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REACTIONS OF SUGAR THIO-ORTHOESTERS: NUCLEOPHILIC SUBSTITUTION OF AN ARYLTHIO GROUP DURING ZEMPLÉN DEACYLATION

LEON V. BACKINOWSKY, NARGUIZ E. BYRAMOVA, YURY E. TSVETKOV, AND VITALI I. BETANELI
N. D. Zelinsky Institute of Organic Chemistry, Academy of Sciences of the U.S.S.R., Moscow (U.S.S.R.)

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ABSTRACT

Deacylation of acetylated and benzoylated sugar 1,2-thio-orthoesters bearing an *S*-aromatic residue with methanolic sodium methoxide is accompanied by inter- and intra-molecular nucleophilic substitution of the arylthio group with formation of the corresponding bi- and tri-cyclic orthoesters. Stereochemical aspects and a possible mechanism for this reaction are discussed. Free arylthio-orthoesters were obtained by performing the deacylation with methanolic sodium methoxide in pyridine.

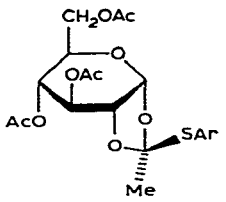
INTRODUCTION

Acetylated sugar thio-orthoesters are effective glycosylating agents in the reaction with sugar trityl ethers[1]. Monotritylated, acylated thio-orthoesters offer the same potential for polycondensation as the tritylated 1,2-*O*-cyanoethylidene derivatives that have been successfully applied to the synthesis of polysaccharides of regular structure[2–5]. In order to synthesise such monomers, the acylated thio-orthoesters require deacylation, selective tritylation, and acetylation. Preliminary experiments revealed the destruction of the arylthio-orthoester group under the conditions of Zemplén deacetylation and on treatment with triethylamine in methanol. A study of the behaviour of thio-orthoesters under deacetylation conditions is now reported.

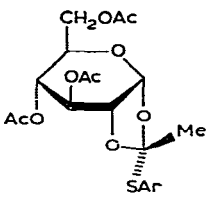
RESULTS AND DISCUSSION

The following thio-orthoesters were studied: 3,4,6-tri-*O*-acetyl-1,2-*O*-[1-(*exo*- and *endo*-*p*-tolylthio)ethylidene]-α-D-glucopyranose[6] (*exo*-**1** and *endo*-**1**), 3,4,6-tri-*O*-acetyl-1,2-*O*-[1-(*exo*-*p*-tolylthio)ethylidene]-β-D-mannopyranose[1] (**2**), 3,4-di-*O*-acetyl-1,2-*O*-[1-(*exo*- and *endo*-*p*-tolylthio)ethylidene]-β-L-rhamnopyranose[7] (*exo*-**3** and *endo*-**3**), 3,4-di-*O*-benzoyl-1,2-*O*-(α-*p*-tolylthio)benzylidene-β-L-rhamnopyranose (**4**), and, for purposes of comparison, 3,4-di-*O*-acetyl-1,2-*O*-(1-ethylthioethylidene)-β-L-rhamnopyranose[7] (**5**).

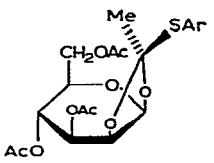
Thio-orthoester **4** was obtained by condensation of tri-*O*-benzoyl-α-L-rhamno-



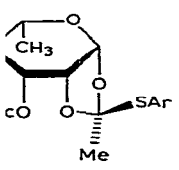
exo-1



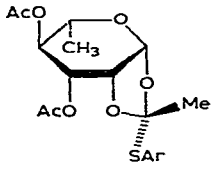
endo-1



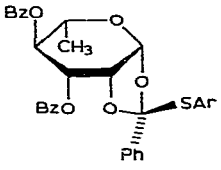
exo-2



exo-3



endo-3



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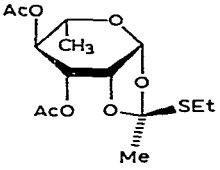


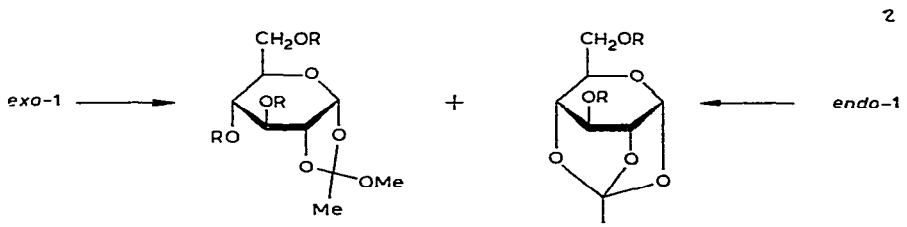
5

Ar = *p*-$CH_3C_6H_4$—

pyranosyl bromide with thio-*p*-cresol in dichloromethane–acetonitrile in the presence of 2,4,6-trimethylpyridine.

Each thio-orthoester was treated with 0.1M methanolic sodium methoxide (0.15–0.2 equiv.) at room temperature, and the products were acetylated and subjected to p.m.r. investigation either directly or following fractionation on silica gel.

Two syrupy products were obtained from *exo*-**1**; that of lower t.l.c.-mobility, isolated in 67% yield, was a 7:1 mixture of 3,4,6-tri-*O*-acetyl-1,2-*O*-[1-(*exo*- and *endo*-methoxy)ethylidene]-α-D-glucopyranoses (**6a**). The product of higher mobility (12% yield) was 3,6-di-*O*-acetyl-1,2,4-*O*-orthoacetyl-α-D-glucopyranose[8] (**7a**). Analogous results were obtained with *endo*-**1**.

