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SYNTHESIS OF 1,2-*trans*-DISACCHARIDES *via* SUGAR THIO-ORTHOESTERS

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ABSTRACT

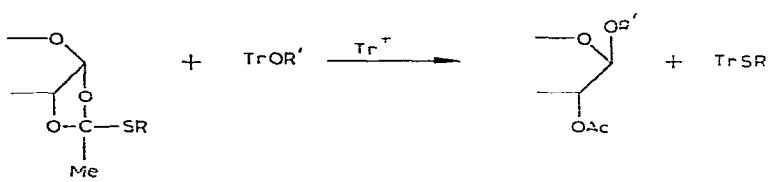
The reaction of sugar 1,2-thio-orthoesters in the D-*gluco*, D-*galacto*, D-*manno*, and L-*rhamno* series with primary and secondary trityl ethers of monosaccharides, in the presence of triphenylmethylium perchlorate as catalyst, affords, stereospecifically, derivatives of 1,2-*trans*-disaccharides in good yields. 4-Trityl ethers of benzyl 2-acetamido-3,6-di-*O*-acetyl-2-deoxy-α-D-glucopyranoside and methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside exhibit low reactivity in glycosylation by thio-orthoesters. A reaction scheme for the glycosylation is discussed.

INTRODUCTION

Syntheses of 1,2-*trans*-disaccharides (*i.e.*, disaccharides where the substituents at positions 1 and 2 in the non-reducing residue are *trans*) from bicyclic precursors (sugar 1,2-orthoesters and 1,2-*O*-cyanoethylidene derivatives) are believed to proceed *via* 1,2-acyloxonium ions formed by elimination of the exocyclic group (OR or CN) by the action of an electrophilic catalyst[1,2]. We have recently demonstrated[3] that 1,2-thio-orthoesters apparently belong to this group of glycosylating agents. We now describe syntheses of various disaccharides *via* 1,2-thio-orthoesters and discuss the scope and limitations of this glycosylation reaction.

RESULTS AND DISCUSSION

The disaccharide syntheses involved the reaction of 1,2-thio-orthoesters with trityl ethers in the presence of triphenylmethylium perchlorate as catalyst.



The starting thio-orthoesters **1–5** were obtained by reaction of the appropriate peracetylglycosyl bromides with thiols in nitromethane in the presence of 2,6-lutidine

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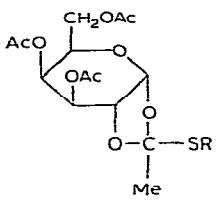
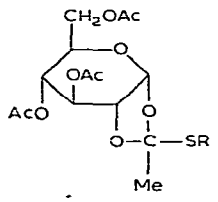
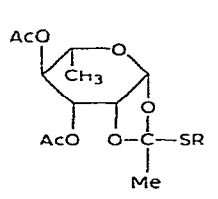
or 2,4,6-collidine[3–5]. Analogous treatment of tetra-*O*-acetyl-D-mannopyranosyl bromide with thio-*p*-cresol afforded thio-orthoester **6** as a mixture of two isomers. On the basis of the chemical shifts for the Me group of the dioxolane ring in the p.m.r. spectra of the major and minor isomers (δ 1.79 and 1.54), the *endo*-Me configuration was ascribed to the former by analogy with 1,2-orthoesters[6] (also see ref. 5).



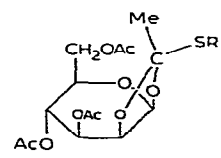
1



2,3



4,5



6

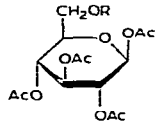
1,2,4 R = Et
3,5,6 R = *p*-MeC$_6$H$_4$

Syntheses of the primary trityl ethers **7a–9a** were performed by known procedures[7–9]. Several secondary trityl ethers of monosaccharides have been synthesised by the action of triphenylmethylium perchlorate in dichloromethane in the presence of 2,4,6-tri-*tert*-butylpyridine[10], 2,6-di-*tert*-butyl-4-methylpyridine[11], or 2,4,6-collidine[12]. We performed the tritylation of partially protected monosaccharides by a recent modification[12] of the original procedure[10], *i.e.*, by using triphenylmethylium perchlorate in the presence of 2,6-lutidine or 2,4,6-collidine. The properties of **10a–13a** thus obtained were in agreement with those reported in literature.

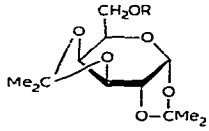
Trityl ethers **14a** and **15b** were prepared analogously. It is noteworthy that tritylation of all the compounds proceeded readily within 1 h, with the exception of **15a** for which reaction was incomplete after 1 day. Detritylation of **15b** by 90% trifluoroacetic acid regenerated **15a**.

Monotritylation of methyl 4-*O*-acetyl-α-L-rhamnopyranoside gave an ~1:1 mixture of **16a** and **17a**, which were separated by chromatography and acetylated to give **16b** and **17b**, respectively. It should be mentioned that acetylation of **17a** with acetic anhydride in pyridine proceeded slowly; addition of 4-dimethylaminopyridine, as expected[13], accelerated this process. The structures of **16b** and **17b** were established by p.m.r. data. In the low-field region of the spectrum of **16a**, there was a signal due to H-4 (δ 5.25, t, J 9.5 Hz), the signals of other ring-protons being located at 3.6–4.0. In the low-field region of the spectrum of **16b**, in addition to a signal for H-4 (δ 5.44, *t*, J 10 Hz), there was a signal for H-3 attached to a carbon atom bearing an acetoxyl group (δ 5.09, dd, $J_{3,4}$ 10, $J_{3,2}$ 3 Hz). Thus, the trityloxy group is located at C-2 in **16b**.

