ACTA CHEMICA SCANDINAVICA 21 (1967) 2083–2086

Synthesis of 1-*O*-β-D-Galactofuranosyl-D-glyceritol

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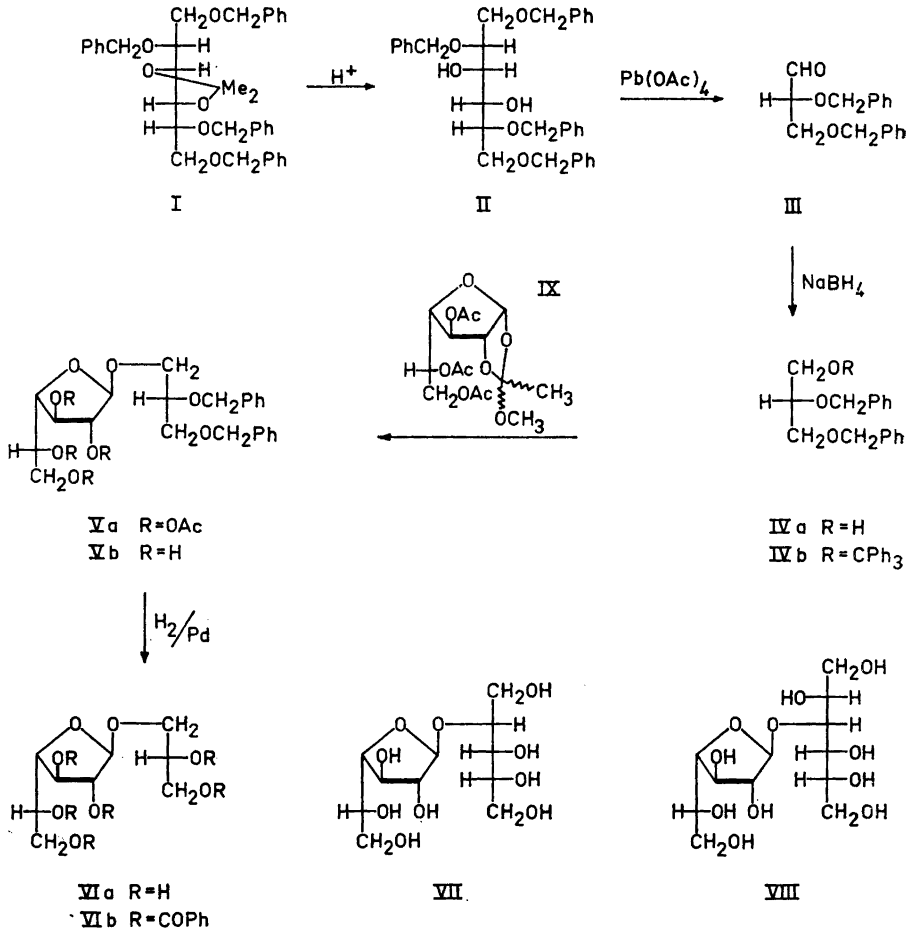
1-*O*-β-D-Galactofuranosyl-D-glyceritol has been synthesised by an unambiguous route and has been shown to be identical with the 1-*O*-β-D-galactofuranosylglyceritol previously isolated from the lipid of *Bacteroides symbiosus*. The synthesis shows that the glyceritol moiety in the natural product has the D-configuration.

Reeves *et al.*[1] have reported the isolation of a galactosylglyceritol from the lipid of *Bacteroides symbiosus*. The compound was a syrup which, however, gave a crystalline hexabenzoate. The galactosylglyceritol was characterized by periodate oxidation, optical rotation and by the rate of acid hydrolysis of the glycosidic linkage. The results showed that the compound was 1-*O*-β-D-galactofuranosylglyceritol. No decision with regard to whether the glyceritol moiety had the D- or L-configuration could be made on the basis of the results. Of the 1-*O*-glycosylglyceritols previously encountered in natural products, the *O*-α-D-galactopyranosyl-(1→6)-*O*-β-D-galactopyranosyl-(1→1)-glyceritol, found in the algae *Polysiphonia fastigata*,[2] *Corallina officinalis*,[3] and in wheat flour lipids,[4] has the D-configuration in the glyceritol moiety.[3] The 1-*O*-α-D-galactopyranosylglyceritol of *Porphyra umbilicalis* [5] on the other hand is an isomorphous mixture of D- and L-glyceritol derivatives.[6] In an attempt to resolve the configuration of the galactosylglyceritol isolated by Reeves *et al.*[1] the synthesis of 1-*O*-β-D-galactofuranosyl-D-glyceritol was undertaken.