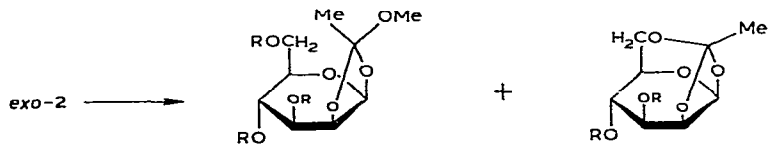


6 R = H
6a R = Ac

7 R = H
7a R = Ac

On deacetylation (which was complete within 45 min) and subsequent acetylation, **2** afforded 35% of a 10:1 mixture of 3,4,6-tri-*O*-acetyl-1,2-*O*-[1-(*exo*- and *endo*-methoxy)ethylidene]-β-D-mannopyranoses (**8a**) and 43% of hitherto unknown 3,4-di-*O*-acetyl-1,2,6-*O*-orthoacetyl-β-D-mannopyranose (**9a**). From the *exo,endo*

mixture **8a**, the known[9] *exo*-methoxy isomer was isolated by crystallisation. The p.m.r. spectrum of **9a** exhibited a characteristic signal for the orthoacetyl C-Me group (δ 1.65), a doublet for the anomeric proton (δ 5.78, $J_{1,2}$ 6 Hz), and signals for two acetyl groups; **9a** was completely hydrolysed by acid under the conditions that hydrolyse orthoesters[10]. The tricyclic structure of **9a** was proved by methylation[11]; deacetylation of **9a** followed by Hakomori methylation, acid hydrolysis, borohydride reduction, and acetylation afforded, as the only product, 3,4-di-*O*-methylhexitol tetra-acetate, identified by mass spectrometry.

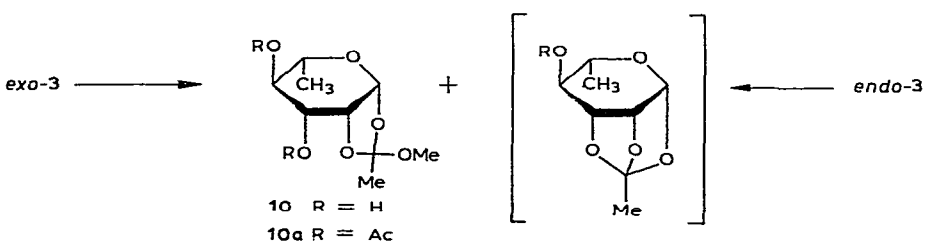


8 R = H
8a R = Ac

9 R = H
9a R = Ac

The structure of **9a** was additionally proved by its synthesis in ~90% yield (*a*) by intramolecular, acid-catalysed trans-esterification of the bicyclic orthoester **8** (*cf.* ref. 12), and (*b*) by intramolecular, $HgBr_2$-catalysed trans-esterification of the deacylation product (**17**) of **2**. The latter process is analogous to the intermolecular trans-esterification of sugar thio-orthoesters[7].

Treatment of the L-rhamnose thio-orthoesters (*exo*-**3** and *endo*-**3**) with methanolic sodium methoxide afforded 90% of a 10:1 mixture of 3,4-di-*O*-acetyl-1,2-*O*-[1-(*exo*- and *endo*-methoxy)ethylidene]-β-L-rhamnopyranoses (**10a**); the known[9] *exo*-isomer was isolated by crystallisation.



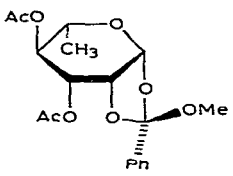
10 R = H
10a R = Ac

11

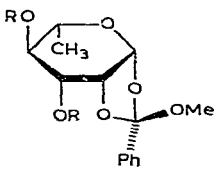
The tricyclic rhamnose orthoester **11** was not isolated, but its presence in the product mixture from *exo*-**3** was indicated by minor p.m.r. signals at δ 1.50 and 5.25, which may be tentatively attributed to the orthoacetyl C-Me group and H-1, respectively, of the tricyclic orthoester. Neutralisation of the alkaline reaction mixture and subsequent acetylation apparently led to decomposition of **11**, and the bicyclic orthoesters **10a** were the only isolable products.

Treatment of **4** with methanolic sodium methoxide followed by acetylation afforded 51% of 3,4-di-*O*-acetyl-1,2-*O*-(α-methoxybenzylidene)-β-L-rhamnopyranose

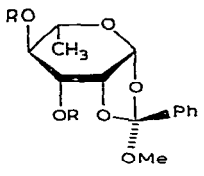
(**12**) together with a 1 : 1 mixture of 3,4-di-*O*-acetyl-1,2-*O*-(α-*p*-tolylthiobenzylidene)-β-L-rhamnopyranose and *p*-tolyl 2,3,4-tri-*O*-acetyl-1-thio-L-rhamnopyranoside (p.m.r. data). The formation of thioglycosides isomeric to the starting thio-orthoesters was detected by t.l.c. in all the reactions with methanolic sodium methoxide. The structure of the hitherto unknown orthoester **12** followed from its p.m.r. spectrum and was proved by synthesis.



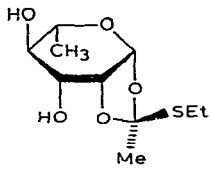
12



13a R = Bz
13b R = H
13c R = Ac



14a R = Bz
14b R = H
14c R = Ac



15

Condensation of 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide with methanol in the presence of 2,6-dimethylpyridine afforded the known[13] (minor) crystalline methyl orthobenzoate **14a** and the major (amorphous) methyl orthobenzoate **13a**. Deacylation of these benzoates gave crystalline **13b** and amorphous **14b**, which were acetylated to **13c** and **14c**, respectively. On the basis of the chemical shifts for the OMe group in **13a,b,c** (δ 3.14, 3.25, and 3.22) as compared with those for **14a,b,c** (3.62, 3.45, and 3.62) (*cf.* also ref. 14), the OMe-group should be *exo* in compounds **13a–c** and *endo* in compounds **14a–c**. The *exo*-configuration of the OMe group in **12** was deduced from the fact that its p.m.r. spectrum was very similar to that of **13c** and different from that of **14c**.