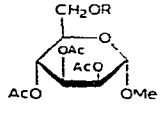
In the spectrum of **17b**, as compared with that of **17a**, a low-field shift of the H-2 signal was observed (δ 2.85→4.15, dd, $J_{2,1}$ 2, $J_{2,3}$ 3 Hz); the position of the H-3 signal remained practically unchanged. Thus, **17b** is the 3-trityl ether.



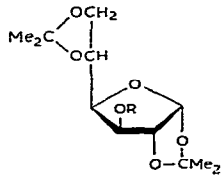
7a R = Tr
7b R = Glc
7c R = Rha



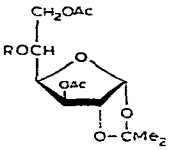
8a R = Tr
8b R = Rha



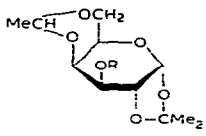
9a R = Tr
9b R = Man



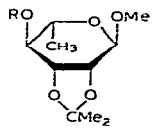
10a R = Tr
10b R = Rha



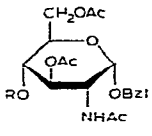
11a R = Tr
11b R = Rha



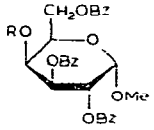
12a R = Tr
12b R = Rha



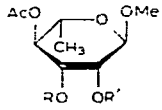
13a R = Tr
13b R = Rha
13c R = Man
13d R = Glc



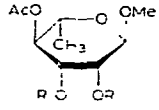
14a R = Tr
14b R = Gal



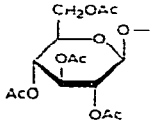
15a R = H
15b R = Tr
15c R = Glc

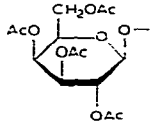


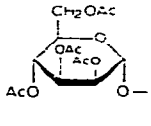
16a R = H,R' = Tr
16b R = Ac,R' = Tr
16c R = Ac,R' = Rha

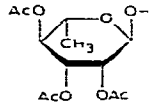


17a R = H,R' = Tr
17b R = Ac,R' = Tr
17c R = Ac,R' = Rha

Glc = 

Gal = 

Man = 

Rha = 

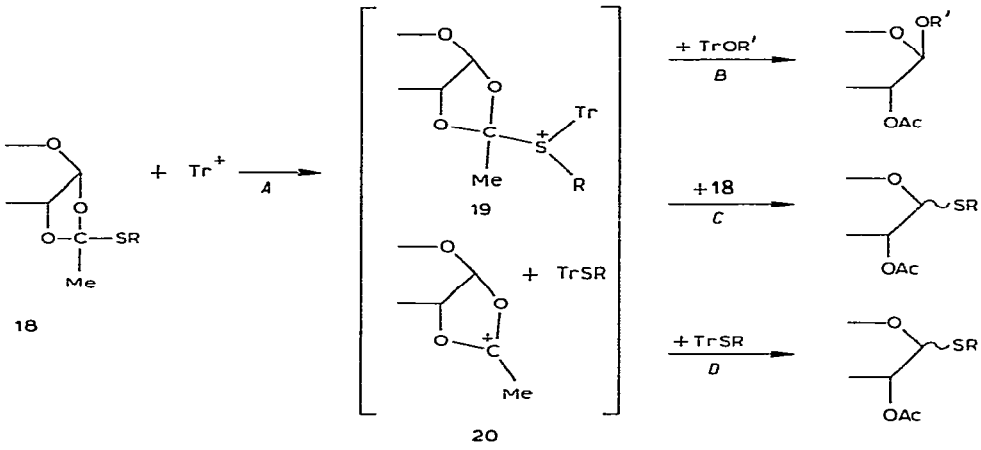
The foregoing trityl ethers were glycosylated with thio-orthoesters. Formerly[3], the reaction was performed by adding a solution of the catalyst to a solution of thio-orthoester plus trityl ether. This was accompanied by immediate disappearance of the yellow colour due to the triphenylmethylium ion, and its restoration after 2–3 min. Considerable amounts of acetylated thioglycosides isomeric with the starting thio-orthoesters were formed in addition to disaccharides. However, when a solution of the thio-orthoester was slowly added to a solution of the trityl ether plus catalyst, with stirring, at such a rate as to maintain the yellow colour of the reaction mixture, there was a considerable decrease in thioglycoside formation and an increase in the yield of disaccharide. The presence of hydroxyl compounds (*e.g.*, alcohol used for crystallisation) or atmospheric moisture could cause detritylation of the "aglyconic" components according to the scheme:

$$H_2O + TrClO_4 \rightleftarrows HOTr + HClO_4$$
$$HClO_4 + ROTr \rightleftarrows ROH + TrClO_4.$$

To prevent this undesirable process, a perchloric acid acceptor (2,4,6-collidine) was usually added to the reaction mixture.

The yields of disaccharides isolated by column chromatography on silica gel were in the range 60 to 90%. The nature of the thio-orthoester did not markedly influence the outcome of glycosylation: **13b** from **4** (and from **5**), **13c**, and **13d** were obtained in yields of 92 (96), 76, and 91%, respectively. The majority of trityl ethers studied were easily glycosylated. In sharp contrast, glycosylation of **14a** with thio-orthoester **1** afforded benzyl *N*-acetyl-lactosaminide acetate in 22% yield, while **15b** was inert towards glycosylation by thio-orthoester **2**, and only traces of the expected disaccharide **15c** could be detected by t.l.c. For both these reactions, anomeric mixtures of acetylated thioglycosides and the starting trityl ethers were isolated.

These results may be explained on the basis of the reactions in Scheme 1.



