino-4,5-dihydro-2-furancarboxylic acid[11] in several steps*. This demonstrates that, although ester **7a** was produced in only 22% yield from **3a**, it is feasible to prepare it in sufficient quantity to permit its use as a synthetic intermediate.

The experiments described support and extend Defaye and Horton's work[2]. Arabinose derivatives are, indeed, resistant to cyclization, but the reaction proceeds under forcing conditions.

EXPERIMENTAL

General methods. — Solvents were dried by distillation from barium oxide. Melting points were obtained on a Thomas–Hoover Unimelt apparatus and are uncorrected. Column chromatography was conducted on silica gel 60 (70–230 mesh) in a flash column. N.m.r. spectra were recorded at 90 MHz with an EM 360L spectrometer, except where noted otherwise. The 300-MHz spectra and 2D spectra were recorded with a Varian VXR-300 instrument.

L-*Arabinose dipropyl dithioacetal.* — This compound was prepared by the procedure of Zinner *et al.*[12], described for the D enantiomer, except that zinc chloride was omitted from the mixture, only concentrated hydrochloric acid being used. The product was recrystallized from isobutyl alcohol, to give needles; m.p. 130–131° (lit.[12] 130°), $[\alpha]_D^{20}$ +12.4° (*c* 1.2, MeOH) (lit.[12] $[\alpha]_D^{24}$ −10.6° for enantiomer); ^{1}H-n.m.r. (300 MHz, Me_2SO-d_6): δ 0.94 (t, 3 H, *J* 7.3 Hz, CH_3), 0.95 (t, 3 H, *J* 7.3 Hz, CH_3), 1.54 (sextet, 4 H, *J* 7.1 Hz, CH_2CH_3), 2.59 (m, 4 H, SCH_2), 3.37–3.49 (m, 2 H), 3.61 (dd after exch., 1 H, *J* 2.7, 10.4 Hz, OC*H*), 3.71 (m, 2 H, OC*H*), 3.99 [d, 1 H, *J* 8.8 Hz, $CH(SR)_2$], 4.34 (m, 2 H, O*H*), 4.48 (d, 1 H, *J* 5.4

*The dimesylate **7a** was converted into the 4-aminodihydrofurancarboxylic acid previously prepared in this research institute[11] from (*S*)-glutamic acid. Here, the following reagents were used: (*a*) excess NaN_3/DMF at 100° giving bis-azide; (*b*) MeI/$CaCO_3$/H_2O/CH_3CN (to aldehyde); (*c*) Jones oxidation (to acid); (*d*) CH_2N_2 (to methyl ester); (*e*) DBU–benzene (to α,β-unsaturated ester); (*f*) Lindlar–H_2 (to amino ester); and (*g*) LiOH/Dowex resin (to amino acid).

Hz, O*H*), and 4.57 (d, 1 H, *J* 7.3 Hz, O*H*). ^{13}C-n.m.r. (Me_2SO-d_6): δ 13.6, 22.4, 32.0, 32.4, 55.4, 63.7, 70.7, 71.6, and 71.9.

Anal. Calc. for $C_{11}H_{24}O_4S_2$: C, 46.45; H, 8.51. Found: C, 46.41; H, 8.84.

5-O-p-Tolylsulfonyl-L-arabinose dipropyl dithioacetal (**3a**). — Dithioacetal **1a** was treated with tosyl chloride, using Defaye and Horton's conditions[2] for the diisobutyl dithioacetal. *p*-Toluenesulfonyl chloride (33.99 g, 178 mmol) was added to **1** (46.0 g, 162 mmol) in ice-cooled pyridine (100 mL). The ice bath was removed, the mixture stirred for 28 h at room temperature, poured into ice-cold, 6M hydrochloric acid (400 mL) and extracted with EtOAc (1 L). The extract was concentrated to 50 mL, and filtered. The filtrate was applied to a flash column and eluted with 1:1 ether–hexane. Early fractions containing tosyl chloride were discarded. Later fractions afforded 62.2 g (88%) of **3a** as an oil, which solidified on standing. A sample was recrystallized, to give a white solid, m.p. 66–68° (ether–hexane). The rest was used as such after careful drying *in vacuo*. Recrystallization leads to some decomposition. Compound **3a** had $[\alpha]_D^{20}$ −2.7° (*c* 0.55, MeOH), +57.3° (*c* 0.52, $CHCl_3$); ^{1}H-n.m.r. (300 MHz, $CDCl_3$): δ 1.00 (t, 3 H, *J* 7.3 Hz, C*H*$_3$), 1.01 (t, 3 H, *J* 7.4 Hz, C*H*$_3$), 1.63 (sextet, 4 H, *J* 7.4 Hz, 2 C*H*$_2$CH$_3$), 2.46 (s, 3 H, Ar-C*H*$_3$), 2.55–2.72 (m, 4 H, 2 SC*H*$_2$), 3.76 [d, 1 H, *J* 9.3 Hz, C*H*(SR)$_2$], 3.93–3.98 (m, 3 H), 4.15–4.21 (m, 1 H, OC*H*), 4.32–4.36 (m, 1 H, OC*H*), 7.37 (d, 1 H, *J* 8.3 Hz), and 7.82 (d, 1 H, *J* 8.3 Hz, arom.).