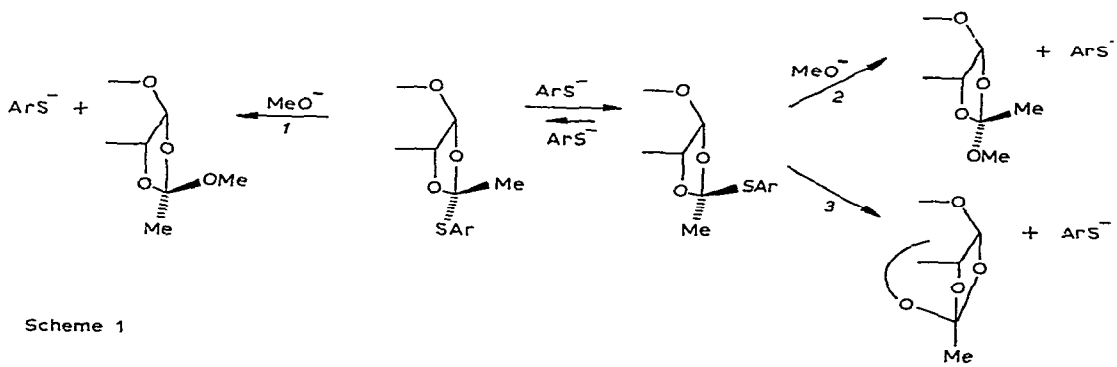
Unlike the arylthio-orthoesters **1–4**, treatment of the ethylthio-orthoacetate **5** with methanolic sodium methoxide gave 1,2-*O*-(1-ethylthioethylidene)-β-L-rhamnopyranose (**15**).

Thus, the arylthio-orthoesters undergo C–S-bond scission under mild conditions of deacetylation, with intermolecular (formation of bicyclic orthoesters) and intramolecular (formation of tricyclic orthoesters) trans-esterification. The trans-esterification observed seems to parallel the nucleophilic rupture of the C–S bond in aryl 2,4-dinitrophenyl sulfides by the action of sodium methoxide[15], to produce an arenethiol and 2,4-dinitrophenylmethyl ether. In the former case, the electrophilic site is apparently C-2 of the dioxolane ring, and the presence of a good leaving-group is a prerequisite for the reaction.

The only known example of a base-catalysed trans-esterification of sugar orthoesters is the cyclisation of α-D-glucopyranose1,2-(allyl orthoacetate) and 1,2-(allyl orthobenzoate) [but not the 1,2-(methyl orthoacetate] into 1,2,4-*O*-orthoacetyl- and -orthobenzoyl-α-D-glucopyranose, respectively. This reaction requires treatment of the orthoesters with ~0.8M aqueous sodium hydroxide for 20 min at 140°, and

proceeds[8] *via* isomerisation to the 1-propenyl-orthoester possessing a good leaving-group.

Irrespective of the configuration at C-2 of the dioxolane ring of the starting thio-orthoester, the main bicyclic orthoester formed had the methoxyl group *exo*, and the *exo,endo* ratio was the same. Control experiments showed that there was no *endo*⇌*exo* isomerisation of orthoesters under the reaction conditions. Both of the glucose thio-orthoesters (*exo*-**1** and *endo*-**1**) gave bi- and tri-cyclic orthoesters in approximately the same ratio, which rules out a simple S_N2 substitution that would proceed with inversion of configuration at C-2 of the dioxolane ring and result in exclusive formation of *endo*- and *exo*-methoxy-orthoesters, respectively. These results suggest that the reaction proceeds through the same intermediate species, most probably involving the rapid, reversible *exo*⇄*endo* isomerisation (Scheme 1) of thio-orthoesters by the *p*-toluenethiolate anion formed initially as a result of intramolecular cyclisation and/or intermolecular reaction of the starting thio-orthoester with methoxide.



Scheme 1

The following data support the suggested isomerisation of thio-orthoesters. The product of deacylation and subsequent acetylation of *endo*-**3** contained (p.m.r. spectrum, $CDCl_3$) ~5% of *exo*-**3** in addition to the main components, the bicyclic orthoesters **10a**. Signals at δ 0.84 (d, J 6 Hz, C-Me of rhamnose) and 1.57 (s, dioxolane C-Me), which are characteristic for *endo*-**3**, were absent, while a singlet at δ 1.80 corresponded to the dioxolane C-Me of *exo*-**3**. The p.m.r. spectra (CD_3OD) of the products of deacylation of both *endo*- and *exo*-**3** contained, *inter alia*, a signal at δ 1.68 for the dioxolane C-Me of the *exo*-thio-orthoester **18**.

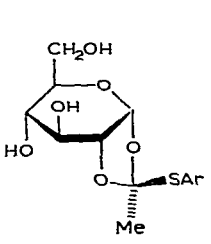
Since the rate of reaction *1* in Scheme 1 is higher than that of *2* (regarding the preferential direction of nucleophilic attack by methoxide), the major orthoester formed should possess an *exo*-OMe group regardless of the configuration of the starting thio-orthoester. The formation of the tricyclic orthoester is determined by the rate of reaction *3*, *i.e.*, by the monosaccharide structure.

Attempts were made to suppress the trans-esterification by lowering the concentration of the sodium methoxide solution. Treatment of thio-orthoester **2** with 0.04M or 0.01M methanolic sodium methoxide (0.1 equiv. per acetoxyl group) for

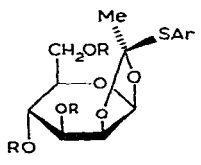
15 min gave the bi- and tri-cyclic orthoesters (**8** and **9**) together with the "normal" deacetylation product, thio-orthoester **17**. In the latter reaction, unreacted **2** and its partially deacetylated products were also detected (t.l.c.). Neutralisation of these reaction mixtures after 30 min followed by acetylation gave **2** and orthoesters **8a** and **9a** in ~1 : 1 : 1 ratios (t.l.c.). Analogous results were obtained when 0.02 equiv. of 0.01M methanolic sodium methoxide was used.

By contrast, treatment of solutions of *exo*-**1**, **2**, *exo*-**3**, and *endo*-**3** (0.5 mmol) in dry pyridine with 0.1M methanolic sodium methoxide for 5–10 min (deacetylation being completed within 5 min) gave the free thio-orthoesters **16**, **17**, and **18**, respectively, as the only products. More-prolonged treatment (>0.5 h) caused formation of trans-esterification products. Deacylation of the thio-orthoester **4** was complete within 16 h. Reacetylation of the products gave *exo*-**1**, **2**, and *exo*-**3** in 75–95% yields, with m.p.s and p.m.r. spectra identical with those of the starting thio-orthoesters.

