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Synthesis of 4-thio-L-rhamnofuranose

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ABSTRACT

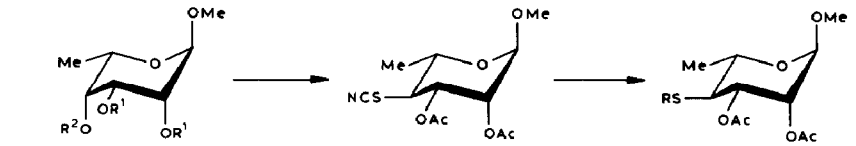
Sulfonylation of the HO-4 group of methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-talopyranoside (**1**) afforded the mesyl (**2**), nosyl (**3**), and triflyl (**4**) derivatives. Attempted nucleophilic displacement of the sulfonyloxy group of **2**, **3**, and **4** by potassium thiocyanate was unsuccessful. Removal of the isopropylidene acetal from **3** and **4** gave the corresponding 4-nosylate (**5**) and 4-triflate (**6**) of methyl 6-deoxy-α-L-talopyranoside. On acetylation, **5** and **6** gave the 2,3-di-*O*-acetyl derivatives **7** and **8**, respectively. Nucleophilic substitution of the sulfonate in **7** and **8** by potassium thiocyanate in *N*,*N*-dimethylformamide gave methyl 2,3-di-*O*-acetyl-4-deoxy-4-thiocyano-α-L-rhamnopyranoside (**9**) in 28 and 52% yields, respectively. Reduction of the thiocyano group of **9**, followed by acetolysis, gave 1,2,3-tri-*O*-acetyl-4-*S*-acetyl-4-thio-α-L-rhamnopyranoside (**12**), which on deacetylation led to 4-thio-L-rhamnose (**13**). Acetylation of **13** afforded the α (**14**) and β (**15**) tetraacetates of 4-thio-L-rhamnofuranose.

INTRODUCTION

In previous reports[1,2] we have described the synthesis of 4-thiohexose derivatives by a nucleophilic-displacement reaction. This type of reaction was also studied[3] for various 4-*O*-sulfonyl derivatives having the *manno* configuration, where ring contraction, solvolysis, or substitution products were obtained. Now we have studied the nucleophilic substitution of 4-*O*-sulfonyl derivatives of the L-*talo* configuration to prepare 4-thio-L-rhamnose. As L-rhamnose is a rather common sugar in lipopolysaccharides of Gram-negative bacteria[4], the 4-thio analog might act as an inhibitor on bacterial enzyme systems[5].

RESULTS AND DISCUSSION

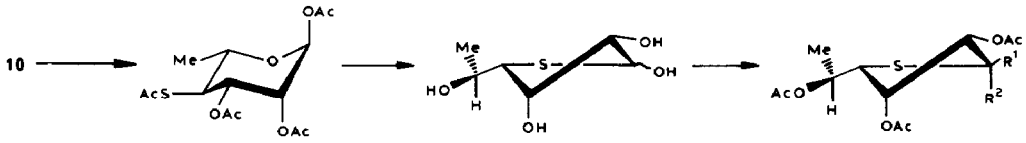
Methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside[6], was converted into the L-*talo* isomer (**1**) using the known oxidation–reduction sequences, but RuO_2–$NaIO_4$ was used instead of pyridinium dichromate[7]. Sulfonylation of HO-4 of **1** with methanesulfonyl chloride (mesyl chloride) or *p*-nitrobenzenesulfonyl chloride (nosyl chloride) gave the corresponding mesylate (**2**) and nosylate (**3**). The mesylate (**2**) was obtained in 91% yield, but the nosylate underwent partial deisopropylidenation during the reaction workup and chromatographic purification, lowering the yield of **3** to 62%. However, the overall yield of 4-nosylated products (**3** + **5**) was 87%.