Hydrolysis of syrupy 1,2,5,6-tetra-*O*-benzyl-3,4,-*O*-isopropylidene-D-mannitol (I) yielded the tetrabenzyl derivative (II) which was characterized by oxidation with lead tetraacetate (mole oxidant consumed per mole sugar was 0.94). The product of oxidation (III) was an oil which was characterized as the semicarbazone. The aldehyde (III) was reduced with sodium borohydride to 2,3-di-*O*-benzyl-D-glyceritol (IVa). The overall yield of IVa from I was 91 %. The trityl ether of IVa (IVb) was enantiomeric with 2,3-di-*O*-benzyl-1-*O*-triphenyl-methyl-L-glyceritol previously prepared by Wickberg [6] by a different route. Condensation of 3,5,6-tri-*O*-acetyl-1,2-*O*-methylorthoacetyl-α-D-galactofuranose (IX) with IVa, under the conditions described by Kochetkov *et al.*[7], yielded impure Va. The product of deacetylation, (Vb), was purified



by chromatography on alumina. Removal of the benzyl groups from Vb by catalytic hydrogenation and perbenzoylation of the product yielded VIb which was undistinguishable from the hexabenzoate obtained from the natural product. The overall yield from I to VIb was 23 %.

Since the synthesis of 2,3-di-*O*-benzyl-D-glyceritol by the route described above is unambiguous and since the glycoside synthesis of Kochetkov *et al.*[7] from 3,5,6-tri-*O*-acetyl-1,2,-*O*-methylorthoacetyl-α-D-galactofuranose is known to give anomerically pure β-D-galactofuranosides the present synthesis shows that the galactosylglyceritol isolated by Reeves *et al.*[1] is VIa.

So far, three galactofuranosylalditols have been found in nature, 2-*O*-β-D-galactofuranosyl-D-arabinitol (VII),[8–11] 3-*O*-β-D-galactofuranosyl-D-mannitol (VIII),[12] and 1-*O*-β-D-galactofuranosyl-D-glyceritol (VI).[1] Of these VIII has

previously been synthesised by Kotchetkov *et al.*[7,13] The biosynthetic precursor of the galactofuranosyl moiety of these substances does not appear to be known.

EXPERIMENTAL

All melting points are corrected. Optical rotations were measured at room temperature (20—22°). Evaporations were carried out under reduced pressure at a bath temperature below 50°.

1,2,5,6-Tetra-O-*benzyl-3,4*-O-*isopropylidene*-D-*mannitol (I).* 3,4-*O*-Isopropylidene-D-mannitol[14] (34.5 g, $[\alpha]_D$ +29° (*c* 1, water), m.p. 85—86°) was treated with benzyl chloride (525 ml) and powdered potassium hydroxide (300 g) at 130°—140° for 2 h. After cooling to room temperature, water (1100 ml) was added and the mixture extracted with chloroform. The chloroform extract was dried over sodium sulphate and concentrated to an oil (85.0 g) which was shown to be pure by thin layer chromatography (silica gel, ether-benzene 1:40).

1,2,5,6-Tetra-O-*benzyl*-D-*mannitol (II).* Compound I (83 g) was hydrolysed in 70 % aqueous acetic acid (1700 ml) at 100° for 1.5 h. Concentration yielded II (77.5 g) as an oil which was shown to be pure by thin layer chromatography (silica gel, ether). On oxidation with lead tetraacetate in acetic acid as devised by Perlin,[15] II consumed 0.94 mole oxidant per mole diol.

2,3,-Di-O-*benzyl*-D-*glyceraldehyde (III).* Compound II (76 g) was oxidised with lead tetraacetate (60 g) in acetic acid (750 ml) at room temperature until all the lead tetraacetate was consumed. Small portions of oxidant were added until the solution gave a positive starch-iodine test. Lead salts were then removed with oxalic acid. The mixture was filtered, and concentrated to give III as an oil (73.5 g) which was shown to be pure by thin layer chromatography (silica gel, ether). The semicarbazone of III had m.p. 122—123°, $[\alpha]_D$ +41° (*c* 0.7, chloroform). (Found: C 65.9; H 6.43; O 14.7; N 12.7. $C_{18}H_{21}N_3O_3$ requires: C 66.1; H 6.42; O 14.7; N 12.8).