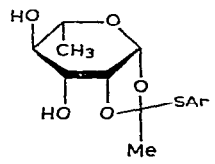
The completeness of deacylation was evident from the following data. (*1*) There were no signals due to acetyl groups in the p.m.r. spectra of the deacetylated thio-orthoesters **16**–**18**. (*2*) Benzoylation (benzoyl chloride in pyridine) of the product from thio-orthoester **2** gave crystalline 3,4,6-tri-*O*-benzoyl-1,2-*O*-(1-*p*-tolylthio)ethylidene-β-D-mannopyranose (**20**) in 93% yield. (*3*) Debenzoylation of thio-orthoester **4** gave **19**, whose subsequent acetylation afforded the diacetate **21**. The structures of **20** and **21** were confirmed by p.m.r.-spectral data and positive thio-orthoester tests[7].



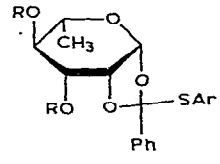
16



17 R = H
20 R = Bz



18



19 R = H
21 R = Ac

The unsubstituted thio-orthoesters obtained by deacetylation in pyridine followed by neutralisation with dry cation-exchange resin (H^+) were unstable. Thus, syrupy **16** decomposed almost completely (t.l.c.) when kept for 48 h at room temperature, whereas **18** remained intact. Dissolution of *endo*-**18** in trideuteriomethanol caused its gradual transformation into the trideuteriomethoxy analogue of orthoester **10**, which was complete (p.m.r. and t.l.c.) in 16 h; *exo*-**1** was much less susceptible to trans-esterification. The p.m.r. spectrum of a methanolic solution of **17** (with prior storage in the syrupy state for 48 h and 3 h in solution) contained three C-Me signals due to the starting thio-orthoester **17**, the tricyclic orthoester **9** (which is probably formed from **17** by spontaneous cyclisation), and the ortho-ester **8**. Compound **8** may be formed as a result of trans-esterification of both the tricyclic orthoester **9** and the starting thio-orthoester **17**. Indeed, the transformation **9**→**8** was demonstrated as follows: crystalline **9a** was deacetylated with methanolic sodium

methoxide, the solution was diluted with pyridine, deionised with cationic resin (H^+), and taken to dryness. In a methanolic solution of the resulting product, the presence of **8** was detected by p.m.r. spectroscopy after 3 h. At the same time, both **9** and 1,2,4-*O*-orthoacetyl-α-D-xylopyranose[16] were stable in methanolic sodium methoxide solution for at least 48 h.

Thus, the occurrence of mild, methoxide-catalysed trans-esterification of arylthio-orthoesters of sugars has been established. The protective effect of pyridine may be associated with the lowering of both the methoxide-ion concentration and the polarity of the medium.

EXPERIMENTAL

General methods. — Acetonitrile was distilled from P_2O_5 and CaH_2. Pyridine was distilled from KOH and from metallic Na or from P_2O_5. Dichloromethane was washed with concentrated H_2SO_4 and water, dried ($CaCl_2$), and distilled from CaH_2. Optical rotations were determined for solutions in chloroform, unless otherwise stated, at ambient temperature with a Perkin–Elmer 141 polarimeter. Melting points were determined with a Kofler apparatus and are uncorrected. N.m.r. spectra were recorded with Varian DA-60-IL and Tesla BS-497 (100 MHz, CSSR) spectrometers with $(Me_3Si)_2O$ (HMDS) as the internal standard. Chemical shifts are given in p.p.m. relative to tetramethylsilane ($\delta = \delta_{HMDS} + 0.05$). G.l.c.–m.s. was performed on a Varian MAT-111 GNOM apparatus with a column packed with 5% of SE-30 on Chromaton N-AW. Column chromatography was performed on Silica Gel L 100/250 μm (CSSR), and t.l.c. on Silica Gel L 5/40 μm (CSSR); the plates were sprayed with 25% sulfuric acid and heated at ~150°. The following solvent systems were used: benzene–ethyl acetate, 19:1 (*A*); chloroform–methanol, 4:1 (*B*); benzene–ether, 1:1 (*C*); and chloroform–methanol, 9:1 (*D*). Solutions were concentrated *in vacuo* at 40°.

3,4-Di-O-benzoyl-1,2-O-(α-p-tolylthiobenzylidene)-β-L-rhamnopyranose (**4**). — A mixture of 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide[13] (3.19 g, 5.9 mmol), thio-*p*-cresol (1 g, 8 mmol), and 2,4,6-trimethylpyridine (1.6 ml, 12 mmol) in dichloromethane (3 ml) and acetonitrile (15 ml) was stirred for 72 h at room temperature; more thio-*p*-cresol (2.4 mmol) was added and agitation was continued for 24 h. The mixture, which then contained the starting bromide (R_F 0.55; t.l.c., solvent *A*), thio-orthoester **4** (R_F 0.48), and decomposition products, was taken to dryness, and partitioned between water (50 ml) and 2:1 light petroleum–chloroform (100 ml). The lower, aqueous layer was washed with the same mixture (30 ml), and the combined organic layers were filtered through a pad of alumina and taken to dryness. Column chromatography of the residue (benzene→19:1 benzene–ethyl acetate) gave the starting bromide (450 mg, 14%) and thio-orthoester **4** (1.18 g, 34.2%) as a foam, $[\alpha]_D$ +128° (*c* 2); p.m.r. data (CCl_4): δ 1.03 (d, 3 H, *J* 6 Hz, CH_3 of rhamnose), 2.16 (s, 3 H, CH_3-Ar), 3.63 (m, 1 H, H-5), 4.78 (m, 1 H, H-2), 5.13–5.54 (m, 3 H, H-1,3,4), 6.54–7.57 and 7.78–8.12 (2 m, 19 H, aromatic).