Apparently, the first and the fastest step, electrophilic attack of triphenylmethylium ion on the thio-orthoester **18**, leads to sulphonium (**19**) and/or acyloxonium (**20**) ion(s) (path *A*). Each of these reactive intermediates can react further with trityl ether to give the glycoside (path *B*), and with starting thio-orthoester **18** or with the resulting trityl alkyl (aryl) sulphide to form the thioglycoside (paths *C* and *D*). When the reaction is performed by adding a solution of thio-orthoester to a mixture of trityl ether and catalyst [*i.e.*, in the absence of excess of **18** (relative to **19** or **20**), thus excluding path *C*], 1,2-*trans*-disaccharides are the main products, and only traces of thioglycosides are formed. These findings indicate that, for reactive trityl ethers, the rate of the reaction *B* surpasses that of *D*. Should an excess of thio-orthoester **18** be present in the reaction mixture, as when a solution of catalyst is being added to a mixture of thio-orthoester and trityl ether, comparable amounts of glycosides and thioglycosides are formed. Bearing in mind the low rate of the reaction *D* in comparison with that of *B*, it can be assumed that the formation of

thioglycosides is mainly due to reaction *C* and hence the rates of reactions *B* and *C* are comparable.

Glycosylation of the weakly reactive, trityl ethers **14a** and **15b** even under conditions that exclude path *C*, *i.e.*, in the absence of excess of thio-orthoester, afforded mainly an anomeric mixture of thioglycosides. In this case, the rate of the reaction *B* is likely to become substantially less than that of reaction *D*, and the latter predominates.

This tentative scheme does not explain the formation of an anomeric mixture of thioglycosides. Preliminary experiments demonstrated that the anomerisation of ethyl 1-thio-β-D-glucoside tetra-acetate by the action of triphenylmethylium perchlorate proceeded to quite a small extent under similar conditions, thus ruling out this reaction as a reason for the formation of anomeric thioglycosides.

The majority of disaccharide derivatives obtained were identified by comparison of their physical constants with literature data. The structures of the others were confirmed mainly by methylation analysis. Thus, deacetylation of **9b** followed by conventional methylation analysis afforded a 1 : 1 mixture of 2,3,4,6-tetra- and 2,3,4-tri-*O*-methylmannitol acetates, which were identified by g.l.c.–m.s.

Glycosylation of **10a** with thio-orthoester **4** gave two disaccharides, the derivative of 3-*O*-rhamnosylglucose **10b** being the main product (isolated in 57% yield). The mass spectrum of **10b** contained, *inter alia*, a peak at *m/e* 517 [$(M - Me)^+$-fragment], a series of ions due to fragmentation of the acetylated rhamnopyranosyl group, and a peak at *m/e* 101, corresponding to the C-5–C-6 fragment of the di-*O*-isopropylideneglucofuranose residue. Removal of the protecting groups from **10b** and from the minor glycosylation-product followed by methylation analysis afforded, besides 2,3,4-tri-*O*-methylrhamnitol diacetate, 2,4,6- and 2,3,4-tri-*O*-methylglucitol acetates from the former and the latter, respectively. Thus, **10b** contained a (1→3) linkage, and the minor product was a (1→6)-linked disaccharide. Migration of the 5,6-*O*-isopropylidene group on glycosylation of **10a** has been reported[11].

Saponification of **11b** followed by methylation analysis gave 2,3,4-tri-*O*-methylrhamnitol and 3,6-di-*O*-methylglucitol acetates, identified by g.l.c.–m.s., in ~1 : 1 ratio.

The successful glycosylation of **12a** by thio-orthoester **4** (in 75% yield) should be mentioned. A previous attempt to glycosylate **12a** with 3,4,6-tri-*O*-acetyl-1,2-*O*-(1-cyanoethylidene)-α-D-glucopyranose failed, possibly due to degradation of the ethylidene group upon prolonged treatment with triphenylmethylium perchlorate[11], since glycosylation with 1,2-cyanoethylidene derivatives usually[11,12] takes from 6 to 18 h. Glycosylation with thio-orthoesters proceeds very quickly and the ethylidene group is practically unaffected. Disaccharide **12b** was identical with the recently described[14] compound.

The properties of **16c** and **17c** were in close agreement with those reported[15], and methylation analysis confirmed the presence of (1→2) and (1→3) linkages in **16c** and **17c**, respectively.

The stereospecificity of glycosylation was evaluated in the syntheses of **7c**,

8b, and **13b**. The products in the mother liquors from the crystallisation of **7c** and **8b** and syrupy **13b** were deacetylated and subjected to ion-exchange chromatography in borate buffer. No β-L-linked disaccharides were detected in association with **8b** and **13b**, and only traces (1.2%) of β-L-rhamnosyl-D-glucose were formed in the synthesis of **7c**. These data on the high stereospecificity of glycosylation by thio-orthoesters accord with previous findings[3]. The synthesis of the authentic β-L-linked disaccharides will be described elsewhere.

EXPERIMENTAL

Nitromethane was distilled from urea at 100 mmHg and then from CaH_2. Dichloromethane was washed with conc. H_2SO_4 and water, dried with $CaCl_2$, and distilled from CaH_2. 2,6-Lutidine and 2,4,6-collidine were distilled from CaH_2. T.l.c. was performed on Silica Gel LS5/40 μm (CSSR), and the plates were sprayed with 25% sulphuric acid and heated for 5–7 min at 150°. Column chromatography was performed on Silica Gel L 100/250 μm (CSSR) with a gradient of benzene→ether. Analytical ion-exchange chromatography of unprotected sugars was performed on a Technicon SC-II System with a glass column (25 × 0.6 cm) packed with DAX4 resin (Durrum) in 0.5M sodium borate buffer (pH 8.95) at 55° and an elution rate of 1 ml/min. Optical rotations were determined with a Perkin–Elmer 141 polarimeter at 20 ± 2° for solutions in chloroform. 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 for solutions in $CDCl_3$ with tetramethylsilane as the internal standard. 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. Triphenylmethylium perchlorate was prepared as previously described[16]. Solutions were concentrated *in vacuo* at 40°.

