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SUGAR ORTHO ESTERS

PART IX[1]. THE SYNTHESIS OF 3,6-ANHYDRO-α-D-GALACTOPYRANOSE 1,2-(METHYL ORTHOACETATE) AND 6-*O*-(2,4-DI-*O*-ACETYL-3,6-ANHYDRO-β-D-GALACTOPYRANOSYL)-1,2:3,4-DI-*O*-ISOPROPYLIDENE-α-D-GALACTOPYRANOSE

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ABSTRACT

3,6-Anhydro-α-D-galactopyranose 1,2-(methyl orthoacetate) and its 4-acetate were synthesized from 2,3,4-tri-*O*-acetyl-6-*O*-tosyl-α-D-galactopyranosyl bromide. Condensation of the above-mentioned, acetylated ortho ester with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose gave 6-*O*-(2,4-di-*O*-acetyl-3,6-anhydro-β-D-galactopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose. The same disaccharide derivative was synthesised from 6-*O*-β-D-galactopyranosyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose by mono-*O*-tosylation followed by treatment with alkali and acetylation.

INTRODUCTION

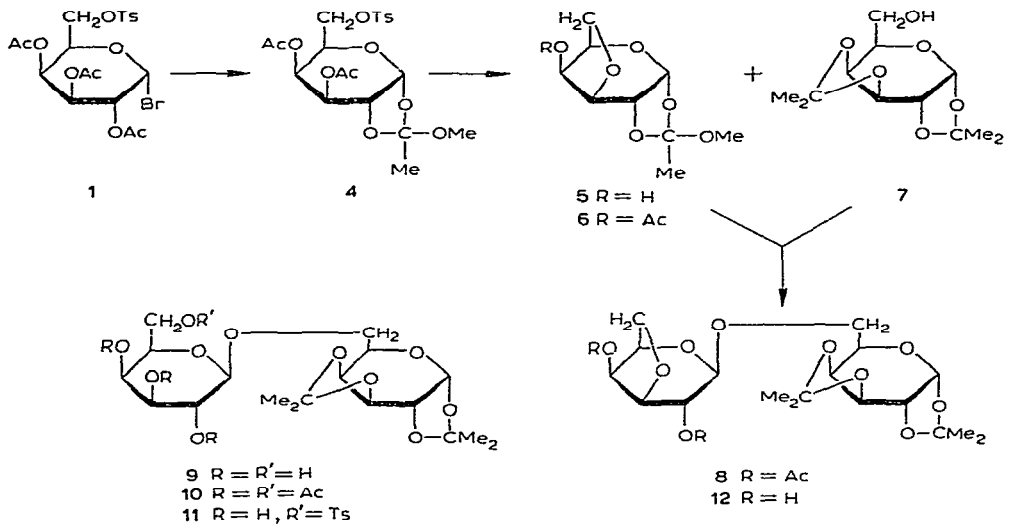
3,6-Anhydro-D- and L-galactoses, as well as their partially methylated derivatives are typical constituents[2] of polysaccharides of red algae. Although several aspects of the chemistry of 3,6-anhydrogalactoses have been investigated[3,4], the glycosidation of these monosaccharides has not been described. We now report the preparation of an ortho ester of 3,6-anhydro-D-galactose and its application in a glycosylation reaction.

RESULTS AND DISCUSSION

The starting material, 2,3,4-tri-*O*-acetyl-6-*O*-tosyl-α-D-galactopyranosyl bromide (**1**), was prepared[3,5] from 1,2:3,4-di-*O*-isopropylidene-6-*O*-tosyl-α-D-galactopyranose (**2**) *via* 6-*O*-tosyl-D-galactose (**3**). When the hydrolysis of the isopropylidene groups of **2** was effected with aqueous acetic acid[5], significant decomposition of the product occurred during the isolation procedure. Formolysis effected the conversion **2** → **3** without degradation of the product.

The procedure for the synthesis of sugar ortho esters from 1,2-*cis*-acylglycosyl bromides[6,7] was used for the conversion of the bromide **1** into the ortho ester **4**.

When **4** was treated with sodium methoxide, deacetylation and cyclization occurred to give the crystalline ortho ester **5** (66% overall yield). The structure of the ortho ester **5** and its crystalline acetate **6** was proved as follows.