Interaction of thio-orthoesters **1–5** *with sodium methoxide in methanol.* — (*a*) endo-**1**. The thio-orthoester (200 mg, 0.44 mmol) was dissolved in 0.1M methanolic sodium methoxide (2 ml); after 2 h, the mixture contained three components with R_F 0.58, 0.48, and 0.40 (main product) (t.l.c., solvent *B*), which corresponded to thio-orthoester **16** and orthoesters **6** and **7**, together with a small proportion of more-polar products. The mixture was kept for 16 h at room temperature, pyridine (0.3 ml) and M acetic acid in toluene (0.25 ml) were added, and the solution was taken to dryness. The residue was treated with pyridine (3 ml) and acetic anhydride (1.5 ml) for 16 h at room temperature, the solvent was evaporated, a solution of the residue in chloroform was washed with water (2 × 25 ml) and evaporated, and the residue was subjected to column chromatography (benzene→ether), to give **7a** (15 mg, 12%) and **6a** (102 mg, 64%). Compound **7a** was a syrup, R_F 0.50 (solvent *C*), $[\alpha]_D$ +33° (*c* 1); lit.[8] $[\alpha]_D$ +30.6° (chloroform); p.m.r. data (CCl_4): δ 1.58 (s, 3 H, C-Me of orthoacetate), 2.03 and 2.07 (2 s, 6 H, 2 OAc), 4.03–4.18 (m, 3 H, H-3,6,6'), 4.31–4.53 (m, 2 H, H-4,5), 5.05 (m, 1 H, H-2), and 5.62 (d, 1 H, $J_{1,2}$ 5 Hz, H-1). Compound **6a** was a syrup, R_F 0.43 (solvent *C*), $[\alpha]_D$ +41° (*c* 2); lit. $[\alpha]_D$ +33° (chloroform)[17], +65° (chloroform)[18]; p.m.r. data (CCl_4): δ 1.47 and 1.62 (2 s, 3 H, *exo*- and *endo*-C-Me); 2.04, 2.05, and 2.06 (3 s, 9 H, 3 OAc); 3.22 and 3.45 (2 s, 3 H, *exo*- and *endo*-C-OMe); 3.65–4.42 (m, 4 H, H-2,5,6,6'); 4.77 (dd, 1 H, $J_{4,5}$ 9.5, $J_{4,3}$ 3 Hz, H-4); 5.02 (t, 1 H, $J_{3,4} = J_{3,2} = 3.5$ Hz, H-3); 5.25 and 5.56 (2 d, 1 H, $J_{1,2}$ 5 Hz, H-1 of *endo*- and *exo*-**6a**). The ratio of integrated intensities of the signals at δ 1.47 and 1.62, and at δ 5.56 and 5.25, was ~1:7.

(*b*) exo-**1**. Analogous treatment of *exo*-**1** (410 mg, 0.9 mmol) afforded **7a** (38 mg, 15%), $[\alpha]_D$ +35° (*c* 2), and **6a** (219 mg, 67%), $[\alpha]_D$ +40° (*c* 2), whose p.m.r. spectra were identical with those of **7a** and **6a** from *endo*-**1**.

(*c*) exo-**2**. Thio-orthoester **2** (180 mg, 0.40 mmol) was treated with 0.1M methanolic sodium methoxide (2 ml) for 45 min, and the reaction mixture [containing two products with R_F 0.35 and 0.20 (t.l.c., solvent *D*)] was neutralised and acetylated as in (*a*), to give, after column chromatography, **9a** (50 mg, 44%) and **8a** (50 mg, 35%). Compound **9a** had m.p. 129.5–131.5° (from ethanol), R_F 0.50 (solvent *C*), $[\alpha]_D$ −110° (*c* 1); p.m.r. data ($CDCl_3$): δ 1.65 (s, 3 H, C-Me of orthoacetate), 2.06 (s, 3 H, OAc), 2.13 (s, 3 H, OAc), 3.92–4.13 (m, 3 H, H-5,6,6'), 4.52 (dd, 1 H, $J_{2,1}$ 6, $J_{2,3}$ 3 Hz, H-2), 5.03–5.15 (m, 2 H, H-3,4), and 5.78 (d, 1 H, $J_{1,2}$ 6 Hz, H-1).

Anal. Calc. for $C_{12}H_{16}O_8$: C, 50.00; H, 5.60. Found: C, 49.89; H, 5.76.

Compound **8a** had R_F 0.37 (solvent *C*); p.m.r. data ($CDCl_3$): δ 1.51 and 1.73 (2 s, 3 H, *exo*- and *endo*-C-Me), 2.05 (s, 6 H, OAc), 2.11 (s, 3 H, OAc), 3.25 and 3.41 (2 s, 3 H, *exo*- and *endo*-C-OMe), 3.68 (m, 1 H, H-5), 3.97–4.33 (m, 2 H, H-6,6'), 4.61 (t, 1 H, $J_{2,1} = J_{2,3} = 2.5$ Hz, H-2), 5.05–5.39 (m, 2 H, H-3,4), and 5.49 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1). The ratio of integrated intensities of the signals at δ 1.51 and 1.73, and at δ 3.41 and 3.25, was ~1:10. Crystallisation from ethanol afforded *exo*-**8a**, m.p. 105–109°, $[\alpha]_D$ −20° (*c* 0.65); lit.[9] m.p. 111–113°, $[\alpha]_D$ −23.5° (chloroform).

(*d*) exo-**3**. The thio-orthoester (200 mg, 0.5 mmol) was treated with 0.1M methanolic sodium methoxide (2 ml), and neutralisation and acetylation, as in (*a*),

gave a product (200 mg) which contained (t.l.c.) ~90% of **10a**, and traces of *exo*-**3** and the isomeric thioglycoside. The p.m.r. spectrum (CCl_4) of this product contained, *inter alia*, signals at δ 1.16 (d, J 6 Hz, CH_3 of rhamnose), 1.40 and 1.62 (2 s, *exo*- and *endo*-C-Me), 1.97 (s, OAc), 2.02 (s, OAc), 3.15 (s, OMe), and 5.27 (d, $J_{1,2}$ 2.5 Hz, H-1). The ratio of integrated intensities of the signals at δ 1.40 and 1.62 was ~1 : 10. Crystallisation from ether–pentane afforded *exo*-**10a** (70 mg, 46%), m.p. 79–83°, $[\alpha]_D$ +33° (*c* 0.6); lit.[9] m.p. 84–86°, $[\alpha]_D$ +34.7° (chloroform).

Thio-orthoester *exo*-**3** (100 mg, 0.25 mmol) was treated with a solution of sodium trideuteriomethoxide (from 10 mg of sodium in 1.2 ml of trideuteriomethanol), as described earlier, followed by neutralisation, acetylation, and column chromatography, to give *exo*-**3** (25 mg), whose p.m.r. spectrum was identical with that of an authentic sample, and **10a** (50 mg, 65%), m.p. 80–83°; p.m.r. spectrum (CCl_4): δ 1.16 (d, 3 H, CH_3 of rhamnose), 1.40 and 1.62 (2 s, 3 H, *exo*- and *endo*-C-Me), 1.97 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 3.38 (m, 1 H, H-5), 4.45 (t, 1 H, $J_{2,1} = J_{2,3}$ = 2.5 Hz, H-2), 4.70–5.05 (m, 2 H, H-3,4), and 5.26 (d, 1 H, J 2.5 Hz, H-1).

