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The Fate of the Methanesulfonyloxy Group on Reduction with LAH

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Abstract: Reduction of 1,6:2,5-dianhydro-3,4-di-O-methanesulfonyl-1-thio-D-glucitol with LAH afforded the corresponding 3,4-dihydroxy compound in a yield of 51% and six by-products were isolated after acetylation. Three differed from the original molecule only in the substituents, which were AcO at C-3 and H, CH_3S and CH_3SCH_2S at C-4, respectively. The other compounds had a rearranged skeleton and were 1,4:2,5-dianhydro-1-thio-D-galactitol derivatives, containing the AcO group at C-3 and the aforementioned three substituents attached to C-6. A mechanism is suggested for the rearrangement, and for the formation of the substituents including the fate of the methanesulfonyloxy groups on reduction with LAH which is generally applicable to any mesyloxy derivative.

Keywords: Sulfonic acids and derivatives, Reduction, Rearrangements, Stereochemistry, Mechanisms.

Introduction

Since the introduction of the toluenesulfonyl esters by Freudenberg et al. [1-3] and the methanesulfonyl esters by Helferich et al [4,5] into carbohydrate chemistry this type of derivative has become an indispensable tool for both the activation as well as protection of the different OH groups. Accordingly already three excellent reviews were published [6-8], dealing with the synthesis as well as the reactions of these esters. Nevertheless it is quite interesting, that in spite of the substantial difference of aliphatic (R-CH_2-SO_2-O-sugar) and aromatic (Ar-SO_2-O-sugar) esters, they are usually discussed together and referred to as sulfonic esters (R-SO_2-O-sugar), regardless of the nature of the R substituent. The difference of these two type of esters is due to the presence, or absence of the protons attached to the α-carbon atom, which can be removed by base as they are activated by the electron withdrawing effect of the -SO_2-O- group. Accordingly both, the synthesis as well as the removal of these esters differ fundamentally in the aromatic and aliphatic series as far as the reaction mechanism is concerned. This fact was already referred to in 1970 by Crossland and Servis [9], who for the synthesis of the

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methanesulfonates, starting from methanesulfonyl chloride suggested an elimination - addition mechanism, i.e. the formation of a sulfene [10-12] as reactive intermediate, which reacts in a second step via addition to the corresponding alcohol (eq 1).

$$CH_3\text{-}SO_2\text{-}Cl \xrightarrow{base} CH_2{=}SO_2 + HO\text{-}R \longrightarrow CH_3\text{-}SO_2\text{-}OR \quad (1)$$

As there are no protons on the α-carbon atom of the aromatic R substituent (e.g. in p-toluenesulfonates) their synthesis, using the corresponding acid chloride must run via an S_N2 type mechanism. The same difference holds for the reductive elimination of these sulfonic acid esters by LAH, which reaction was first described by Schmid and Karrer [13] for the corresponding p-toluenesulfonates (4-$CH_3C_6H_4$-SO_2-O-sugar). According to their findings, either the S-O, or the O-sugar bond is cleaved, leading in the first case to toluenesulfenic acid and the regenerated sugar (eq 2) and in the second case to toluenesulfonic acid and the corresponding deoxy-sugar (eq 3)

$$Ar\text{-}SO_2\text{-}O\text{-}sugar \longrightarrow Ar\text{-}SO_2H + HO\text{—}sugar \quad (2)$$

$$Ar\text{-}SO_2\text{-}O\text{-}sugar \longrightarrow Ar\text{-}SO_2OH + H\text{-}sugar \quad (3)$$

