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1,2:5,6-Di-*O*-isopropylidene-α-D-galactofuranose

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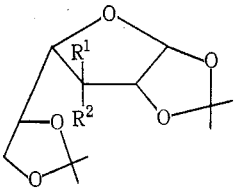
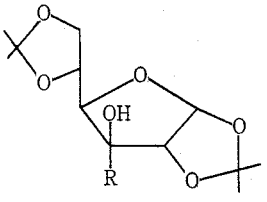
Abstract

The potential use of the title compound in glycoside synthesis is discussed and improvements in its synthesis noted.

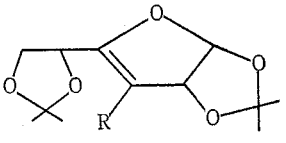
In a program of research into the synthesis of oligosaccharides and aminoglycosides related to the blood group substances we found the recurring need for a D-galactose unit suitably functionalized so as to allow reaction only at the C 3 hydroxyl. We chose 1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranose (1) for reasons of (*a*) the expected high reactivity of the unhindered hydroxyl group on the *exo* side of the molecule and (*b*) the ready conversion of compound (1) into the pyranoid form under acidic conditions.



	R^1	R^2
(1)	OH	H
(6)	H	OAc
(7)	H	OH
(8)	H	OTs
(9)	OBz	H



	R
(3)	H
(4)	OH



	R
(2)	H
(5)	OAc

Paulsen and Behre[1] synthesized compound (1) by the hydroboration–oxidation of 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*hex-3-enofuranose (2); the overall yield from commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (3) was 14%. De Jongh and Biemann[2] observed compound (1) to be the minor (20%) product in the copper(II)-catalysed reaction of D-galactose with acetone. We now wish

[1] Paulsen, H., and Behre, H., *Carbohyd. Res.*, 1966, **2**, 80.
[2] De Jongh, D. C., and Biemann, K., *J. Amer. Chem. Soc.*, 1964, **86**, 67.

to report on improvements to an alternative synthesis of compound (1) from compound (3).

Compound (3) can be oxidized by a variety[3–7] of methods to 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*hexofuranos-3-ulose hydrate (4), but the method of choice utilized ruthenium dioxide–potassium periodate.[8] The diol (4) was made to react with acetic anhydride in pyridine[9] to form pure 3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*hex-3-enofuranose (5). The enol acetate (5) was then converted into 3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose (6)[7] by hydrogenation in ethyl acetate solution over palladium on charcoal.* The acetate (6), treated with resin in methanol, formed 1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose (7).[7]

Tosylation of compound (7) according to Brimacombe *et al.*[10] proceeded slowly, probably owing to the hindered nature of the *endo* hydroxyl group; more forcing conditions allowed the formation of 1,2:5,6-di-*O*-isopropylidene-3-*O*-*p*-toluenesulphonyl-α-D-gulofuranose (8). Brimacombe *et al.*[10] inverted the configuration of C 3 of compound (8) by reaction with sodium benzoate in dimethylformamide at 140° for several days; the use of tetrabutylammonium benzoate allowed a much faster reaction to form 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranose (9). The benzoate (9), treated with resin in methanol, was rapidly hydrolysed to form 1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranose (1).

By employing the above sequence of reactions, with purification of compounds (5), (6) and (1) only, the overall yield of compound (1) from compound (3) was 60%. The use of this now readily available, versatile D-galactose unit in the synthesis of disaccharides[11] and aminoglycosides[12] will presently be demonstrated.

Experimental

Melting points are uncorrected. Proton magnetic resonance spectra were recorded on a Varian A60 spectrometer for deuterochloroform solutions containing tetramethylsilane as internal standard; each signal is described in order by intensity, multiplicity, chemical shift in p.p.m., assignment and coupling constant (s, singlet; d, doublet; t, triplet; m, multiplet; b, broad). All solvent removal was with a rotary evaporator under vacuum.

3-O-Acetyl-1,2:5,6-di-O-isopropylidene-α-D-gulofuranose (6)

The enol acetate (5) (3·00 g, 10·0 mmol) was dissolved in ethyl acetate (10 ml) and hydrogenated (room temperature, atmospheric pressure) over palladium on charcoal (300 mg of 5%). Filtration and evaporation yielded crystalline compound (6) (3·00 g, 99%), m.p. 72–73° (EtOH; lit.[7] 73–74°); p.m.r. 6, d, 1·36 and 1·39, isopropylidene; 6, d, 1·43 and 1·59, isopropylidene; 3, s, 2·12, CH_3COO; 6, m, 3·40–5·24, H2,3,4,5,6,6′; 1, d, 5·82, H1, $J_{1,2}$ 4·0 Hz.