*3,4,6-Tri-*O*-acetyl-1,2-*O*-(1-*p*-tolylthioethylidene)-β-*D*-mannopyranose* (**6**). — To a solution of tetra-*O*-acetyl-D-mannopyranosyl bromide (15.31 g, 37.4 mmol) in nitromethane (15 ml) were added thio-*p*-cresol (5.05 g, 40.5 mmol) and 2,4,6-collidine (10 ml, 76 mmol), and the solution was kept for 3 days at room temperature. The mixture was diluted with ether (70 ml), collidinium bromide was filtered off, and the filtrate was evaporated. Crystallisation of the residue from ethanol (30 ml) yielded the *endo*-C-Me isomer **6** (7.4 g, 43.7%), which was homogeneous in t.l.c., R_F 0.48 (ethyl acetate–benzene, 1:4); m.p. 129–130.5°, $[\alpha]_D$ −80.5° (*c* 1.2); p.m.r. data: δ 1.79 (s, 3 H, C-Me), 1.98 (×2), 2.06 (2 s, 9 H, 3 OAc), 2.28 (s, 3 H, Ar-Me), 5.37 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), 7.05 and 7.35 (2 d, 4 H, each with *J* 8 Hz, aromatic).

Anal. Calc. for $C_{21}H_{26}O_9S$: C, 55.50; H, 5.76; S, 7.04. Found: C, 55.88; H, 5.84; S, 6.79.

The mother liquor from the above crystallisation was evaporated and the residue was chromatographed (benzene–ethyl acetate), to give *endo*-**6** (1.36 g); a mixture of *endo*-,*exo*-**6** (860 mg, 5.1%); and *exo*-**6** (860 mg, 5.1%), syrup, R_F 0.46, $[\alpha]_D$ −83° (*c* 2.9); p.m.r. data: δ 1.54 (s, 3 H, C-Me), 1.97, 2.00, and 2.07 (3 s, 9 H,

3 OAc), 2.33 (s, 3 H, Ar-Me), 5.24 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 7.05 and 7.45 (2 d, 4 H, each with J 8 Hz, aromatic).

1,2:5,6-Di-O-isopropylidene-3-O-trityl-α-D-glucofuranose (**10a**). — This compound (66%) was obtained by a modification[12] of the previous method[10]; m.p. 123–124°, $[\alpha]_D$ −20.8° (*c* 3.0); lit.[10] m.p. 120–122°, $[\alpha]_D^{20}$ −19.5° (chloroform).

3,6-Di-O-acetyl-1,2-O-isopropylidene-5-O-trityl-α-D-glucofuranose (**11a**). — This compound was obtained as previously described[11], in the presence of 2,4,6-collidine; yield, 75%; syrup, $[\alpha]_D$ −34.5° (*c* 2.8); lit.[11] syrup, $[\alpha]_D^{20}$ −35.2° (chloroform).

4,6-O-Ethylidene-1,2-O-isopropylidene-3-O-trityl-α-D-galactopyranose (**12a**). — This compound was obtained as previously described[11], using 2,4,6-collidine as the base. The product was isolated by crystallisation from methanol; yield, 66%; m.p. 145–146°, $[\alpha]_D$ +61° (*c* 1.5); lit.[11] m.p. 146–147°, $[\alpha]_D^{20}$ +60° (chloroform).

Methyl 2,3-O-isopropylidene-4-O-trityl-α-L-rhamnopyranoside (**13a**). — This compound was obtained as previously described[12]; the product was isolated by crystallisation from methanol; yield, 66%; m.p. 83–84°, $[\alpha]_D$ −75° (*c* 2); lit.[12] m.p. 83–84°, $[\alpha]_D^{20}$ −75° (chloroform).

Benzyl 2-acetamido-3,6-di-O-acetyl-2-deoxy-4-O-trityl-α-D-glucopyranoside (**14a**). — To a solution of benzyl 2-acetamido-3,6-di-*O*-acetyl-2-deoxy-α-D-glucopyranoside[17] (1 g, 2.54 mmol) and 2,6-lutidine (0.3 ml, 2.65 mmol) in dichloromethane (15 ml) was added triphenylmethylium perchlorate (0.9 g, 2.62 mmol), and the mixture was kept for 1 h at room temperature, diluted with hexane (30 ml), and washed with water (3 × 20 ml). The organic layer was filtered through a bed of alumina and evaporated, the residue was crystallised from methanol, to afford **14a** (0.88 g). From the mother liquor, an additional crop (0.13 g) of **14a** was obtained; total yield, 1.01 g (62%); m.p. 229–232°, $[\alpha]_D$ +118° (*c* 1.5); p.m.r. data: δ 1.21, 1.80, 1.88 (3 s, 9 H, 2 OAc and 1 NAc), 4.76 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 4.50 and 4.75 (2 d, 2 H, each with J 12 Hz, O-CH_2-Ph), 5.72 (d, 1 H, J 9 Hz, NH), and 7.16–7.50 (m, 20 H, aromatic). Further crystallisation gave an analytical sample of **14a**, m.p. 236–238° (from methanol), $[\alpha]_D$ +104.1° (*c* 1.5).

Anal. Calc. for $C_{38}H_{39}NO_8$: C, 71.57; H, 6.16; N, 2.20. Found: C, 71.46; H, 6.13; N, 2.22.