1 R^1 = Me_2C, R^2 = H
2 R^1 = Me_2C, R^2 = $MeSO_2$
3 R^1 = Me_2C, R^2 = p-$NO_2C_6H_4SO_2$
4 R^1 = Me_2C, R^2 = F_3CSO_2
5 R^1 = H, R^2 = p-$NO_2C_6H_4SO_2$
6 R^1 = H, R^2 = F_3CSO_2
7 R^1 = Ac, R^2 = p-$NO_2C_6H_4SO_2$
8 R^1 = Ac, R^2 = F_3CSO_2

9

10 R = H
11 R = Ac



12

13

14 R^1 = OAc, R^2 = H
15 R^1 = H, R^2 = OAc

All attempts at substitution of the sulfonyloxy group of **2** and **3**, under different conditions, were unsuccessful. Total decomposition of the starting material and the formation of tarry products were observed. As the trifluoromethylsulfonate (triflate) has been described as an excellent leaving group, under smooth reaction conditions[8], we studied substitution in the triflyl derivative **4**. Compound **4** was prepared by treatment of **1** with trifluoromethanesulfonic anhydride in the presence of 2,6-di-*tert*-butyl-4-methylpyridine. T.l.c. monitoring of the mixture showed clean transformation of **1** into **4**, after 4 h. However, **4** was obtained in low yield (32%), as partial hydrolysis of the isopropylidene group took place during the chromatographic purification of **4** on silica gel. The increase of the polarization of the SO_3–C linkage was evidenced in the ^{13}C-n.m.r. spectra of compounds **2**, **3** and **4**, as the signal for C-4 was increasingly shifted downfield by 8.6, 10.3, and 15.0 p.p.m., respectively, with respect to the C-4 signal of **1**, and hence the nucleophilic displacement should be facilitated for compound **4**. However, attempted substitution of the triflate group of **4** by potassium thiocyanate was also unsuccessful, resulting in the decomposition of **4**. In view of these negative results, we undertook a study of the substitution reaction in 4-sulfonates of the *talo* series, having HO-2 and HO-3 acetylated, as replacement of the isopropylidene group by acetate could alleviate the strain developed in the transition state of the reaction by the presence of a five-membered acetal ring fused to the pyranoside. In addition, we have previously observed[3] that the substituents on C-2 and C-3 influenced the stereochemical course of the reaction of 4-*O*-sulfonyl-6-deoxy-D-mannopyranosides with KSCN, and hence the products formed. Sulfonylation of **1** and removal of the acetal function was readily accomplished by a one-pot procedure, involving the addition of water to the reaction

mixture for the sulfonylation of **1**. Under these conditions, the intermediate products **3** and **4** underwent total hydrolysis of the isopropylidene group to give the 4-sulfonates **5** and **6**, in isolated yields >85%. Acetylation of HO-2 and HO-3 of **5** and **6** gave the corresponding di-*O*-acetyl derivatives **7** and **8**.

The nucleophilic displacement of the 4-*O*-nosyl group of **7** by KSCN (DMF, 20h, 110°) led to 2,3-di-*O*-acetyl-4-deoxy-4-thiocyano-α-L-rhamnopyranoside (**9**) in 28% yield. The yield of **9** was improved (52%) when starting from the triflate **8**, which required smoother conditions (DMF, 1.5 h, 70°) for the substitution by thiocyanate. The inversion of configuration at C-4 was evidenced by the change in the magnitude of $J_{3,4}$ and $J_{4,5}$ from ~4 and 1 Hz in the *talo*-sulfonates (**7** and **8**) to 11.0 and 10.3 Hz, respectively, in the thiocyano derivative **9**. The low to moderate yields for the preparation of compound **9**, as well as for other substitution products[9] from 4-sulfonates of the *talo* configuration, indicated that they are resistant to nucleophilic substitution. This behavior contrasts with that of the 4-*O*-mesyl derivatives of the α-D-*galacto* series, which having the same relative stereochemical relationship at C-3–C-5 as compounds **7** and **8**, gave high yields of substitution products[10], even though the mesylate is a poorer leaving group than nosylate and triflate. These results suggested that the axial substituent at C-2 in the *talo* compounds could hinder the displacement reaction. In fact, the absence of the expected substitution products from 4-*O*-sulfonyl derivatives of the *manno* configuration was attributed to the effect of the C-2 substituent, which is *β-trans*-axial to the departing sulfonate[3,11]. This "*β-trans*-axial effect" would be attributable to steric (1,3-diaxial) and polar interactions in the transition state of the reaction, between the electronegative substituent at C-2 and the charged nucleophile[11]. Similar interactions between the C-2 axial substituent and the leaving sulfonate, which would be brought closer together in the transition state of the substitution reaction, would account for the resistance of the sulfonyloxy group of **7** and **8** to displacement. Such a "*β-syn*-axial effect" would also operate in the nucleophilic displacement of the mesylate by thiocyanate in methyl 2,3-di-*O*-benzyl-6-deoxy-4-*O*-mesyl-α-D-idopyranoside, to give the 4-thiocyano-D-*altro* derivative[12] in only moderate (54%) yield.