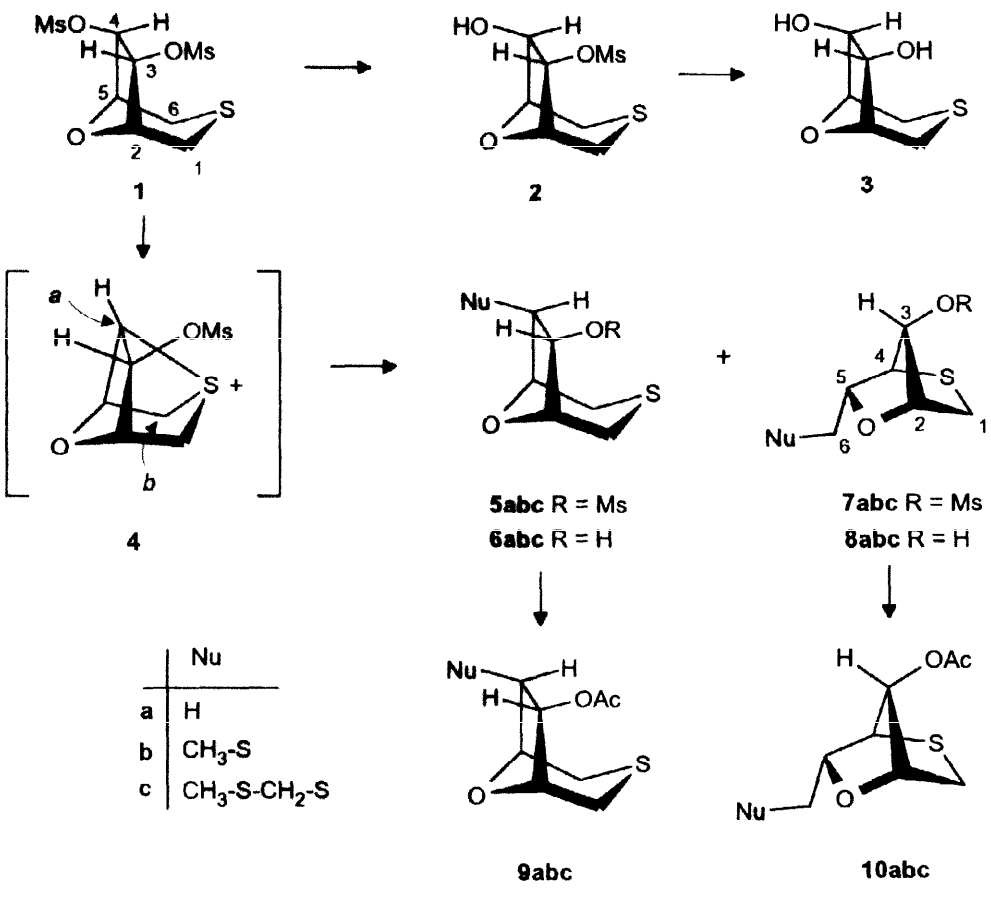
It is worthwhile to mention, that the S-O bond cleavage was observed exclusively for aromatic sulfonates attached to a secondary carbon atom, whereas the cleavage of primary sulfonyloxy groups led to both types of derivative, depending on the structure of the investigated model [13]. In spite of these data, and a vast amount of publications [7] in which even the solvent dependent outcome of these two type of fissions was demonstrated, the erroneous general statement was repeatedly published [6,7] that primary sulfonates react according to eq 3 and yield deoxy sugars.

There is however a further fact, which proves the different behavior of the aromatic and aliphatic sulfonates during the reduction with LAH, and this refers to the fate of the sulfonate ester group. While in the aromatic series the corresponding sulfonic and/or sulfenic acids were isolated as byproducts [13], in the case of the methanesulfonates only the smell of methyl mercaptan was recorded [9], indicating a further, complete reduction of the methanesulfonic acid, liberated. So far no mechanism has been suggested for this reaction. During our large scale reduction of secondary methanesulfonyloxy groups by LAH some byproducts were isolated, the structure of which shed some light onto the mechanism of this reaction, which will be discussed in this paper.

Results

For our ongoing investigation of sulfur containing carbohydrate derivatives [14] a larger amount of 1,6:2,5-dianhydro-1-thio-D-glucitol (**3**) was needed, which had been obtained [15] besides the 3-O-mesylate **2** via LAH reduction of the corresponding 3,4-di-O-mesylate **1**. For