Anal. Calc. for $C_{18}H_{30}O_6S_3$: C, 49.29; H, 6.89. Found: C, 49.26; H, 6.95.

2,5-Anhydro-3,4-di-O-(methylsulfonyl)-L-arabinose dipropyl dithioacetal (**7a**) *and propyl 2,3-di-O-(methylsulfonyl)-5-propylthio-1-thio-β-L-arabinofuranoside* (**6a**). — *Run 1.* Tosylate **3a** (28.0 g, 64 mmol) was heated in 2,4,6-collidine (60 mL) with DMAP (0.78 g, 6.4 mmol) for 4 d at 60°, cooled, poured into cold 2M H_2SO_4 (660 mL), and extracted with EtOAc (600 mL); evaporation gave 19.6 g of brown oil. Flash chromatography with 1:1 ether–hexane afforded 5.5 g of a complex mixture (containing some **4a** and **5a**), followed by 9.9 g (58%) of a mixture of **4a** and **5a** in the ratio of 3:2.

One small fraction (20 mg) consisted of **4a** contaminated with tosylate, from which the n.m.r. spectrum could be assigned: ^{1}H-n.m.r. ($CDCl_3$): δ 1.00 (t, 6 H, *J* 7 Hz, CH$_2$C*H*$_3$), 1.65 (m, 4 H, 2 C*H*$_2$CH$_3$), 2.5–3.2 (m, 7 H, includes C*H*$_2$CH$_2$CH$_3$), 3.75–4.4 (m, 3 H), and 5.30 (d, 1 H, *J* 5 Hz, H-1).

The 9.9 g of **4a** plus **5a**, dissolved in 60 mL of CH_2Cl_2, was treated with 13 mL of Et_3N and 6.34 mL of methanesulfonyl chloride for 2 h at room temperature, and then partitioned between water and chloroform. The organic layer afforded 18.1 g of crude product. Chromatography with 1:1 ether–hexane gave, first, 8.7 g (55%) of **6a**; m.p. 53–54° (hexane–ether); $[\alpha]_D^{20}$ +77.9° in $CHCl_3$; ^{1}H-n.m.r. (300 MHz): δ 0.99 (t, 3 H, *J* 7.3 Hz, C*H*$_3$), 1.00 (t, 3 H, *J* 7.3 Hz, C*H*$_3$), 1.63 (m, 2 H, CH$_2$C*H*$_2$CH$_3$), 1.68 (m, 2 H, CH$_2$C*H*$_2$CH$_3$), 2.59 (t, 2 H, *J* 7.0 Hz, C*H*$_2$CH$_2$CH$_3$), 2.71 (t, 2 H, *J* 7.3 Hz, C*H*$_2$CH$_2$CH$_3$), 2.89 (dd, 1 H, small *J* 3.7 Hz, OCHC*H*$_2$S), 2.96 (dd, 1 H, small *J* 3.2 Hz, OCHC*H*$_2$S), 3.17 (s, 3 H, SO$_2$C*H*$_3$), 3.18 (s, 3 H, SO$_2$C*H*$_3$), 4.17 (td, 1 H, *J* 6.6, 3.9 Hz, H-4), 5.19 (m, 1 H, H-3), 5.26 (dd, 1 H, *J*

1.5, 4.6 Hz, H-2), and 5.36 (d, 1 H, *J* 4.6 Hz, H-1). A NOESY 2-dimensional n.O.e. experiment (on **6a** in $CDCl_3$) revealed that, on irradiating H-1, the H-4 resonance was enhanced; irradiating H-3 enhanced H-5 signals and, to a lesser extent, that of H-4; irradiating H-1 also enhanced the H-2 signal. The substituents at C-1 and C-4 must be *cis* in order to provide the H-1 to H-4 effect. The coupling constant of 4.6 Hz for H-1 also supports the β configuration.

Anal. Calc. for $C_{13}H_{26}O_7S$: C, 36.95; H, 6.20. Found: C, 36.82; H, 6.03.

Further elution of the column yielded 6.1 g (39%) of **7a**; m.p. 49–53° (hexane–ether); ^{1}H-n.m.r. ($CDCl_3$): δ 1.00 (t, 6 H, *J* 7 Hz, CH_2CH_3), 1.63 (m, 4 H, CH_2CH_3), 2.55–2.75 (m, 4 H, 2 $CH_2CH_2CH_3$), 3.23 (s, 3 H, SO_2CH_3), 3.90–4.35 (m, 4 H), 5.1–5.45 (m, 2 H, 2 CHOMs); *m/z* (M) and 347 (M $-$ C_3H_7S).

Anal. Calc. for $C_{13}H_{26}O_7S_4$: C, 36.95; H, 6.20. Found: C, 36.88; H, 6.40.

Run 2 (large scale, in pyridine). Similarly, 52.1 g of tosylate **3a**, 1.44 g of DMAP, and 160 mL of pyridine were heated for 6 d at 60°. Workup as in Run 1 gave 13.1 g of crude product. The n.m.r. data indicated that **5a** was the major product, together with 20–25% of **4a**. Flash chromatography gave 8.2 g of a fraction containing only **4a** and **5a** (26%); treatment of this with mesyl chloride as in Run 1 gave 5.8 g of a mixture of **6a** and **7a**, followed by 6.5 g (55% from the 8.2 g) of pure **7a**.

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