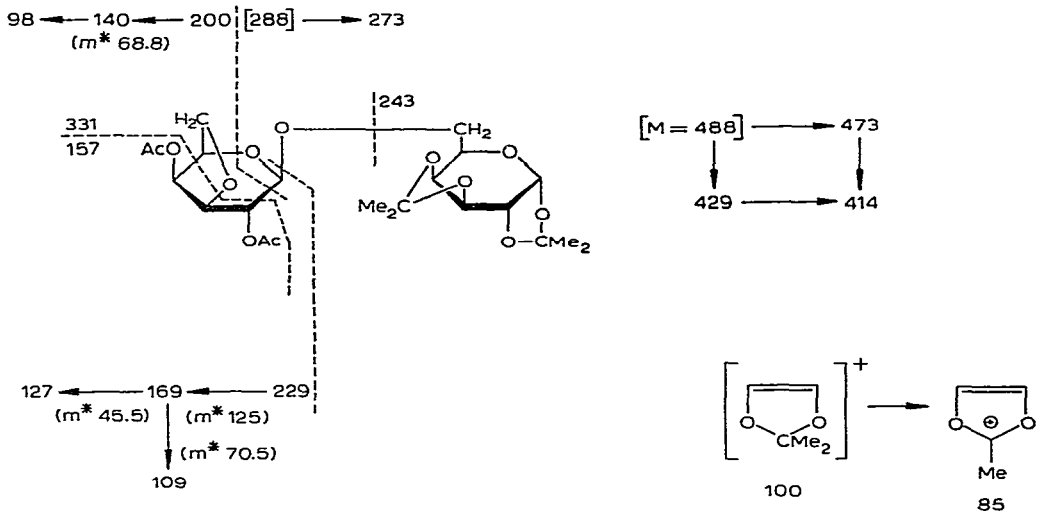


Both **5** and **6** were completely hydrolysable under the conditions of the hydrolytic test for sugar ortho esters[7], and the 3,6-anhydrogalactose content[8] of **5** was as expected. The p.m.r. spectrum of the acetate **6** contained, *inter alia*, signals characteristic of the OMe [δ 3.2 (*exo*) and 3.4 (*endo*), ratio 3:1] and CMe [δ 1.47 (*exo*) and 1.65 (*endo*)] groups of the orthoacetate moiety, and of OAc (δ 2.0). The *exo* and *endo* assignments were made on the basis of analogy with literature data[9–11]. The spectrum of **6** is therefore the sum of two very related spectra.

The glycosylating activity of the ortho ester **6** was studied by using 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**7**) as a model substrate. When the reaction was carried out in boiling nitromethane in the presence of mercury(II) bromide[7], 70% of the disaccharide derivative **8** was obtained and identified as follows.

The specific rotation (−92°) of **8** was in agreement with the value (−91°) calculated by Klyne's rule[12] from the specific rotation of methyl 2,4-di-*O*-acetyl-3,6-anhydro-β-D-galactopyranoside[3] and that of **7**[13]. The p.m.r. spectrum of **8** contained, *inter alia*, signals for four isopropylidene Me groups and two OAc groups. The mass spectrum of **8** contained, *inter alia*, peaks which are characteristic[14,15] of the whole disaccharide molecule, and of the monosaccharide components (see Scheme 1).

The disaccharide derivative **8** was also obtained by an alternative synthesis. The known[16] disaccharide **9** was prepared by deacetylation of the acetate **10** formed by condensation of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide with **7**, using Helferich's procedure[6]. Treatment of **9** with one equivalent of tosyl chloride



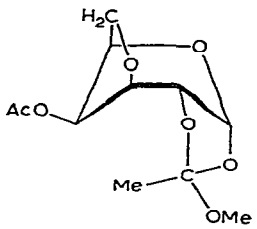
Scheme 1. Mass-spectral fragmentation of the disaccharide derivative **8**. Some of the fragmentations were associated with metastable ions (m*).

in pyridine gave the monosulphonate **11**, which was converted into the 3,6-anhydro derivative **12** by heating with potassium hydroxide. Acetylation of **12** then gave **8**, which was identical to the product synthesized by the ortho ester method.

Certain observations associated with the syntheses described above are noteworthy. The cyclization of the toluene-*p*-sulphonate **4** proceeded under alkaline conditions milder than those used[3] for the cyclization of the 6-toluene-*p*-sulphonates of methyl α- and β-D-galactopyranoside, as well as for the cyclization of the disaccharide derivative **11**.