(*e*) endo-**3**. The thio-orthoester (170 mg, 0.43 mmol) was treated with methanolic sodium methoxide for 16 h as in (*a*). The product mixture, which contained ~90% of **10** and traces of **18** and *p*-tolyl 1-thio-L-rhamnoside (t.l.c.), was diluted with pyridine (2 ml) and methanol (5 ml), treated with KU-2 (H^+) resin pre-washed with methanol, filtered, and concentrated to dryness with co-evaporation of heptane–chloroform–methanol. The p.m.r. spectrum of the product (CD_3OD) contained, *inter alia*, signals at δ 1.23 (d, J 6 Hz, CH_3 of rhamnose), 1.38 and 1.58 (2 s in the ratio ~1 : 10, *exo*- and *endo*-C-Me), 1.68 (s, C-Me of thio-orthoester *exo*-**18**), and 5.33 (d, J 2 Hz, H-1). Conventional acetylation gave a product (120 mg) whose p.m.r. spectrum (in CCl_4) contained, *inter alia*, signals at δ 1.62, 1.41, and 1.75 p.p.m. in the ratios ~10 : 1 : 0.5, which corresponded to the C-Me groups at C-2 of the dioxolane ring in *exo*-**10a**, *endo*-**10a**, and *exo*-**3**, respectively.

(*f*) Thio-orthoester **4** (180 mg, 0.31 mmol) was treated with 0.1M methanolic sodium methoxide (3 ml) for 20 h at room temperature, whereafter **4** (R_F 0.45) had completely disappeared and new products with R_F 0.35 (main product), 0.38, and 0.20 (t.l.c., solvent *D*) had formed. The mixture was neutralised with M acetic acid in methanol and evaporated, and the residue was acetylated, as described previously, and subjected to column chromatography (benzene→19 : 1 benzene–ether). Eluted first were the products (35 mg) with R_F 0.40 (t.l.c., solvent *A*; according to p.m.r. data, a 1 : 1 mixture of acetylated thio-orthoester and the isomeric *p*-tolyl 1-thio-L-rhamnoside). Further elution gave **12a** (57 mg, 52.5%) as an amorphous solid, R_F 0.35 (solvent *A*), $[\alpha]_D$ +98° (*c* 2.85); p.m.r. data (CCl_4): δ 1.05 (d, 3 H, J 6 Hz, CH_3 of rhamnose), 1.95 (s, 3 H, OAc), 2.03 (s, 3 H, OAc), 3.15 (s, 3 H, OMe), 3.47 (m, 1 H, H-5), 4.67 (dd, 1 H, $J_{2,3}$ 4, $J_{2,1}$ 3 Hz, H-2), 4.83–5.17 (m, 2 H, H-3,4), 5.42 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), and 7.10–7.65 (m, 5 H, aromatic).

(*g*) Thio-orthoester **5** (170 mg, 0.51 mmol) was dissolved in 0.1M methanolic sodium methoxide (4 ml); the starting material disappeared in 15 min (t.l.c.) and a new, more polar product, which gave a positive thio-orthoester test, was formed. The

mixture was kept for 16 h, neutralised with dry KU-2 (H^+) resin following dilution with pyridine (5 ml), filtered, evaporated, and co-evaporated with heptane. A chloroform solution of the residue was passed through a pad of alumina and evaporated to dryness, to give chromatographically homogeneous, crystalline **15** (80 mg, 63%). Recrystallisation from ether–pentane gave **15** (70 mg, 55%), m.p. 95–98°, $[\alpha]_D$ +16° (*c* 0.8); p.m.r. data (CD_3OD): δ 1.22 (t, 3 H, *J* 7.5 Hz, CH_3 of ethyl), 1.24 (d, 3 H, *J* 6 Hz, CH_3 of rhamnose), 1.84 (s, 3 H, C-Me), 2.63 (q, 2 H, *J* 7.5 Hz, CH_2 of ethyl), 3.24–3.42 (m, 2 H, H-3,4), 3.68 (m, 1 H, H-5), 4.49 (dd, 1 H, $J_{2,3}$ 4, $J_{2,1}$ 2.5 Hz, H-2), and 5.25 (d, 1 H, *J* 2.5 Hz, H-1). Additional crystallisation from the same solvent system gave the analytical sample of **15**, m.p. 99–101.5°.

Anal. Calc. for $C_{10}H_{18}O_5S$: C, 47.98; H, 7.25; S, 12.81. Found: C, 48.48; H, 7.41; S, 12.61.

Deacetylation of arylthio-orthoesters with sodium methoxide in pyridine. — General procedure. A solution of a thio-orthoester (0.5 mmol) in pyridine (5 ml) was treated with 0.1M methanolic sodium methoxide (0.5 ml) for 5–10 min, the reaction being completed within 5 min (t.l.c., solvent *D*). A 0.1M solution of acetic acid in toluene (0.55 ml) was added, the solution was taken to dryness, and pyridine was evaporated from the residue, which was then dissolved in pyridine (3 ml) and treated with acetic anhydride (1.5 ml) for 16 h. Conventional work-up gave, quantitatively, the starting thio-orthoesters, which were recrystallised from an appropriate solvent (the yields and properties refer to the recrystallised products): *exo*-**1** (83%) m.p. and mixture m.p. 111–115° (from ethanol), $[\alpha]_D$ +82° (*c* 1); lit.[6] m.p. 115–116°, $[\alpha]_{578}$ +85.9°; lit.[7] m.p. 115–115.5°, $[\alpha]_D$ +81.4°; *exo*-**2** (75%), m.p. and mixture m.p. 124–129° (from carbon tetrachloride–ether–light petroleum), $[\alpha]_D$ −77° (*c* 1); lit.[1] m.p. 129–130.5° (from ethanol), $[\alpha]_D$ −80.5°; *exo*-**3** (85%), m.p. and mixture m.p. 151–152° (from ethanol), $[\alpha]_D$ +107° (*c* 1); lit.[7] m.p. 141–142° (erroneous data); authentic *exo*-**3** has m.p. 151–152°, $[\alpha]_D$ +113°; *endo*-**3**, a syrup whose p.m.r. spectrum was indistinguishable from that of authentic *exo*-**3**.