The thiocyano group of **9** was reduced to the thiol with zinc–acetic acid, to give compound **10** in 65% yield. On acetylation compound **10** aforded the corresponding thioacetate (**11**) whose ^{13}C-n.m.r. spectrum showed signals for the CH_3COS carbons at 30.5 and 192.6 p.p.m., well differentiated from those of the *O*-acetyl groups in the molecule.

Treatment of **10** with a mixture of acetic acid, acetic anhydride, and sulfuric acid afforded a single product, isolated in 95% yield. The ^{13}C-n.m.r. spectrum of the product was similar to that of **11**, as it showed the signals for thioacetate (δ 192.6 and 30.5) and for the anomeric carbon, at a δ value (90.8) similar to that of acetylated derivatives of related compounds having the α configuration[13]. On the basis of the spectral data, the acetolysis product was formulated as 1,2,3-tri-*O*-acetyl-4-*S*-acetyl-4-thio-α-L-rhamnopyranoside (**12**).

Similar to the results here on acetolysis of the 4-thio-L-rhamnopyranoside **10**, 4-thiohexopyranose derivatives having the 6-deoxy-D-*altro*[12], D-*manno*[14], and 6-deoxy-

D-*gulo*[15] configurations gave on acetolysis the pyranoid peracetates as main products. In contrast, the 6-deoxy-*ido*-4-thio[12] and *galacto*-4-thiohexopyranosides[1,2] underwent ring contraction during acetolysis, to give 4-thiofuranose peracetates. These results may be explained by the general mechanism that we have proposed[1,2] for the acetolysis of 4-thiohexopyranoses. *O*-Deacetylation of **12** by sodium methoxide led to an anomeric mixture of 4-thio-L-rhamnoses, whose ^{13}C-n.m.r. spectrum showed no signal for the pyranose forms. The upfield shifting for the C-1 and C-4 signals indicated a shielding effect of the sulfur on these carbons, and therefore a furanose structure for the thio sugar. The α:β ratio ($\sim$ 1.5:1) was established by averaging the relative intensity of the C-3, C-4, and C-5 signals for each anomer.

Acetylation of **13** gave the per-*O*-acetyl-4-thio-α,β-L-rhamnofuranosides (**14**, **15**), which were separated by column chromatography. The anomeric configuration for the major product was assigned as α, as it was strongly levorotatory[16] and the C-1 signal in its ^{13}C-n.m.r. spectrum appeared shifted downfield (80.1 p.p.m.) with respect to that of the β anomer (77.2 p.p.m.), as observed[13] for mannofuranose derivatives and for the peracetates of lyxofuranose, which bear the same stereochemical relationship for the ring substituents as **14** and **15**. Although the $J_{1,2}$ values for both anomers (7.1 and 5.1 Hz) were larger than the limiting value (4 Hz) employed for assessing the anomeric configuration of furanoses[17], their magnitudes were similar to those reported[14] for the α (6.6 Hz) and β (5.0 Hz) pentaacetates of 4-thio-D-mannofuranose. On application of our pseudorotation analysis[18] for conformational assignments of thiofuranose derivatives, we concluded that compound **14** would populate the $^2T_3$ segment of the pseudorotational itinerary, as the calculated coupling constants ($J_{1,2}$ 6.6, $J_{2,3}$ 3.4, and $J_{3,4}$ 3.9 Hz, for $^2T_3$) were in good agreement with the experimental values (Table I). Also, the $^2T_3$ conformer seems to contribute considerably to the conformational equilibrium of **15**. The $^2T_3$ conformation possesses the bulky side-chain at C-4 quasiequatorially disposed, and it is free of eclipsing interactions. Furthermore, the anomeric acetate is in a favorable quasiaxial disposition in the β anomer **15**, whereas it is quasiequatorially oriented in the α anomer **14**. However, as the anomeric effect is weaker for sulfur systems than for oxygen systems[19], the stability of the $^2T_3$ form of **14** does not seem to be strongly affected. In contrast, an analog of **14**, methyl α-L-mannofuranose tetraacetate, is partly in the opposite $^3T_2$ conformation[16], probably owing to the stronger anomeric effect of the ring-oxygen atom.