improving the modest published yield (29%) of **3**, the reduction was carried out at higher temperature (50 °C) and for a longer time (24 h), until all the starting material was consumed. This way the yield could be enhanced to 51%, and from the mother liquor six side products (**6a,b,c** and **8a,b,c**) could be isolated after column chromatography. Three of them possessed the unchanged bicyclic structure of the starting material, differing only in the substituent at C-4, which was H in **6a**, CH_3S in **6b** and CH_3SCH_2S in **6c**, while the C-3 substituent was a hydroxy group in all three derivatives. The other three isolated compounds (**8a**, **8b** and **8c**) had a rearranged bicyclic skeleton and were 1,4:2,5-dianhydro-1-thio-D-galactitol derivatives, containing the aforementioned three substituents (H, CH_3S and CH_3SCH_2S) at C-6 and the hydroxy group at C-3. The formation of these structures was not unexpected and can be explained via attack of the nucleophile on the hypothetical cyclic sulfonium intermediate **4** which has already been suggested [16] for the substitution reactions of **1**. For further structure elucidation all derivatives were converted into their corresponding O-acetates (**9a**, **9b**, **9c**, **10a**, **10b** and **10c**) which gave well resolved NMR spectra. (For data see Tables 1 and 2).

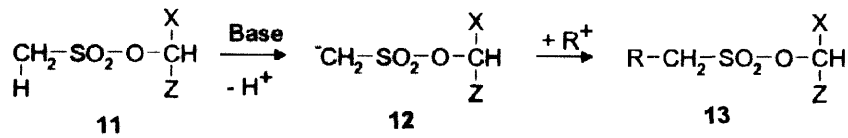


Attack of any nucleophile at C-4, the most polar bridge atom (pathway *a*) will lead with retention of configuration (double inversion!) to **5**, the remaining mesyloxy group of which can undergo a normal S-O bond fission affording **6**. If the nuleophile attacks the C-6 bridge atom

(pathway *b*), the rearranged skeleton **7** is formed, which gives **8** after the S-O bond fission of the remaining mesyloxy group. It is not surprising, that both the hydride anion (provided by LAH) and the methylthiolate ion (produced by complete reduction of the liberated methanesulfonic acid) can act as nucleophiles, leading after acetylation to **9a**, **9b**, **10a** and **10b**. On the other hand the formation of the methylthiomethylenthio derivatives **9c** and **10** was not obvious. One possible reaction pathway is discussed below.

Discussion

It is known from the literature [17], that the electron withdrawing effect of the sulfonyloxy group polarizes both the carbon atom of the ester and that attached to the sulfur atom (**11**). Accordingly a base can remove the α-situated protons and an added electrophile attacks the so formed anion **12**, resulting in an α-substituted mesyloxy ester **13** (eq 4). It is obvious, that the hydride anion



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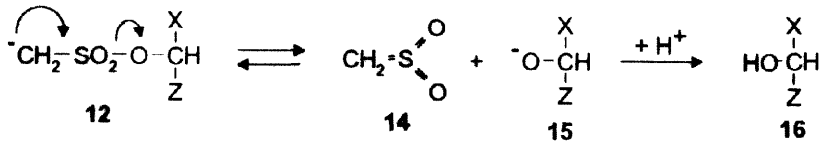

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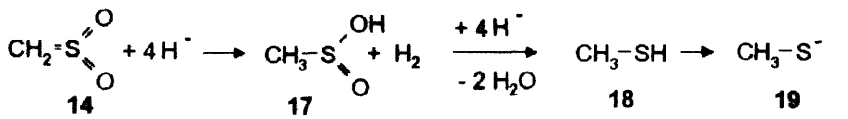

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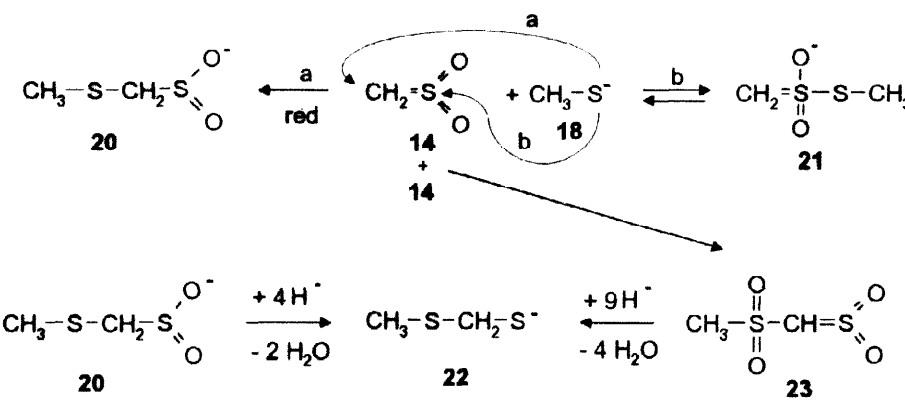