* Care had to be taken in the choice of commercial catalysts available—both Engelhard (New Jersey) and Matheson, Coleman & Bell (New Jersey) were satisfactory.

[3] Sowa, W., and Thomas, G. H. S., *Can. J. Chem.*, 1966, **44**, 836.
[4] Stevens, J. D., *Methods Carbohyd. Chem.*, 1972, **6**, 123.
[5] Pfitzner, K. E., and Moffatt, J. G., *J. Amer. Chem. Soc.*, 1965, **87**, 5670.
[6] Beynon, P. J., Collins, P. M., Doganges, P. T., and Overend, W. G., *J. Chem. Soc., C*, 1966, 1131.
[7] Slessor, K. N., and Tracey, A. S., *Can. J. Chem.*, 1969, **47**, 3989.
[8] Baker, D. C., Horton, D., and Tindall, C. G., *Carbohyd. Res.*, 1972, **24**, 192.
[9] Meyer zu Reckendorf, W., *Methods Carbohyd. Chem.*, 1972, **6**, 129.
[10] Brimacombe, J. S., Gent, P. A., and Stacey, M., *J. Chem. Soc., C*, 1968, 567.
[11] Lemieux, R. U., Hendriks, K. B., Stick, R. V., and James, K., *J. Amer. Chem. Soc.*, in press.
[12] Lemieux, R. U., and Stick, R. V., unpublished data.

1,2:5,6-Di-O-*isopropylidene*-α-D-*gulofuranose* (*7*)

The acetate (6) (2·85 g, 9·4 mmol) was dissolved in methanol (14 ml) and resin (2·5 ml, Amberlite IRA-400 in OH^- form) added with stirring (40 h). Filtration and evaporation yielded crystalline compound (7) (2·40 g, 100%); p.m.r. 12, t(b), 1·28–1·77, isopropylidenes; 1, s(b), 2·83, OH; 6, m, 3·53–4·80, H2,3,4,5,6,6′; 1, d, 5·77, H1, $J_{1,2}$ 4·0 Hz.

1,2:5,6-Di-O-*isopropylidene-3*-O-p-*toluenesulphonyl*-α-D-*gulofuranose* (*8*)

The alcohol (7) (20·0 g, 77 mmol) was dissolved in pyridine (40 ml) and *p*-toluenesulphonyl chloride (17·5 g, 92 mmol) added. The mixture was stirred (45°; 40 h), water (0·3 ml) added and pyridine removed by evaporation. Water (1 l.) was then added and the crystalline material filtered, washed with water (2 × 100 ml) and dried to yield compound (8) (30·6 g, 97%); the p.m.r. spectrum was identical with that reported.[10]

Tetrabutylammonium Benzoate

Tetrabutylammonium bromide (64 g, 0·2 mol) was dissolved in dimethylformamide (325 ml) and silver benzoate (45 g, 0·2 mol) added with stirring. The reaction mixture was left overnight (0°), filtered, and the silver bromide residue washed with dimethylformamide (2 × 25 ml). The combined filtrate and washings yielded 375 ml of an 0·53M solution of tetrabutylammonium benzoate in dimethylformamide.

3-O-*Benzoyl-1,2:5,6-di*-O-*isopropylidene*-α-D-*galactofuranose* (*9*)

The tosylate (8) (30·0 g, 72 mmol) was heated (140°; 6 h) in dimethylformamide (170 ml) containing tetrabutylammonium benzoate (90 mmol), the solvent evaporated and water (1 l.) added. The aqueous layer was extracted with hexane (3 × 300 ml, containing 5% chloroform), the combined extracts washed with sodium bicarbonate (2 × 100 ml of saturated solution) and water (100 ml), dried ($MgSO_4$) and evaporated to yield crystalline compound (9) (25·0 g, 96%); the p.m.r. spectrum was identical with that reported.[10]

1,2:5,6-Di-O-*isopropylidene*-α-D-*galactofuranose* (*1*)

The benzoate (9) (24·5 g, 67 mmol) in methanol (250 ml) was hydrolysed (10 h) by resin (12 ml) according to the method for compound (7). Workup yielded crystalline compound (1) (15·9 g, 91%), m.p. and mixed m.p. 98·5–99° (cyclohexane; lit.[1] 97·5–98°).

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