EXPERIMENTAL

General methods. — Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter at 25°. The ^{1}H- and ^{13}C-n.m.r. spectra were recorded with a Varian XL-100 spectrometer at 100.1 and 25.2 MHz, respectively, for solutions in $CDCl_3$ (internal Me_4Si), unless otherwise indicated. Signal assignments for the ^{13}C-n.m.r. spectra were made on the basis of heteronuclear decoupling experiments. Spectral data are shown in Tables I and II. I.r. spectra were recorded with a Perkin–Elmer 710B

TABLE I

^{1}H-N.m.r. data for compounds **1–12, 14** and **15**

Compd.	*δ, p.p.m.*								*J,Hz*				
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	OCH_3	$(CH_3)_2C$ *or* CH_3CO	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$
1	4.93	4.06	4.20	3.57	3.83	1.35	3.40	1.38,1.59	<1	5.5	4.5	<1	6.3
2	4.90	4.05	4.41	4.66	3.99	1.38	3.42	1.37,1.59	<1	6.0	5.4	2.0	6.3
3	4.85	4.02	4.35	4.89	4.02	1.22	3.40	1.18,1.24	<1	5.8	5.0	2.0	6.5
4	4.89	3.82–4.20	4.40	4.86	3.82–4.20	1.38	3.42		<1	6.0	5.0		6.5
5	4.75	3.64	3.89	4.93	4.09	1.29	3.37	1.26,1.33	1	3.5	3.8	1.5	6.3
6	4.84	3.77	3.99	4.97	4.09	1.37	3.41		1.5	3.5	3.8	1.0	6.5
7	4.70	4.92	5.26	5.09	4.12	1.08	3.38	2.02,2.06	<1	3.2	3.6	1.5	6.3
8	4.75	4.91	5.31	5.14	4.19	1.37	3.42	2.10,2.14	1.6	3.5	3.8	1.0	6.4
9	4.66	5.27	5.37	3.12	4.05	1.53	3.45	2.09,2.15	1.6	3.4	11.0	10.3	6.3
10	4.67	← 5.02–5.22 →		2.95	3.79	1.44	3.40	2.07,2.14	1.5		11.0	10.2	6.0
11	4.69	5.18	5.24	3.78	3.86	1.33	3.40	2.00,2.19 2.37	1.7		10.8	10.6	6.0
12	6.07	5.19	5.31	3.82	3.96	1.33		2.05,2.18 2.22,2.38	1.9	3.4	10.8	10.8	6.0
14	6.05	5.42	5.69	3.84	5.11	1.21		1.98,2.05 2.10,2.12	7.1	3.5	3.5	10.2	6.3
15	6.21	5.22	5.80	3.61	5.20	1.26		1.99,2.06 2.11,2.12	5.1	3.8	4.5	10.5	6.0