3,4,6-Tri-O-benzoyl-1,2-O-(1-p-tolylthioethylidene)-β-D-mannopyranose (**20**). — A solution of thio-orthoester **2** (90 mg, 0.2 mmol) in pyridine (3.5 ml) was treated with 0.05M methanolic sodium methoxide (0.6 ml) for 20 min, neutralised with M acetic acid in methanol, and evaporated; the residue was dissolved in pyridine (2 ml), and benzoyl chloride (0.15 ml) was added at 0°. The mixture was kept for 1.5 h at room temperature, diluted with chloroform (20 ml), and poured into chilled, aqueous, saturated sodium hydrogencarbonate (20 ml). The organic layer was washed with aqueous sodium hydrogencarbonate (2 × 20 ml), filtered through a pad of alumina, and taken to dryness, to give crystalline **20** (120 mg, 93%). Recrystallisation from ethanol gave the analytical sample, m.p. 151–155°, $[\alpha]_D$ −61.5° (*c* 0.4). No signals due to acetyl groups were detected in the p.m.r. spectrum.

Anal. Calc. for $C_{36}H_{32}O_9S$: C, 67.48; H, 5.04; S, 5.00. Found: C, 67.40; H, 5.23; S, 4.70.

3,4-Di-O-acetyl-1,2-O-(α-p-tolylthiobenzylidene)-β-L-rhamnopyranose (**21**). — Thio-orthoester **4** (280 mg, 0.48 mmol) was treated according to the general procedure,

and column chromatography of the acetylated product gave syrupy **21** (100 mg, 45%), $[\alpha]_D$ +54.5° (*c* 2); p.m.r. data (CCl_4): δ 0.94 (d, 3 H, *J* 5.5 Hz, CH_3 of rhamnose), 1.93 (s, 3 H, OAc), 2.09 (s, 3 H, OAc), 2.27 (s, 3 H, CH_3-Ar), 3.38 (m, 1 H, H-5), 4.43–5.10 (m, 3 H, H-2,3,4), 5.32 (d, 1 H, *J* 2.5 Hz, H-1), and 6.88–7.61 (m, 9 H, aromatic).

*Preparation of 3,4-di-*O*-acetyl-1,2,6-*O*-orthoacetyl-β-*D*-mannopyranose* (**9a**) *by trans-esterification.* — (*a*) 3,4,6-Tri-*O*-acetyl-β-D-mannopyranose 1,2-(methyl orthoacetate)[9] (200 mg, 0.55 mmol) was treated with 0.1M methanolic sodium methoxide (2 ml) for 1 h, pyridine (2 ml) and methanol (2 ml) were added, and the solution was neutralised with dry KU-2 (H^+) resin, filtered, and evaporated. A solution of the residue in 1,2-dichloroethane (5 ml) was boiled under reflux in an apparatus[12] fitted with a trap containing molecular sieves 4 Å. In 15 min, the reaction mixture contained both **8** (R_F 0.20; t.l.c., solvent *D*) and **9** (R_F 0.35) in the ratio ~1 : 1. A solution of anhydrous *p*-toluenesulphonic acid (~1 mg) in 1,2-dichloroethane (2 ml) was added and boiling was continued. Complete disappearance of **8** was observed in 10 min (t.l.c.). The reaction mixture was cooled, treated with pyridine (0.2 ml), and evaporated to dryness, and the residue was treated with acetic anhydride (1 ml) in pyridine (2 ml) for 16 h. Conventional work-up afforded **9a** (140 mg, 88%), m.p. 130.5–132° (from ether–pentane), $[\alpha]_D$ −105° (*c* 0.75).

Anal. Calc. for $C_{12}H_{16}O_8$: C, 50.00; H, 5.60. Found: C, 49.89; H, 5.76.

(*b*) A solution of thio-orthoester **2** (230 mg, 0.5 mmol) in pyridine (5 ml) was treated with 0.1M methanolic sodium methoxide (0.75 ml) for 5 min. The reaction mixture, which contained a single product with R_F 0.38 (t.l.c., solvent *D*), was neutralised with dry KU-2 (H^+) resin, filtered, and evaporated. The residue was dissolved in acetonitrile (5 ml) and pyridine (0.1 ml), and treated with mercuric bromide (180 mg, 0.5 mmol) for 2 h at room temperature, to give a single product with R_F 0.30. The solution was decanted, the residue was washed with acetonitrile (3 × 3 ml), the combined solution and washings were evaporated, and the residue was treated with acetic anhydride (2 ml) in pyridine (4 ml) for 16 h, to give, after conventional work-up, crystalline **9a** (135 mg, 92.5%). Recrystallisation from ether–pentane afforded **9a** (100 mg, 68.5%), m.p. 131–132°, $[\alpha]_D$ −107° (*c* 0.8). The melting points of **9a** obtained in (*a*) and (*b*) were undepressed on admixture with the product obtained from **3** by Zemplén deacetylation.

Methylation analysis of **9a**. — Tricyclic orthoester **9a** (5 mg) in pyridine (1 ml) was deacetylated with 0.1M methanolic sodium methoxide (0.2 ml) for 15 min, and the product was subjected to Hakomori methylation[11] followed by acid hydrolysis (M HCl, 100°, 5 h), reduction with sodium borohydride (16 h), and acetylation with acetic anhydride in pyridine (100°, 15 min). The only product obtained was identified as 1,2,5,6-tetra-*O*-acetyl-3,4-di-*O*-methylhexitol by g.l.c.–m.s.