(7) (8)

can act as a base, consequently anion **12** is formed in the presence of LAH. As no electrophile is present, **12** enters an elimination process according to an E1cB mechanism [18,19] (eq 5)

resulting in the neutral sulfene **14** and the alkoxide **15**, which after quenching the reaction by a protic solvent gives the original alcohol **16** with retention of configuration. Naturally, the elimination reaction is an equilibrium, which is usually shifted to the left, according to the mechanism [9] suggested for the mesylation. However, this equilibrium can be shifted to the right, if sulfene **14** is constantly removed. This is done by the excess of LAH, which reduces it stepwise via **17** to the mercaptan **18**, which will be deprotonated to **19** (eq 6). The so formed thiolate ion **19** can attack not only the cyclic sulfonium intermediate **4**, yielding **5b** and **7b**, but also the sulfene **14**. This latter attack accurs either at the carbon atom of the methylene group (route a), yielding after reduction the stable methyltiomethylsulfinate anion **20**, or at the sulfur atom (route b), forming in an equilibrium reaction the unstable thioester-enolate **21** (eq 7). Further reduction of **20** affords the methylthiomethylthiolate ion **22** which acts as a nucleophile converting the sulfonium ion **4**, into the isomers **5c** and **7c** which are transformed via **6c** and **8c** into the isolated **9c** and **10c**, respectively.

Table 1: ^{1}H NMR data for solutions in $CDCl_3$

Comp.	Chemical shifts (ppm)									
	H-1a	H-1b	H-2	H-3	H-4	H-5	H-6a	H-6b	SMe	Others
9a	3.14	2.21	4.45	5.15	2.23;2.68	4.51	3.31	2.12	-	2.13 (OAc)
9b	3.14	2.05	4.68	5.17	3.79	4.32	3.29	2.26	2.12	2.14 (OAc)
9c	3.15	2.08	4.66	5.23	4.04	4.39	3.28	2.34	2.19	2.15 (OAc); 3.70 and 3.81 (-S-CH_2-S-)
10a	2.85	2.92	4.36	5.28	3.52	4.48	1.39		-	2.11 (OAc)
10b	2.85	2.95	4.43	5.27	3.78	4.44	2.87	3.08	2.12	2.14 (OAc)
10c	2.87	2.95	4.44	5.27	3.77	4.47	3.11	2.11		2.10 (OAc); 3.60 and 3.70 (-S-CH_2-S-)

Comp.	Coupling constants (Hz)											
	$J_{1a,1b}$	$J_{1a,2}$	$J_{1b,2}$	$J_{1b,6b}$	$J_{2,3}$	$J_{2,5}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	Others
9a	13.5	3.4	2.0	0.5	6.5	-	4.8;11.0	1.8;7.8	2.5	1.9	13.0	$J_{4a,4b}$ 13.2
9b	13.7	3.4	1.6	1.0	6.6	1.4	4.8	1.8	2.5	1.9	13.0	-
9c	13.7	3.4	1.6	1.0	6.7	1.4	4.8	1.7	2.5	1.9	13.0	$J_{7a,7b}$ 13.7
10a	10.4	1.0	1.8	-	2.7	-	2.5	2.0	6.7			
10b	10.6	1.3	2.0	-	2.9	-	2.3	2.6	5.7	8.2	13.4	$J_{1b,5}$ 0.4
10c	10.7	1.1	2.0	-	3.0	-	2.4	2.1	6.9		-	$J_{7a,7b}$ 13.5

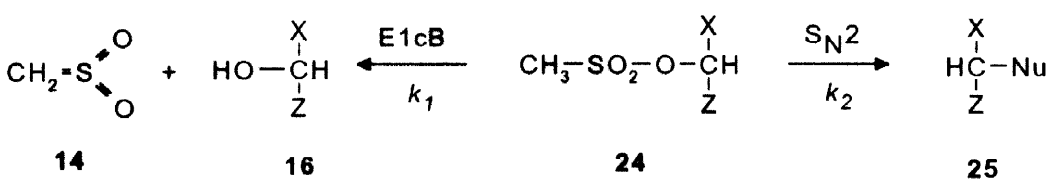
Table 2: ^{13}C NMR data for solutions in $CDCl_3$