Methyl 2,3,6-tri-O-benzoyl-4-O-trityl-α-D-galactopyranoside (**15b**). — To a solution of **15a**[18] (2.03 g, 4 mmol) and 2,6-lutidine (0.68 ml, 6 mmol) in dichloromethane (25 ml) was added triphenylmethylium perchlorate (2.12 g, 6 mmol), and the mixture was kept for 5 days at room temperature. After dilution with chloroform (50 ml), the mixture was washed with water (3 × 50 ml), passed through a short column of alumina, and evaporated. Crystallisation of the residue from benzene–hexane afforded **15b** (1.77 g). From the mother liquor, an additional crop (0.3 g) of **15b** was obtained after chromatography, to make a total yield of 69%; m.p. 196–198°, $[\alpha]_D$ +63° (*c* 1.4); p.m.r. data: δ 3.42 (s, 3 H, OMe), 3.87 (d, 1 H, $J_{4,3}$ 3 Hz, H-4), 5.37 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.63 (dd, 1 H, $J_{3,2}$ 11, $J_{3,4}$ 3 Hz, H-3), 6.19 (dd, 1 H, $J_{2,1}$ 4, $J_{2,3}$ 11 Hz, H-2), and 7.10–8.00 (m, 30 H, aromatic). For

analytical purposes, a small amount was recrystallised from methanol; m.p. 195.5–197°, $[\alpha]_D$ +60.2° (*c* 1.0).

Anal. Calc. for $C_{47}H_{40}O_9$: C, 75.38; H, 5.38. Found: C, 75.20; H, 5.26.

A solution of **15b** (20 mg) in 90% trifluoroacetic acid (0.5 ml) was kept for 30 min at room temperature, pyridine (1 ml) was then added, and the mixture was diluted with chloroform (15 ml), washed with water (3 × 20 ml), and evaporated. Crystallisation of the residue from ether–pentane afforded **15a**, m.p. 138–141°, $[\alpha]_D$ +122° (*c* 0.13); lit.[18] m.p. 135.5–137° (ethanol), $[\alpha]_D^{30}$ +120° (chloroform).

*Methyl 4-*O*-acetyl-α-*L*-rhamnopyranoside.* — To a solution of methyl 4-*O*-acetyl-2,3-*O*-isopropylidene-α-L-rhamnopyranoside[19] (3.05 g, 1.17 mmol) in chloroform (90 ml) was added 99% trifluoroacetic acid (10 ml), and the mixture was kept for 1 h at room temperature and evaporated. Ethanol and toluene were evaporated from the residue, to give the crude, crystalline diol (R_F 0.50, ethyl acetate) contaminated with a small amount of a substance having R_F 0.05. Chromatography (benzene–ethyl acetate) then gave the title compound (2.2 g, 85%), m.p. 115–116° (from ether–light petroleum), $[\alpha]_D$ −103.5° (*c* 1.1), $[\alpha]_D$ −60.5° (*c* 0.91, water); p.m.r. data: δ 1.32 (d, 3 H, *J* 6 Hz, Me of rhamnopyranose), 2.07 (s, 3 H, OAc), 3.32 (s, 3 H, OMe), 4.66 (s, 1 H, H-1), and 4.80 (t, 1 H, $J_{4,3}$ 9 Hz, H-4); lit.[19] m.p. 112–116°, $[\alpha]_D$ −55° (water); lit.[20] m.p. 106–109°, $[\alpha]_D$ −90° (chloroform).

*Methyl 4-*O*-acetyl-2-*O*- and -3-*O*-trityl-α-*L*-rhamnopyranoside* (**16a** and **17a**). — To a mixture of methyl 4-*O*-acetyl-α-L-rhamnopyranoside (440 mg, 2 mmol) and triphenylmethylium perchlorate (687 mg, 2 mmol) in dichloromethane (5 ml) was added a solution of 2,4,6-collidine (0.26 ml, 2 mmol) in dichloromethane (2 ml), and the mixture was stirred for 25 min at room temperature. Pyridine–methanol (1 : 3, 0.4 ml) was then added, and the mixture was diluted with dichloromethane (10 ml), washed with water (2 × 10 ml), and evaporated. Chromatography of the residue gave, first, syrupy **16a** (316 mg, 34.2%), R_F 0.60 (benzene–ether, 1 : 1), $[\alpha]_D$ +30.1° (*c* 2.6); p.m.r. data: δ 1.25 (d, 3 H, *J* 6 Hz, Me of rhamnopyranose), 2.05 (s, 3 H, OAc), 3.03 (s, 3 H, OMe), 3.42–3.92 (m, 4 H, H-2,3,5, OH), 4.05 (s, 1 H, H-1), 5.25 (t, 1 H, $J_{4,3}$ 9.5 Hz, H-4), and 7.20–7.55 (m, 15 H, aromatic). Eluted second was **17a** (393 mg, 42.5%), R_F 0.30 (ether–benzene, 1 : 1), m.p. 185.5–186.5° (from methanol), $[\alpha]_D$ −94° (*c* 1); p.m.r. data: δ 1.12 (d, 3 H, *J* 6 Hz, Me of rhamnopyranose), 1.91 (s, 3 H, OAc), 2.35 (d, 1 H, *J* 2.5 Hz, OH), 2.85 (s, 1 H, H-2), 3.11 (s, 3 H, OMe), 3.99 (dd, 1 H, $J_{3,2}$ 3, $J_{3,4}$ 9 Hz, H-3), 4.35 (s, 1 H, H-1), 5.27 (t, 1 H, $J_{4,3}$ 9 Hz, H-4), 3.52 (m, 1 H, H-5), and 7.18–7.51 (m, 15 H, aromatic).