TABLE II

^{13}C-N.m.r. data for compounds **1–12**, **14** and **15**

Compd.	*δ, p.p.m.*								
	C-1	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*OCH_3*	*$(CH_3)_2C$ or CH_3CO*	*$(CH_3)_2C$ or CH_3CO*
1	98.3	72.8*	73.1*	66.6	64.2	16.5	54.8	109.0	25.6,25.0
2	98.5	73.0	70.6	75.2	63.3	17.1	55.2	110.1	25.9,25.0
3	98.7	73.2	70.6	76.9	63.3	17.1	55.4	102.2	25.6,24.8
4	98.6	72.6	69.8	81.6	62.4	16.7	55.2	110.5	25.5,24.5
5	101.1	68.9	65.0	84.3	63.8	16.8	55.2		
6	101.1	68.7	64.8	88.3	63.4	16.6	55.5		
7	99.1	66.7	65.5	78.7	64.2	16.6	55.2	169.6,169.3	20.6,20.5
8	99.1	66.4	65.1	83.5	63.9	16.3	55.3	169.8,169.1	20.4
9[a]	98.3	69.0*	68.4*	50.6	67.1	19.0	55.4	169.3,168.9	20.7,20.5
10	98.5	71.6*	70.0*	42.7	68.8*	19.1	54.9	169.6,169.5	20.7,20.6
11[b]	98.5	68.7*	67.8*	45.7	67.6*	18.5	55.2	170.0,169,9	21.0,20.7
12[c]	90.8	67.5*	70.1	45.4	67.1*	18.4		169.4,168.0	20.8,20.7 20.5
14	80.2	77.5	70.9	50.0	68.3	18.7		170.1,169.7 169.4	20.8,20.5 20.4
15	77.2	74.1	71.4	49.8	69.0	18.8		169.7,169.6 169.4,169.1	20.8,20.4 20.3

[a] *SCN* appeared at 108.6 p.p.m. [b] *CH_3COS* appeared at 193.3 and 30.8 p.p.m. [c] 192.6 and 30.5 p.p.m. *Signals may be interchanged.

spectrophotometer with polystyrene absorption at 1602 cm^{-1} as the reference. T.l.c. was carried out on precoated aluminium plates (0.2 mm) of Silica Gel $60F_{254}$ (Merck) with *A*, 3:1 hexane–EtOAc; *B*, 1:3 hexane–EtOAc, and *C*, 10:1 EtOAc–MeOH, and detection with u.v. light or charring with 5% (v/v) H_2SO_4 in EtOH. Column chromatography was performed on Silica Gel 60 (Merck). *N,N*-Dimethylformamide (DMF) was purified by sequential drying[20] with 3Å molecular sieves and distillation.

*Methyl 6-deoxy-2,3-*O*-isopropylidene-*α*-*L*-talopyranoside* (**1**). — Oxidation[21] of methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside[6] (1.41 g, 6.47 mmol) with RuO_2–$NaIO_4$ gave the glyc-4-ulose derivative (1.29 g, 92%) which was quantitatively reduced[7] with $NaBH_4$ to give compound **1**; $[\alpha]_D$ −39.8° (*c* 0.8, $CHCl_3$); lit.[7] $[\alpha]_D$ −38.3°.

*Methyl 6-deoxy-2,3-*O*-isopropylidene-4-*O*-(methylsulfonyl)-*α*-*L*-talopyranoside* (**2**). — To a stirred solution of **1** (50 mg, 0.23 mmol) in dry pyridine (1.5 mL), mesyl chloride (54 μL, 0.69 mmol) was added dropwise, with external cooling. The mixture was kept for 24 h at 4°, and then poured into ice–water, and extracted with CH_2Cl_2 (2 × 50 mL). The organic extract was washed with 5% aq. HCl, water and sat. aq. $NaHCO_3$, dried ($MgSO_4$) and the solvent evaporated. The residue, which showed a single spot by t.l.c. (R_F 0.34, solvent *A*), crystallized from EtOAc–hexane, to give 62 mg (91% yield) of compound **2**; m.p. 117–118°; $[\alpha]_D$ −18.7° (*c* 0.6, $CHCl_3$); lit.[9] m.p. 116–117°; $[\alpha]_D$ −19°.

*Methyl 6-deoxy-2,3-*O*-isopropylidene-4-*O*-[(*p*-nitrophenyl)sulfonyl]-*α*-*L*-talopyranoside* (**3**) and *methyl 6-deoxy-4-*O*-[(*p*-nitrophenyl)sulfonyl]-*α*-*L*-talopyranoside* (**4**).