Comp.	Chemical shifts (ppm)									
	C-1	C-2	C-3	C-4	C-5	C-6	OAc	SMe	-S-CH_2-S-	CO
9a	25.0	73.2	73.3	33.9	73.0	31.3	20.6	-	-	170.7
9b	24.5	75.3	80.7	50.7	79.9	30.8	20.8	14.1	-	170.6
9c	24.6	74.9	80.7	49.6	80.3	30.4	20.8	14.6	38.1	170.5
10a	36.1	76.4	77.2	52.0	78.8	17.4	20.9	-	-	170.4
10b	35.9	76.6	76.7	50.4	82.0	35.3	20.8	16.1	-	170.2
10c	33.2	77.8	77.8	51.6	83.1	37.1	22.0	15.5	39.4	171.3

Theoretically **22** could also be formed via reduction of **23**, the dimer of sulfene **14**. But the dimerisation reaction takes place only in the absence of any nucleophile [20], consequently this reaction pathway is less probable in the present case.

Conclusion

The fact, that in the reaction of dimesylate **1** with LAH the diol **3** was obtained as the main product with retention of configuration means that in this case the base promoted elimination reaction (eq 5) is the dominant process, and the "reductive cleavage of the O-C bond" is actually a two step process, in which the mesyloxy group is first eliminated via the transannular participation of the ring sulfur atom in an S_Ni type process and the so formed sulfonium intermediate is attacked by the hydride ion in an S_N2 type reaction.



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Furthermore, for mesylates in which no participating groups are present the reaction with LAH can proceed via two mechanisms (E1cB and/or S_N2) according to eq 9. The result will depend on their relative rates. In sterically hindered (secondary) mesylates $k_1 > k_2$, consequently the original hydroxyl goup will be restored, while in the case of primary mesylates the relation is an opposite one $k_1 < k_2$, therefore the predominant process is the substitution of the mesyloxy group by a nucleophile, which is first of all the hydride ion, being present in a large excess.

Experimental

General methods. Acetylation was carried out in pyridine solution with acetic anhydride. When, according to TLC, the reaction was complete the mixture was poured into water,

extracted with CH_2Cl_2, washed with 5% aq H_2SO_4, water, 6% aq $NaHCO_3$ and water. Organic solutions were dried over $MgSO_4$ and concentrated under reduced pressure at or below 40 °C. TLC: E. Merck precoated Silica Gel 60 F_{254} plates, with hexane - EtOAc mixtures (*A*, 1:1; *B*, 2:1), and EtOAc (*C*); detection by spraying the plates with a 0.02 M solution of I_2 and a 0.30 M solution of KI in 10% aqueous H_2SO_4 solution followed by heating at ca. 200 °C. For column chromatography Kieselgel 60 (Macherey-Nagel) was used. The mp are uncorrected. Optical rotations were determined at 20 °C. IR spectra were recorded with Bruker Vector 22 spectrometer. NMR spectra were recorded with a Bruker AC 250 spectrometer at 250 MHz (^1H) and 62.9 MHz (^{13}C) for solutions in $CDCl_3$ (internal Me_4Si) unless stated otherwise. Multiplicities of the ^{13}C NMR spectra were obtained from DEPT experiments. The assignment of the protons was based on homonuclear decoupling experiments. Connectivities between identified protons and protonated carbons were observed by means of HETCOR and selective INEPT experiments.