Anal. Calc. for $C_{28}H_{30}O_6$: C, 72.70; H, 6.53. Found: C, 72.79; H, 6.72.

*Methyl 3,4-di-*O*-acetyl-2-*O*-trityl-α-*L*-rhamnopyranoside* (**16b**). — To a solution of **16a** (400 mg, 0.86 mmol) in pyridine (5 ml) was added acetic anhydride (2.5 ml), and the mixture was kept overnight at room temperature and evaporated. Toluene–heptane (1 : 1, 5 × 5 ml) was added to, and evaporated from, the residue. Crystallisation of the residue from ether–pentane afforded **16b** (390 mg, 87%), m.p. 145.5–147°, $[\alpha]_D$ +39.4° (*c* 0.9); p.m.r. data: δ 1.25 (d, 3 H, *J* 6 Hz, Me of rhamnopyranose), 1.85 and 1.99 (2 s, 6 H, 2 OAc), 2.97 (s, 3 H, OMe), 3.53 (s, 1 H, $J_{1,2}$ 1 Hz, H-1),

3.61 (m, 1 H, H-5), 3.85 (dd, 1 H, $J_{2,1}$ 1, $J_{2,3}$ 3.5 Hz, H-2), 5.09 (dd, 1 H, $J_{3,4}$ 10, $J_{3,2}$ 3.5 Hz, H-3), 5.44 (t, 1 H, $J_{4,3}$ 10 Hz, H-4), and 7.21–7.51 (m, 15 H, aromatic).

Anal. Calc. for $C_{30}H_{32}O_7$: C, 71.41; H, 6.39. Found: C, 71.62; H, 6.68.

*Methyl 2,4-di-*O*-acetyl-3-*O*-trityl-α-*L*-rhamnopyranoside* (**17b**). — (*a*) To a solution of **17a** (330 mg, 0.7 mmol) in pyridine (10 ml) was added acetic anhydride (5 ml), and the mixture was kept for 12 days at room temperature. Methanol (10 ml) was added at 0° and the mixture was evaporated to dryness. Toluene–heptane (1 : 1; 5 × 10 ml) was added to, and evaporated from, the residue. A solution of the residue in methanol (30 ml) was decolorised with charcoal and evaporated, and the residue was crystallised from ether–pentane, to give **17b** (330 mg, 90%), m.p. 160.5–162°, $[\alpha]_D$ −9° (*c* 1.2); p.m.r. data: δ 1.11 (d, 3 H, *J* 6 Hz, Me of rhamnopyranose), 1.88 and 2.13 (2 s, 6 H, 2 OAc), 3.07 (s, 3 H, OMe), 3.45 (m, 1 H, H-5), 3.85 (dd, 1 H, $J_{3,2}$ 3, $J_{3,4}$ 9.5 Hz, H-3), 4.15 (dd, 1 H, $J_{2,3}$ 3, $J_{2,1}$ 2 Hz, H-2), 4.41 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), 5.25 (t, 1 H, $J_{4,3}$ 9.5 Hz, H-4), and 7.33–7.65 (m, 15 H, aromatic).

Anal. Calc. for $C_{30}H_{32}O_7$: C, 71.41; H, 6.39. Found: C, 71.49; H, 6.57.

(*b*) A mixture of **17a** (580 mg, 1.26 mmol), pyridine (3 ml), acetic anhydride (1.5 ml), and 4-dimethylaminopyridine (100 mg, 0.79 mmol) was kept overnight at room temperature. Ice–water (10 ml) was added, and the mixture was stirred for 30 min and then extracted with chloroform (3 × 10 ml). The combined extracts were washed with water (3 × 7 ml), passed through a short column of alumina, and evaporated. The residue was processed as in (*a*), to give **17b** (550 mg, 83.5%), m.p. 160.5–161.5°, $[\alpha]_D$ −10.5° (*c* 2); the p.m.r. spectrum was identical with that of **17b** obtained in (*a*).

Glycosylations of trityl ethers by thio-orthoesters: general procedure. — To a stirred solution of trityl ether (1.1 mmol) and triphenylmethylium perchlorate (0.3–0.4 mmol) in dichloromethane (5 ml) containing 2,4,6-collidine (0.02 ml, 0.2 mmol) was added a solution of thio-orthoester (1 mmol) in dichloromethane (10 ml) at such a rate as to retain the yellow colour of the reaction mixture (~30 min). The mixture was then quenched with 1 : 3 methanol–pyridine (0.5 ml), diluted with chloroform, and washed with water. The organic layer was evaporated and the syrupy residue was subjected to column chromatography.

*1,2,3,4-Tetra-*O*-acetyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)-β-*D*-glucopyranose* (**7b**). — From **7a** and **3** (in the absence of base); yield, 56%; m.p. 192–195° (from ethanol), $[\alpha]_D$ −4° (*c* 1.5); lit.[21] m.p. 191–193°, $[\alpha]_D$ −5.5° (chloroform).

*1,2,3,4-Tetra-*O*-acetyl-6-*O*-(2,3,4-tri-*O*-acetyl-α-*L*-rhamnopyranosyl)-β-*D*-glucopyranose* (**7c**). — From **7a** and **4**; yield, 90.5%: after crystallisation from ethanol, **7c** was obtained in 85% yield, m.p. 167–168°, $[\alpha]_D$ −28° (*c* 1.3); lit.[22] m.p. 168–169°, $[\alpha]_D$ −29.6° (chloroform). The product obtained by evaporation of the mother liquor was deacetylated, to give (ion-exchange chromatography) 6-*O*-α-L-rhamnopyranosyl-D-glucose (*T* 58 min) and 6-*O*-β-L-rhamnopyranosyl-D-glucose (*T* 44 min) in 4 : 1 ratio.