*3,4-Di-*O*-benzoyl-1,2-*O*-(α-methoxybenzylidene)-β-L-rhamnopyranoses* (**13a**, **14a**). — To a solution of 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide[13] (43 g, 0.08 mol) in dry benzene (220 ml) were added 2,6-dimethylpyridine (18 ml, 0.18 mol) and dry methanol (200 ml) with stirring. The mixture was left for 70 h at room

temperature, diluted with 7:4 light petroleum–ether (550 ml), and washed with water (150 ml). The aqueous layer was extracted with the same solvent mixture (100 ml), the combined organic layers were washed with M $AgNO_3$ (100 ml) and water (4 × 200 ml), filtered through cotton, and evaporated to dryness. The residue (33 g, 84.4%) was dissolved in benzene (35 ml), ether (200 ml) and light petroleum (300 ml) were added, and the solution was left overnight at −5° for crystallisation. Solvent was removed by decantation, and the crystals were washed with cold light petroleum–ether (3:2; 100 ml) and dried, to give **14a** (6.3 g, 16.1%). Recrystallisation from benzene–ethyl acetate–ether–light petroleum (4:3:8:10) afforded **14a** (4.5 g), m.p. 173–174°, $[\alpha]_D$ +37° (*c* 3); lit.[13] m.p. 174–175°, $[\alpha]_D$ +37.5° (*c* 0.98, chloroform). The p.m.r. spectrum ($CDCl_3$) contained, *inter alia*, a singlet at δ 3.62 for an OMe group.

The mother liquor from the first crystallisation was evaporated, to give chromatographically homogeneous **13a** (26 g). A signal for an OMe group was present at δ 3.14 in the p.m.r. spectrum ($CDCl_3$).

β-L-Rhamnopyranose 1,2-(methyl orthobenzoates) (**13b, 14b**). —Crystalline **14a** (3 g, 6.1 mmol) was suspended in 0.1M methanolic sodium methoxide (25 ml); dissolution occurred in 3 h at room temperature. The solution was then diluted with chloroform (100 ml) plus 2–3 drops of pyridine, washed with water (3 × 30 ml), filtered through cotton, and evaporated. The residue was dried at 10^{-5} mmHg at room temperature for 2 h, to give amorphous **14b** (1.36 g, 78.8%), $[\alpha]_D$ −1° (*c* 2.6, methanol); p.m.r. data ($CDCl_3$): δ 1.27 (d, 3 H, *J* 6 Hz, CH_3 of rhamnose), 3.45 (s, 3 H, OMe), 3.32–3.63 (m, 3 H, H-3,4,5), 3.95 (broad t, 1 H, H-2), 5.15 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), and 7.10–7.53 (m, 5 H, aromatic). No carbonyl absorption was observed in the i.r. spectrum (KBr disc).

Anal. Calc. for $C_{14}H_{18}O_6$: C, 59.56; H, 6.43. Found: C, 59.41; H, 6.60.

Debenzoylation of **13a** (26 g, 53 mmol) was performed with 0.1M methanolic sodium methoxide (100 ml), as described earlier, and the solution was diluted with chloroform (300 ml) and washed with water (100 ml). The aqueous layer was extracted with chloroform (2 × 50 ml), and the combined organic layers were washed with water (3 × 100 ml), filtered through cotton, evaporated, and dried *in vacuo* at 50° for 1 h. Trituration with light petroleum (50 ml) gave **13b** (12.6 g, 84.2%), m.p. 135.5–137°, $[\alpha]_D$ +79° (*c* 2.5, methanol). Two recrystallisations from methanol–ether–light petroleum (2:15:20) gave the analytical sample of **13b**, m.p. 136–137°, $[\alpha]_D$ +80° (*c* 2, methanol); p.m.r. data ($CDCl_3$): δ 1.15 (d, 3 H, *J* 5.5 Hz, CH_3 of rhamnose), 3.25 (s, 3 H, OMe), 3.20–3.73 (m, 3 H, H-3,4,5), 4.63 (broad t, 1 H, H-2), 5.44 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), and 7.27–7.72 (m, 5 H, aromatic). No carbonyl absorption was observed in the i.r. spectrum (KBr disc).

Anal. Calc. for $C_{14}H_{18}O_6$: C, 59.56; H, 6.43. Found: C, 59.33; H, 6.38.

3,4-Di-O-acetyl-β-L-rhamnopyranose 1,2-(methyl orthobenzoates) (**13c≡12, 14c**). — Crystalline orthoester **13b** (370 mg, 1.31 mmol) was treated with acetic anhydride (2 ml) in pyridine (10 ml) for 2 days. The solution was treated with methanol (15 ml), left for 30 min, concentrated to half-volume, and poured into water

(25 ml). The product was extracted with ether–light petroleum (1 : 1, 150 ml), and the organic layer was washed with saturated, aqueous sodium hydrogencarbonate (2 × 30 ml) and water (3 × 30 ml), filtered through cotton, and evaporated. Heptane (3 × 30 ml) was evaporated from the residue, which was then dried *in vacuo* at room temperature for 1 h, to give chromatographically homogeneous, amorphous **13c** (450 mg, 93.7%), $[\alpha]_D$ +116° (*c* 4.5); p.m.r. data ($CDCl_3$): δ 1.06 (d, 3 H, *J* 6 Hz, CH_3 of rhamnose), 1.98 (s, 3 H, OAc), 2.07 (s, 3 H, OAc), 3.22 (s, 3 H, OMe), 3.52 (m, 1 H, H-5), 4.77 (dd, 1 H, $J_{2,3}$ 4, $J_{2,1}$ 2.5 Hz, H-2), 4.97–5.25 (m, 2 H, H-3,4), 5.50 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), and 7.26–7.73 (m, 5 H, aromatic).

Amorphous orthoester **14b** (320 mg, 1.13 mmol) was acetylated, as described above, to give crystalline **14c** (300 mg, 72.2%), m.p. 142–144° (from chloroform–ether–light petroleum, 1 : 10 : 20), $[\alpha]_D$ +1° (*c* 6.7); p.m.r. data ($CDCl_3$): δ 1.23 (d, 3 H, *J* 6 Hz, CH_3 of rhamnose), 2.03 (s, 3 H, OAc), 2.07 (s, 3 H, OAc), 3.53 (m, 1 H, H-5), 3.62 (s, 3 H, OMe), 4.20 (dd, 1 H, $J_{2,3}$ 4, $J_{2,1}$ 2.5 Hz, H-2), 4.97–5.38 (m, 2 H, H-3,4), 5.30 (d, 1 H, $J_{1,2}$ 2.5 Hz), and 7.22–7.62 (m, 5 H, aromatic).

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