2,3,-Di-O-*benzyl*-D-*glyceritol (IVa).* Compound III (70 g) was treated with sodium borohydride (49 g) and sodium methoxide (from 1.5 g of sodium) in methanol (1500 ml) at 0° for 18 h. Excess water was added and the base neutralised with sulphuric acid. Extraction with chloroform and concentration of the chloroform extracts yielded IVa as a syrup (66.0 g) which was shown to be pure by thin layer chromatography (silica gel, ether-benzene 2:1). Part of the syrup was distilled, b.p.$_{0.01}$ 152—155°, n_D^{25} 1.5490, in agreement with Wickberg's values for the enantiomer.[6] The triphenylmethyl ether (IVb) of IVa had m.p. 84—84.5°, $[\alpha]_D$ +9.2° (*c* 1, chloroform) also in agreement with the data for the enantiomer. (Found: C 84.0; H 6.76; O 9.44. Calc. for $C_{36}H_{34}O_3$: C 84.0; H 6.61; O 9.34).

3,5,6-Tri-O-*acetyl-1,2,*-O-*methylorthoacetyl*-α-D-*galactofuranose.*[7] 2,3,5,6-Tetra-*O*-acetyl-β-D-galactofuranosylchloride[16] (4.2 g) was dissolved in 2,6-lutidine (5 ml, distilled over phosphorus pentoxide). Anhydrous methanol (50 ml) was added and the solution was allowed to stand at room temperature overnight. The solution was diluted with chloroform (200 ml) and extracted three times with water, dried over magnesium sulphate, filtered and concentrated. The resulting syrup was dissolved in light petroleum (40—60°) and ether and shaken with 2 M silver nitrate. A dark precipitate in the chloroform phase was filtered off. The filtrate was concentrated to dryness and dissolved in ether. The ether solution was dried over sodium sulphate, filtered and concentrated to yield a syrup (2.7 g), $[\alpha]_D$ +18° (*c* 0.4, chloroform).

1-O-*(2,3,5,6-Tetra*-O-*acetyl*-β-D-*galactofuranosyl)-2,3-di*-O-*benzyl*-D-*glyceritol. (Va).* 3,5,6-Tri-*O*-acetyl-1,2,-*O*-methylorthoacetyl-α-D-galactofuranose (IX) (2.6 g) and the dibenzylglyceritol (IVa) (1.6 g) were dissolved in nitromethane (30 ml). Methanol together with nitromethane was removed by distillation, the volume being kept constant by continuous addition of nitromethane. The distillation was followed by gas chromatography. After 3.5 h mercury(II) bromide (104 mg) was added and the distillation at constant volume continued for a further 1.5 h. The mixture was diluted with ether (50 ml) and a brown precipitate filtered off. Further dilution with benzene gave more precipitate which was removed. The filtrate was concentrated to yield a yellow oil (4.7 g), which was used directly in the subsequent steps.

1-O-β-D-Galactofuranosyl-D-glyceritol (VIa). The above product Va (4.7 g) was dissolved in methanol (50 ml); 10 % ammoniacal methanol (10 ml) was added and the solution was allowed to stand overnight at room temperature. Concentration gave the deacetylated product Vb (3.4 g). This was purified by chromatography on an aluminium oxide column using propanol-water (85:15) as solvent. The fractionation was followed by thin layer chromatography. Concentration of the fractions of pure 1-*O*-β-D-galactofuranosyl-2,3-di-*O*-benzyl-D-glyceritol yielded an oil (1.4 g, 54 % yield from IVa) which was used directly in the next step. Hydrogenation of this dibenzyl derivative with 5 % palladium on charcoal in methanol yielded (VIa) as a syrup (714 mg). This on benzoylation yielded crystals (1.3 g) m.p. 135—136.5°, $[\alpha]_D$ −6.8° (*c* 1, chloroform). The values given by Reeves *et al.*[1] are m.p. 133—134° (uncorr.), $[\alpha]_D$ −6 ± 3° (*c* 1, chloroform). (Found: C 70.0; H 4.83. Calc. for $C_{51}H_{42}O_{14}$: C 69.7; H 4.82 also in agreement with Reeves' values [1]).

The crystalline material VIb was indistinguishable from the hexabenzoate prepared from the natural product (mixed m.p., IR) kindly supplied by Dr. Reeves.

Debenzoylation of VIb with barium oxide gave syrupy 1-*O*-β-D-galactofuranosyl-D-glyceritol, $[\alpha]_D$ −78° (*c* 1, water). Reeves reports $[\alpha]_D$ −73° for the natural product.

Acknowledgement. The authors are indebted to Professor Bengt Lindberg for his interest and helpful advice.

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Received April 24, 1967.