*1,2 : 3,4-Di-*O*-isopropylidene-6-*O*-(2,3,4-tri-*O*-acetyl-α-*L*-rhamnopyranosyl)-α-*D*-*

galactopyranose (**8b**). — From **8a** and **4**; yield, 90%; after crystallisation from hexane, **8b** was obtained in 87% yield, m.p. 114–115°, $[\alpha]_D$ −89° (*c* 1.8); lit.[23] m.p. 114°, $[\alpha]_D$ −91° (chloroform). The product obtained by evaporation of the mother liquor was subjected to mild hydrolysis with acid and subsequent deacetylation, to give (ion-exchange chromatography) only 6-*O*-α-L-rhamnopyranosyl-D-galactose (*T* 50 min); 6-*O*-β-L-rhamnopyranosyl-D-galactose has *T* 38 min.

Methyl 2,3,4-tri-O-*acetyl-6*-O-(*2,3,4,6-tetra*-O-*acetyl*-α-D-*mannopyranosyl*)-α-D-*mannopyranoside* (**9b**). — From **9a** and **6**; yield, 74%; foam, $[\alpha]_D$ +62.5° (*c* 0.6). To a solution of **9b** (30 mg) in chloroform (0.8 ml) was added 0.01M methanolic sodium methoxide (5 ml). After 16 h at room temperature, the solution was made neutral with KU-2 (H^+) resin and evaporated, and the residue was subjected in sequence to Hakomori methylation[24], hydrolysis with 0.3M hydrochloric acid (100°, 16 h), reduction with sodium borohydride, and acetylation with acetic anhydride in pyridine. Acetates of 2,3,4,6-tetra- and 2,3,4-tri-*O*-methylmannitol were identified in 1:1 ratio by g.l.c.–m.s.

1,2:5,6-Di-O-*isopropylidene-3*-O-(*2,3,4-tri*-O-*acetyl*-α-L-*rhamnopyranosyl*)-α-D-*glucofuranose* (**10b**). — From **10a** and **4**. After column chromatography, a 77% yield of a mixture of disaccharide derivatives was obtained (R_F 0.61 and 0.65; benzene–ether, 1:1). Crystallisation of the mixture from 1:2 ether–pentane afforded **10b** (57%), R_F 0.61, m.p. 151–152°, $[\alpha]_D$ −66.5° (*c* 1.4); p.m.r. data: δ 1.17 (d, 3 H, *J* 6 Hz, Me of rhamnopyranose), 1.29, 1.33, 1.38, and 1.48 (4 s, 12 H, 2 CMe_2), 1.98, 2.02, and 2.16 (3 s, 9 H, 3 OAc), and 5.85 (d, 1 H, $J_{1,2}$ 4 Hz, H-1 of glucofuranose). Mass spectrum: *m/e* 101 (100%), 111 (58), 153 (65), 273 (60), and 517 (55).

Anal. Calc. for $C_{24}H_{36}O_{13}$: C, 54.15; H, 6.81. Found: C, 53.82; H, 6.84.

Samples (10 mg) of **10b** and of the mother-liquor product, which contained mainly a component having R_F 0.65, were dissolved separately in 0.1M methanolic sodium methoxide (1 ml). After 1 h at room temperature, each solution was made neutral with KU-2 (H^+) resin and evaporated to a residue, which was treated with 99% trifluoroacetic acid (1 ml) for 1 h at room temperature. The mixture was evaporated and subjected to methylation analysis as described above. 1,3,5-Tri-*O*-acetyl-2,4,6-tri-*O*-methylglucitol and 1,5,6-tri-*O*-acetyl-2,3,4-tri-*O*-methylglucitol were identified for crystalline **10b** and for the mother-liquor product (R_F 0.65), respectively.

3,6-Di-O-*acetyl-1,2*-O-*isopropylidene-5*-O-(*2,3,4-tri*-O-*acetyl*-α-L-*rhamnopyranosyl*)-α-D-*glucofuranose* (**11b**). — From **11a** and **4**; yield, 74%; syrup, $[\alpha]_D$ −35.8° (*c* 1.4); p.m.r. data: δ 1.11 (d, 3 H, *J* 6 Hz, Me of rhamnopyranose), 1.26 and 1.47 (2 s, 6 H, CMe_2), 1.96, 2.00, 2.06, 2.08, and 2.14 (5 s, 15 H, 5 OAc), and 5.71 (d, 1 H, *J* 4 Hz, H-1 of glucofuranose).

Anal. Calc. for $C_{25}H_{36}O_{15}$: C, 52.08; H, 6.29. Found: C, 51.74; H, 6.39.

A portion of **11b**, after saponification with sodium methoxide, was subjected to methylation analysis, and acetates of 2,3,4-tri-*O*-methylrhamnitol and 3,6-di-*O*-methylglucitol were identified in a 1:1 ratio (g.l.c.–m.s.).

4,6-O-*Ethylidene-1,2*-O-*isopropylidene-3*-O-(*2,3,4-tri*-O-*acetyl*-α-L-*rhamnopyranosyl*)-α-D-*galactopyranose* (**12b**). — From **12a** and **4**; yield, 75%; syrup, $[\alpha]_D$

+2.8° (*c* 1.6); lit.[14] $[\alpha]_D$ +1.5° (chloroform); p.m.r. data: δ 1.14 (d, 3 H, *J* 7 Hz, Me of rhamnopyranose), 1.32 (d, 3 H, *J* 5 Hz, Me of ethylidene), 1.35 and 1.45 (2 s, 6 H, CMe_2), 1.93, 1.97, and 2.13 (3 s, 9 H, 3 OAc), 4.62 (q, 1 H, *J* 5 Hz, C-H of ethylidene), and 5.71 (d, 1 H, *J* 4 Hz, H-1 of galactopyranose).