— To a solution of **1** (0.46 g, 2.1 mmol) in dry CH_2Cl_2 (15 mL), *p*-nitrobenzenesulfonyl chloride (2.81 g, 12.7 mmol) Et_3N (0.86 mL) and 4-dimethylaminopyridine (10 mg) were added. The mixture was kept in the dark for 72 h at room temperature, and diluted with CH_2Cl_2 (100 mL). The solution was washed with 2% aq. HCl, water, and sat. aq. $NaHCO_3$, dried ($MgSO_4$) and the solvent evaporated. The residue, which showed a main spot on t.l.c. (R_F 0.30, solvent *A*), was chromatographed on silica gel with 4:1 hexane–EtOAc. Fractions containing the product of R_F 0.30 were pooled and the solvent evaporated, affording crystalline compound **3**. Recrystallization from EtOH yielded 0.52 g (62%); m.p. 139–140°, $[\alpha]_D$ −18.2° (*c* 1.0, $CHCl_3$).

Anal. Calc. for $C_{16}H_{21}NO_9S$: C, 47.64; H, 5.25. Found: C, 47.84; H, 4.98.

From the next chromatographic fraction [R_F 0.05 (solvent *A*), R_F 0.43 (solvent *B*)], crystalline compound **5** was isolated (0.18 g, 25%); recrystallized from EtOAc–hexane; m.p. 139–141°, $[\alpha]_D$ −84.6° (*c* 1.1, $CHCl_3$).

Anal. Calc. for $C_{13}H_{17}NO_9S$: C, 42.97; H. 4.72. Found: C, 42.95; H, 4.53.

Addition of water (0.1 mL) to the mixture, when t.l.c. inspection showed the complete conversion of **1** into **3**, caused the removal of the isopropylidene group to give **5**, isolated by column chromatography in 85–90% yield.

Methyl 6-deoxy-2,3-O-isopropylidene-4-O-(trifluoromethylsulfonyl)-α-L-talopyranoside (**4**) and *methyl 6-deoxy-4-O-(trifluoromethylsulfonyl)-α-L-talopyranoside* (**6**). — A solution of compound **1** (0.30 g, 1.38 mmol) in dry CH_2Cl_2 (7 mL) containing 2,6-di-*tert*-butyl-4-methylpyridine (0.49 g, 2.37 mmol) was cooled at −20° and trifluoromethanesulfonic anhydride (0.35 mL, 2.1 mmol) was added under nitrogen. The suspension obtained after 4 h of stirring at 0° was filtered, and the filtrate was poured into 0.01M aq. $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the organic extract was dried ($MgSO_4$) and concentrated. The resulting syrup showed a main product on t.l.c. (R_F 0.50, solvent *A*), which was isolated by column chromatography using 7:1 hexane–EtOAc as eluent. The product isolated as a syrup (0.18 g, 37%), was characterized as compound **4**; $[\alpha]_D$ −71.7° (*c* 1.0, $CHCl_3$).

From later fractions of the column (R_F 0.07, solvent *A*), crystalline compound **6** was isolated (0.12 g, 28%). Recrystallized from EtOAc–hexane; m.p. 90–92°, $[\alpha]_D$ −68.1° (*c* 1.3, $CHCl_3$).

Anal. Calc. for $C_8H_{13}F_3SO_7$: C, 30.97; H, 4.22. Found: C, 30.97, H, 3.98.

Compound **6** was also obtained (~ 90% yield) on hydrolysis of crude **4**, as indicated for the preparation of **8**.

Attempted substitution of methyl 2,3-O-isopropylidene-4-O-sulfonyl-α-L-talopyranoside (**2**, **3**, or **4**), *by KSCN*. — Solutions of compound **2**, **3** or **4** in DMF, containing different amounts of KSCN, were heated under nitrogen, at various temperatures. In all the cases, t.l.c. examination of the mixture revealed the formation of various decomposition products, and the mixtures were not analyzed. The only instance when the expected substitution product (methyl 4-deoxy-2,3-*O*-isopropylidene-4-thiocyano-α-L-rhamnopyranoside) was obtained (5 mg, 9% yield), was on treatment of compound **4** (75 mg, 0.21 mmol) with KSCN (0.16 g, 0.16 mmol) in DMF (0.5 mL) for 4 h at 20°.