Reduction of 1 with LAH. To a suspension of LAH (10 g) in THF (500 mL) **1** [16] (15.75 g) was added and the mixture was stirred at 60 °C for 15 h. Then the reaction was quenched by adding EtOAc (2 x 50 mL), water (10 mL), 20 % aq NaOH (10 mL) and water (3 x 30 mL). The mixture was filtered through Celite, washed with hot EtOAc (250 mL), the filtrate was concentrated and the residue submitted to column chromatography (solvent *A*, then *C*). Concentration of the first fraction gave 1,6;2,5-dianhydro-4-S-methylthiomethyl-1,4-dithio-D-glucitol (**6c**, 0.7 g, 6%); R_f = 0.8 (solvent *A*), which after acetylation afforded 3-O-acetyl-**1,6;2,5-dianhydro-4-S-methylthiomethyl-1,4-dithio-D-glucitol** (**9c**, 0.8 g, 97%); R_f = 0.8 (solvent *B*), $[\alpha]_D$ +107 (*c* 0.5, $CHCl_3$); ν_{max} (liqiud film) 1737, 1234 cm^{-1}. Anal. Calcd. for $C_{10}H_{16}O_3S_3$: C, 42.83; H, 5.75; S, 34.30. Found: C, 42.95; H, 5.81; S, 34.42.
Concentration of the second fraction gave 1,6;2,5-dianhydro-4-S-methyl-1,4-dithio-D-glucitol (**6b**, 0.75 g, 8%); R_f = 0.7 (solvent *A*), which after acetylation afforded **3-O-acetyl-1,6;2,5-dianhydro-4-S-methyl-1,4-dithio-D-glucitol** (**9b**, 0.85 g, 93%); R_f = 0.7 (solvent *B*); mp 42-46 °C (hexane); $[\alpha]_D$ +33 (*c* 0.5, $CHCl_3$); ν_{max} (liqiud film) 1738, 1235 cm^{-1}. Anal. Calcd. for $C_9H_{14}O_3S_2$: C, 46.13; H, 6.02; S, 27.36. Found: C, 46.20; H, 6.11; S, 27.43.
Concentration of the third fraction gave 1,4;2,5-dianhydro-1,6-dithio-6-S-methylthiomethyl-D-galactitol (**8c**, 0.3 g, 2.5%); R_f = 0.5 (solvent *A*), which after acetylation afforded **3-O-acetyl-1,4;2,5-dianhydro-1,6-dithio-6-S-methylthiomethyl-D-galactitol** (**10c**, 0.3 g, 85%); R_f = 0.6 (solvent *B*), $[\alpha]_D$ -46 (*c* 0.5, $CHCl_3$); ν_{max} (liqiud film) 1742, 1234 cm^{-1}. Anal. Calcd. for $C_{10}H_{16}O_3S_3$: C, 42.83; H, 5.75; S, 34.30. Found: C, 42.74; H, 5.90; S, 34.26.
Concentration of the fourth fraction gave 1,4;2,5-dianhydro-6-S-methyl-1,6-dithio-D-galactitol (**8b**, 0.5 g, 5%); R_f = 0.4 (solvent *A*), which after acetylation afforded **3-O-acetyl-1,4;2,5-dianhydro-6-S-methyl-1,6-dithio-D-galactitol** (**10b**, 0.55 g, 90%); R_f = 0.5 (solvent *B*), $[\alpha]_D$ -39 (*c* 0.5, $CHCl_3$); ν_{max} (liqiud film) 1744, 1234 cm^{-1}. Anal. Calcd. for $C_9H_{14}O_3S_2$: C, 46.13; H, 6.02; S, 27.36. Found: C, 46.08; H, 6.08; S, 27.41.
Concentration of the fifth fraction gave a mixture of 1,6;2,5-dianhydro-4-deoxy-1-thio-D-glucitol and 1,4;2,5-dianhydro-6-deoxy-1-thio-D-galactitol (**6a** + **8a**, 0.5 g, 7%); R_f = 0.3 (solvent *A*),

which after acetylation and crystallization with acetone afforded **3-O-acetyl-1,6;2,5-dianhydro-4-deoxy-1-thio-D-glucitol** (**9a**, 0.18 g, 28%); R_f = 0.5 (solvent *B*), mp 87-88 °C, $[\alpha]_D$ +5 (*c* 0.5, $CHCl_3$); ν_{max} (KBr) 1732, 1241 cm^{-1}. Anal. Calcd. for $C_8H_{12}O_3S$: C, 53.98; H, 6.04; S, 16.01. Found: C, 53.91; H, 6.08; S, 16.12. Concentration of the mother liquor gave a 3:4 mixture of **9a** and **3-O-acetyl-1,4;2,5-dianhydro-6-deoxy-1-thio-D-galactitol 10a** (0.42 g, 65%).
Concentration of the sixth fraction gave **1,6;2,5-dianhydro-1-thio-D-glucitol 3** (4.1 g, 51%); R_f = 0.3 (solvent *C*); mp 110-112 °C (acetone); lit [12] 113-115 °C.

Acknowledgements

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