Anal. Calc. for $C_{23}H_{34}O_{13}$: C, 53.28; H, 6.61. Found: C, 53.03; H, 6.62.

Methyl 2,3-O-isopropylidene-4-O-(2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (**13b**). — (*a*) From **13a** and **4**; yield, 92%; syrup, $[\alpha]_D$ −69° (*c* 1.5). (*b*) From **13a** and **5**; yield, 96%; syrup, $[\alpha]_D$ −71.4° (*c* 2.4); lit.[25] $[\alpha]_D$ −74° (chloroform).

A portion of the product from (*a*) was converted into the unprotected disaccharide[25] and analysed by ion-exchange chromatography. Only 4-*O*-α-L-rhamnopyranosyl-L-rhamnose (*T* 35 min) was detected; 4-*O*-β-L-rhamnopyranosyl-L-rhamnose has *T* 24 min.

Methyl 2,3-O-isopropylidene-4-O-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-α-L-rhamnopyranoside (**13c**). — From **13a** and **6**; yield, 76.4%; m.p. 116.5–117.5° (from ether–light petroleum), $[\alpha]_D$ +28.4° (*c* 1.8); lit.[26] m.p. 119–120°, $[\alpha]_D$ +30.7° (chloroform).

Methyl 2,3-O-isopropylidene-4-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-α-L-rhamnopyranoside (**13d**). — From **13a** and **3**; yield, 91%; m.p. 156–158° (from ethanol), $[\alpha]_D$ −29° (*c* 1.3); lit.[27] m.p. 158–159°, $[\alpha]_D$ −30.6° (chloroform).

Benzyl 2-acetamido-3,6-di-O-acetyl-2-deoxy-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-α-D-glucopyranoside (**14b**). — To a solution of **14a** (410 mg, 0.64 mmol) and triphenylmethylium perchlorate (60 mg, 0.175 mmol) in dichloromethane (4 ml) was added a solution of thio-orthoester **1** (250 mg, 0.64 mmol) in dichloromethane (8 ml) during 1 h with stirring. The mixture was quenched by addition of 1:3 methanol–pyridine (0.5 ml) and evaporated to a residue, which was treated with acetic anhydride in pyridine for 16 h at room temperature. After addition of methanol (1 ml) and dilution with 1:2 chloroform–hexane (40 ml), the mixture was washed with water (3 × 50 ml) and evaporated, and the resulting material was chromatographed to yield ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α,β-D-galactopyranoside (150 mg, 60%) (1:1 ratio, p.m.r.), **14a** (230 mg, 57%), and **14b** (140 mg, 30%). Crystallisation of **14b** from ether afforded material (100 mg, 22%) having m.p. 103–104°, $[\alpha]_D$ +63° (*c* 0.8); lit.[17] m.p. 107–108.5°, $[\alpha]_D^{25}$ +68° (chloroform).

The reaction of **15b** *with thio-orthoester* **2**. — To a solution of trityl ether **15b** (550 mg, 0.73 mmol) and triphenylmethylium perchlorate (80 mg, 0.23 mmol) in dichloromethane (6 ml) was added a solution of **2** (290 mg, 0.74 mmol) in dichloromethane (5 ml) dropwise during 40 min with stirring. The mixture was quenched with 1:3 methanol–pyridine (0.5 ml), diluted with chloroform (20 ml), washed with water (3 × 20 ml), and evaporated to dryness. Chromatography of the residue yielded **15b** (330 mg, 60%), m.p. 197–198° (from benzene–ether), $[\alpha]_D$ +63° (*c* 1.3). Further elution gave **15a** (70 mg, 19%), m.p. 139–141° (from ether–pentane), $[\alpha]_D$ +123° (*c* 0.7); followed by a mixture (310 mg) of **15a**, ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α,β-D-glucopyranoside, and traces of **15c**. This mixture (310 mg) was treated

with 0.02M methanolic sodium methoxide for 5 h at room temperature, the mixture was then made neutral with acetic acid and evaporated to dryness, and the residue was acetylated with acetic anhydride in pyridine in the usual manner. Chromatography of the product gave a mixture of ethyl 2,3,4,6-tetra-*O*-acetyl-α- and -β-D-glucopyranosides (150 mg, 52%) in a 1:2 ratio (g.l.c.).

Methyl 3,4-di-O-acetyl-2-O-(2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (**16c**). — From **16b** and **5**; yield, 64.5%; m.p. 148–151° (from ether–light petroleum), $[\alpha]_D$ −54.5° (*c* 0.7); lit.[15] m.p. 149–150° $[\alpha]_D$ −44.8° (chloroform). Deacetylation of **16c** and subsequent methylation analysis afforded 1,5-di-*O*-acetyl-2,3,4-tri-*O*-methylrhamnitol and 1,2,5-tri-*O*-acetyl-3,4-di-*O*-methylrhamnitol in a 1:1 ratio (g.l.c.–m.s.).

Anal. Calc. for $C_{23}H_{34}O_{14}$: C, 51.68; H, 6.41. Found: C, 51.67; H, 6.33.

Methyl 2,4-di-O-acetyl-3-O-(2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl)-α-L-rhamnopyranoside (**17c**). — From **17b** and **5**; yield, 63%; m.p. 136.5–137.5° (from ether–pentane), $[\alpha]_D$ −42° (*c* 1.4); lit.[15] m.p. 135–136°, $[\alpha]_D$ −43.6°. After deacetylation and subsequent methylation analysis of the product, 2,3,4-tri- and 2,4-di-*O*-methylrhamnitol acetates were identified (g.l.c.–m.s.) in a 1:1 ratio.

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