Methyl2,3-di-O-acetyl-6-deoxy-4-O-[(p-nitrophenyl)sulfonyl]-α-L-talopyranoside (**7**). — To a solution of **5** (0.33 g, 0.91 mmol) in dry pyridine (3 mL), Ac_2O (3 mL) was added dropwise at 0°. The mixture was stirred for 20 h at room temperature, and then MeOH (3 mL) was added with external cooling. The solution was concentrated to a syrup, which was purified by column chromatography, affording compound **7** (0.39 g, 97%), which crystallized from EtOH; m.p. 128–129°, $[\alpha]_D$ −93.3° (*c* 0.7, $CHCl_3$).

Anal. Calc. for $C_{17}H_{21}NO_{11}S$: C, 45.64; H,4.73; S, 7.17. Found: C, 45.76; H,4.78; S, 7.30.

Methyl 2,3-di-O-acetyl-6-deoxy-4-O-(trifluoromethylsulfonyl)-α-L-talopyranoside (**8**). — Compound **1** (1.15 g, 5.2 mmol) was sulfonylated with trifluormethanesulfonic anhydride as already described. The salts were filtered off, and water (0.1 mL) was added to the filtrate. After 0.5 h of stirring at room temperature, the mixture, which showed a single spot by t.l.c. with mobility identical to that of **6** (R_F 0.07, solvent *A*), was dried ($MgSO_4$) and concentrated. The residue was dissolved in dry pyridine (3.5 mL) and Ac_2O (3.5 mL) was added dropwise at 0°. The solution was kept for 18 h at 4°, then water (3 mL) was added and the mixture stirred for 1 h at 0°. The mixture was diluted with CH_2Cl_2 (200 mL) and washed with water, 5% aq. HCl, water and sat. aq. $NaHCO_3$, dried ($MgSO_4$) and concentrated. The syrup was chromatographed through a short column of silica gel with 8:1 hexane–EtOAc affording 1.82 g (87% yield from **5**) of compound **8**; $[\alpha]_D$ −61.2° (*c* 0.9, $CHCl_3$).

Methyl 2,3-di-O-acetyl-4-deoxy-4-thiocyano-α-L-rhamnopyranoside (**9**). — (*a*) *From methyl 2,3-di-O-acetyl-6-deoxy-4-O-[(p-nitrophenyl)sulfonyl]-α-L-talopyranoside* (**7**). To a stirred solution of **7** (0.24 g, 0.54 mmol) in dry DMF (2 mL), KSCN (0.42 g, 4.29 mmol) was added. The mixture was stirred under nitrogen at 110° for 24 h, and then poured into water (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The extracts were combined, washed with water, dried ($MgSO_4$) and the solvent evaporated. The residue was chromatographed on silica gel (3:1 hexane–EtOAc) affording, upon evaporation of the fractions of R_F 0.26 (solvent *A*), 45 mg (28%) of compound **9**, which recrystallized from EtOH, m.p. 144–146°, $[\alpha]_D$ +5.7° (*c* 1.4, $CHCl_3$).

Anal. Calc. for $C_{12}H_{17}NO_6S$: C, 47.52; H, 5.65; S, 10.57. Found: C, 47.56; H, 5.81; S, 10.89.

(*b*) *From methyl 2,3-di-O-acetyl-6-deoxy-4-O-(trifluormethylsulfonyl)α-L-talopy ranoside* (**8**). To a stirred solution of **8** (0.86 g, 2.18 mmol) in dry DMF (11 mL), KSCN (1.71 g, 17 mmol) was added. After 1.5 h of heating at 70° under nitrogen, no starting material (**8**) was detected by t.l.c., and the mixture was treated as described in (*a*) to give 0.35 g (52%) of compound **9**.

Methyl 2,3-di-O-acetyl-4-thio-α-L-rhamnopyranoside (**10**). — To a solution of **9** (0.22 g, 0.72 mmol) in AcOH (10 mL), powdered zinc (0.9 g) was added. The suspension was heated under reflux for 18 h, and then diluted with CH_2Cl_2 and filtered. The residue was washed with CH_2Cl_2 and the filtrates were washed with sat. aq. $NaHCO_3$ and water, dried ($MgSO_4$) and the solvent evaporated. The residue was purified through a short column of silica gel (6:1 hexane–EtOAc) affording 0.13 g (65% yield) of compound **10**, $[\alpha]_D$ −44.2° (*c* 0.7, $CHCl_3$); i.r. (film) 2550 cm^{-1} (SH).