Also, the glycosylation of **7** by the ortho ester **6** proceeded more rapidly, gave a higher yield of product, and required a tenth of the amount of catalyst ($HgBr_2$) than in comparable reactions of ortho esters of other sugars[1,7,11]. Moreover, for other ortho esters, *e.g.*, of D-glucopyranose, low concentrations of catalyst cause re-esterification rather than glycosylation[7,11]. Under similar conditions, no re-esterification was observed with the ortho ester **6**. These differences may be explained by the assumption that **6** adopts a $B_{1,4}$ (**13**) rather than $^1C_4$ (**14**) conformation. Re-esterification seems to be prevented by steric hindrance at the ortho ester group by C-4 and H-4 in the conformation **13**, whereas glycosylation appears to be promoted by the absence of hindrance at the β-position of the glycosidic centre. In the conformation **14**, the reverse relations will occur. The p.m.r. spectral data of the ortho ester **6** are consistent with conformation **13**. The $J_{1,2}$ value for **6** is 5.0 Hz, which is similar to the value (4.7 Hz) found[17,18] for α-D-xylopyranose 1,2,4-(ortho esters), which adopt conformations close to $B_{1,4}$ (as found by X-ray studies[19]), and to the average value (~5 Hz) for the 1,2-(ortho esters)[9,11,18] of α-D-gluco-, α-D-galacto-, and α-D-xylo-pyranose, where the substituents at C-1 and C-2 are axial and equatorial, respec-

tively. In contrast, the 1,2-(ortho esters) of β-D-manno- and β-L-rhamno-pyranose, where C-1 and C-2 substituents are equatorial and axial, respectively, and the conformation is similar to **14** rather than to **13**, are characterized[10,11] by $J_{1,2}$ values of 2.7–3.0 Hz.



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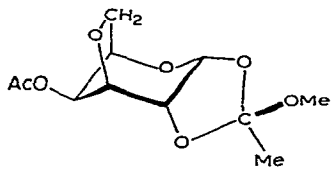

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EXPERIMENTAL

General methods. — Solvents were purified as previously described[7]. T.l.c. was performed on silica gel, using chloroform–acetone mixtures: *A* 95:5, and *B* 1:1. Column chromatography was performed on silica gel, using an adsorbent-to-substance ratio of 100:1 and a solvent gradient benzene–chloroform–acetone. Solutions were concentrated under diminished pressure below 40°. M.p.s. were determined with a Kofler apparatus. P.m.r. spectra were recorded at 60 MHz with a Varian DA60IL spectrometer, with HMDS as an internal standard. I.r. spectra were recorded for KBr pellets with a Perkin–Elmer Model 137 instrument. Optical rotations were determined with a Perkin–Elmer polarimeter Model 141.

The ortho esters **4**, **5**, and **6** were completely hydrolysable under the conditions of the hydrolytic test for sugar ortho esters[7]. All the compounds synthesized were chromatographically homogeneous.

6-O-Tosyl-D-galactose (**3**). — 1,2:3,4-Di-*O*-isopropylidene-6-*O*-tosyl-α-D-galactopyranose[5] (**2**; 20 g, 48 mmoles) was dissolved in 85% formic acid (60 ml) with occasional agitation, and the solution was kept for 16 h at room temperature. The resulting, yellow solution was evaporated and the residue was crystallized from water to give **3** (13 g, 81%), m.p. 130°, $[\alpha]_D^{18}$ +31° (*c* 1, pyridine); lit.[5] m.p. 130°, $[\alpha]_D^{18}$ +32°.

3,6-Anhydro-α-D-galactopyranose 1,2-(methyl orthoacetate) (**5**). — To a solution of 2,3,4-tri-*O*-acetyl-6-*O*-tosyl-α-D-galactopyranosyl bromide (**1**; 3 g, 5.60 mmoles, prepared[3,5] from **4**) in nitromethane (10 ml) was added a mixture of methanol (1.13 ml, 28 mmoles), 2,6-dimethylpyridine (1.26 ml, 11.2 mmoles) and nitromethane (5 ml). The resulting mixture was kept for 4 days at room temperature and then treated with a solution of silver nitrate (8.4 mmoles) in water (12 ml) and acetone (17 ml). The precipitate was removed, and the filtrate was diluted with chloroform (30 ml) and hexane (60 ml), washed with water (2 × 20 ml) and saturated, aqueous sodium chloride (20 ml), filtered, and evaporated. The residue (2 g, 76%) was the chromatographically homogeneous (solvent *B*) ortho ester **4**. It was dissolved in

methanol (20 ml), M methanolic sodium methoxide (5 ml, 5 mmoles) was added, and the solution was kept for 2 h at room temperature, then neutralized with carbon dioxide, and evaporated. The residue was extracted with boiling acetone (3 × 20 ml), and the combined extracts were filtered and evaporated. The residue (0.8 g, 66% from **1**) crystallized spontaneously when dried, and recrystallization from methanol gave **5**, m.p. 95–97°, $[\alpha]_{589}$ +19° (*c* 1.4, chloroform) (Found: C, 49.62; H, 6.43. $C_9H_{14}O_6$ calc.: C, 49.54; H, 6.43%).