Anal. Calc. for $C_{11}H_{18}O_6S$: C, 47.47; H, 6.52; S, 11.52. Found: C, 47.81; H, 6.70; S, 11.77.

A sample (20 mg) of **9** was acetylated (1:1 Ac_2O–pyridine) to give the *S*-acetyl derivative (**11**) whose ^1H- and ^{13}C-n.m.r. spectra were recorded.

*1,2,3-Tri-*O*-acetyl-4-*S*-acetyl-4-thio-α-*L*-rhamnopyranoside* (**12**). — A solution of compound **10** (70 mg, 0.25 mmol) in glacial AcOH (5.6 mL), Ac_2O (5.6 mL) and H_2SO_4 (0.3 mL) was kept at 4° for 16 h, and NaOAc (1.8 g) was added. The mixture was stirred at room temperature for 0.5 h and then poured into ice–water and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed with sat. aq. $NaHCO_3$ and water, dried ($MgSO_4$) and the solvent evaporated. The residue was filtered through a short column of silica gel with 4:1 hexane–EtOAc affording 91 mg (95% yield) of compound **12**; $[\alpha]_D$ −38.2 (*c* 1.2, $CHCl_3$).

Anal. Calc. for $C_{14}H_{20}O_8S$: C, 48.27; H, 5.79; S, 9.20. Found: C, 47.96; H, 6.06; S, 9.66.

*4-Thio-*L*-rhamnofuranose* (**13**). — To a stirred solution of **12** (89 mg, 0.25 mmol) in dry MeOH (70 mL) at 0°, a solution prepared by dissolving sodium (33 mg, 1.4 mmol) in MeOH (15 mL), was added. The mixture was stirred under nitrogen for 1.5 h at 0°, when no starting **12** was detected by t.l.c. The solution was neutralized with Dowex 50W (H^+) resin, filtered, and the solvent evaporated. The residue was purified by column chromatography with 20:1 EtOAc–MeOH, affording 37 mg (81% yield) of 4-thio-L-rhamnofuranose (**13**); R_F 0.36 (solvent *C*); $[\alpha]_D$ −62.0° (*c* 0.8, water, 10 min) → −63.7° (24 h); ^{13}C-n.m.r. (1:1 D_2O–H_2O): δ 83.0, 82.8, 80.9 and 77.3 (C-1 α, β and C-2 α, β), 75.2 (C-3 β), 74.2 (C-3 α), 68.5 (C-5 β), 67.8 (C-5 α), 54.4 (C-4 β), 54.1 (C-4 α), and 21.9 (C-6 α, β).

Anal. Calc. for $C_6H_{12}O_4S$: C, 39.98; H, 6.71; S, 17.79. Found: C, 40.04; H, 6.69; S, 18.03.

*1,2,3,5-Tetra-*O*-acetyl-4-thio-α-*L*-rhamnofuranose* (**14**) *and 1,2,3,5-tetra-*O*-acetyl-4-thio-β-*L*-rhamnofuranose* (**15**). — Compound **12** (89 mg, 0.25 mmol), was deacylated as already described, and the resulting crude 4-thio-L-rhamnofuranose (**13**) was treated with pyridine (1 mL) Ac_2O (1 mL). The mixture was stirred for 5 h at 0°, MeOH was added at 0°, and after 0.5 h the mixture was concentrated to a syrup, which showed two spots by t.l.c.: R_F 0.30 and 0.25 (solvent *A*). The mixture was separated by column chromatography with 5:1 hexane-EtOAc. The faster-migrating component (52 mg, 58% yield from **12**) was identified as compound **14**, m.p. 74–76° (from EtOAc–hexane); $[\alpha]_D$ -256° (*c* 0.8, $CHCl_3$).

Anal. Calc. for $C_{14}H_{20}O_8S$: C, 48.27; H, 5.79; S, 9.20. Found: C, 48.35; H, 5.78; S, 9.60.

From the fraction having R_F 0.25, the β-tetraacetate **15** was isolated (23 mg, 26% yield from **12**), $[\alpha]_D$ +82.5° (*c* 0.9, $CHCl_3$).

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