The 4-acetate (**6**) of **5**, prepared conventionally with acetic anhydride–pyridine, had m.p. 105–106° (from methanol), $[\alpha]_{589}^{18}$ +11° (*c* 1, chloroform) (Found: C, 50.96; H, 6.07. $C_{11}H_{16}O_7$ calc.: C, 50.76; H, 6.19%). P.m.r. data ($CDCl_3$): δ 1.47 (*s*, 0.75H, *exo*-CMe), 1.65 (*s*, 2.25H, *endo*-CMe), 2.0 (*s*, 3H, OAc), 3.2 (*s*, 1H, *exo*-OMe), 3.4 (*s*, 2H, *endo*-OMe). 5.5 (*d*, $J_{1,2}$ 5.0 Hz, H-1).

6-O-(3,6-Anhydro-β-D-galactopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (**12**). — A solution of 6-*O*-β-D-galactopyranosyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[16] (**9**) (1.1 g, 2.6 mmoles) in a mixture of anhydrous acetone (3 ml) and pyridine (5 ml) was cooled to −10° and tosyl chloride (0.434 g, 2.6 mmoles) was added with stirring. The mixture was kept for 2 days at −5°, then poured into cold water, and extracted with chloroform. The combined extracts were washed with 1.5M sulphuric acid, saturated, aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and evaporated. The residue (0.34 g) was a mixture of two components having R_F values (solvent *B*) 0.5 (**11**, major component) and 0.82 (disulphonate, minor component). Preparative chromatography on silica gel gave **11** (0.20 g), and the material (0.30 g, 0.52 mmole), from two preparations, was dissolved in ethanol (5 ml), M potassium hydroxide (0.52 ml, 0.52 mmole) was added, and the solution was boiled under reflux until cyclization was complete (1 h, monitoring by t.l.c., solvent *B*). The solution was neutralized with carbon dioxide and evaporated to dryness, and the residue was extracted with boiling acetone (3 × 20 ml). The combined extracts were filtered and evaporated to give **12** (188 mg, 90% from **11**) as a syrup, $[\alpha]_{589}^{18}$ −96° (*c* 1.18, chloroform).

6-O-(2,4-Di-O-acetyl-3,6-anhydro-β-D-galactopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (**8**). — (*a*) A solution of **6** (0.3 g, 1.15 mmoles) and **7** (0.3 g, 1.15 mmoles) in nitromethane (20 ml) was boiled with distillation of solvent under atmospheric pressure and with the addition of fresh solvent to maintain a constant volume of the mixture. After 45 min, mercury(II) bromide (1.3 mg, 3.6 μmoles) was added and boiling was continued for 1 h (t.l.c. then showed the reaction to be complete). The solution was diluted with benzene (75 ml), twice washed with water, and evaporated. The residue containing **8** (R_F 0.45, solvent *A*, major component) and a product with R_F 0.6 (minor component) was twice fractionated on a column of silica gel to give **8** as a thick syrup (0.4 g, 70%), $[\alpha]_{589}^{18}$ −92° (*c* 1, chloroform) (Found: C, 54.82; H, 6.57. $C_{22}H_{32}O_{12}$ calc.: C, 54.94; H, 6.5€%). P.m.r. data (CCl_4): δ 1.25 (*s*, 6H, CMe_2), 1.33 and 1.41 (2*s*, 6H, CMe_2), 2.00 and 2.05 (2*s*, 6H, 2OAc). Mass-spectral data (Varian CH-6 instrument, 120°): *m/e* 473 (17%), 429 (7), 331 (4), 302 (5.5), 273 (4), 245 (6), 243 (6), 229 (100), 200 (60), 187 (5), 185 (10), 169 (10),

157 (13), 140 (23), 127 (>100), 113 (21), 109 (24), 102 (10), 100 (35), 98 (47), 85 (35), 81 (45), 71 (22), 69 (50).

(*b*) Conventional acetylation of **12** (0.16 g, 0.40 mmole) with pyridine (0.40 ml) and acetic anhydride (0.1 ml, 0.80 mmole) gave a syrupy product (0.15 g, 87%), $[\alpha]_{589}^{18}$ −97° (*c* 1.2, chloroform), which was identical chromatographically (solvent *A*) with **8** described above. The two compounds gave identical n.m.r. and mass spectra.

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