CHEMISTRY

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1965

SovietRxiv

Abstract

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A NEW ROUTE TO THE SYNTHESIS OF FURANOSIDES.

SYNTHESIS OF 3-O-(β-D-GALACTOFURANOSYL)-D-MANNITOL

The development of convenient methods for constructing the glycosidic bond—the principal type of bond in natural carbohydrate-containing polymers—is one of the most important problems in the synthetic chemistry of carbohydrates. Recently we proposed a new convenient method for the synthesis of glycopyranosides, consisting in the condensation of sugar orthoesters with the corresponding alcohols ([1, 2]). Along with pyranosides, furanose structures are also widely distributed among natural carbohydrate-containing compounds; however, the absence of a satisfactory method for the synthesis of O-furanosides makes this very important class of glycosides one of the least accessible. Indeed, the Koenigs–Knorr reaction, as applied to these compounds, has been carried out in only a few examples, while the number of known sterically homogeneous furanose acylhaloses of suitable configuration, necessary for carrying out such a reaction, is extremely limited. Therefore the extension of the method of glycoside synthesis proposed by us ([1, 2]) to the synthesis of furanosides seemed to us highly timely. The present communication is devoted to this question.

As an example of the synthesis of a natural furanoside we chose 3-O-(β-*D*-galactofuranosyl)-*D*-mannitol (III), recently isolated by Lindberg and co-workers ([3]) from the lichen *Peltigera horizontalis*. The synthesis of this compound was carried out by us according to the following scheme:

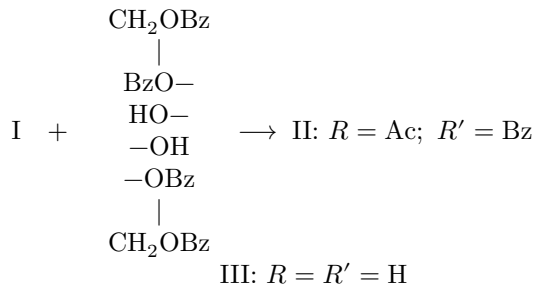

Fig. 1. IR spectra in Vaseline oil of 3-*O*-(*β*-*D*-galactofuranosyl)-*D*-mannitol: 1 —synthetic, 2—natural

Figure 1: Fig. 1. IR spectra in Vaseline oil of 3-*O*-(*β*-*D*-galactofuranosyl)-*D*-mannitol: 1—synthetic, 2—natural

For the preparation of the corresponding orthoester—the previously unknown 3,5,6-tri-O-acetyl-1,2-O-methyl orthoacetyl-*α*-*D*-galactofuranose (I)—the standard scheme for converting a 1,2-trans-halose into the corresponding orthoester (treatment with an alcohol in the presence of a hindered tertiary amine) was applied, in a modification close to that which was used for the synthesis of the orthoester from 4,6-O-benzylidene-2,3-di-O-acetyl-*β*-*D*-glucopyranosyl chloride ([4]):

3,5,6-tri-O-acetyl-*α*-*D*-galactofuranosyl chloride $\xrightarrow[\text{2,6-lutidine}]{\text{CH}_3\text{OH}}$ 3,5,6-tri-O-acetyl-1,2-O-methyl orthoacetyl-*α*-*L*

The key stage of the synthesis, the condensation of ortho ester I with 1,2,5,6-tetra-*O*-benzoyl-*D*-mannitol, was carried out in complete analogy with the synthesis of pyranosides from ortho esters ([1,2]), i.e., in the presence of catalytic amounts of $HgBr_2$ in nitromethane with azeotropic removal of the methanol that is split off. In this way, 3-*O*-(2′,3′,5′,6′-tetra-*O*-acetyl-*β*-*D*-galactofuranosyl)-1,2,5,6-tetra-*O*-benzoyl-*D*-mannitol (II) was obtained for the first time, in 28% yield. Examination of the reaction mixture by thin-layer chromatography ([5,6]) showed the absence of any side condensation products. After saponification of II, 3-*O*-(*β*-*D*-galactofuranosyl)-*D*-mannitol (III) was obtained, identical in constants, chromatographic behavior, and IR spectra (see Fig. 1) with the natural preparation.* This synthesis definitively confirmed the structure of natural galactosylmannitol proposed by Lindberg and co-workers ([3]).

Fig. 1. IR spectra in Vaseline oil of 3-*O*-(*β*-*D*-galactofuranosyl)-*D*-mannitol: **1** —synthetic, **2**—natural.

Thus, the method we are developing for the synthesis of glycosides on the basis of new glycosylating reagents—sugar ortho esters—evidently has a general character and can be successfully applied to the synthesis of both pyranosides and furanosides. The proposed synthetic method, suitable, according to our data, for the synthesis of various types of *O*-furanosides, is apparently sufficiently satisfactory. Its advantages include the stereochemical unambiguity of the reaction, leading selectively to the 1,2-*trans* configuration in the furanose ring, as well as the potential availability and sufficient stability of the starting ortho esters.

At present we are carrying out further studies on the application of the ortho ester method to the synthesis of pyranosides and furanosides.

Experimental Part

For preparative and thin-layer chromatography, neutral Al_2O_3 of Brockmann activity grade III was used. $CHCl_3$ and CCl_4 were freed from acidic impurities by distillation over $CaCO_3$. Absolute nitromethane was prepared by distillation over urea followed by two distillations over P_2O_5. Thin-layer chromatography was carried out on an unbound layer of Al_2O_3 ([5],[6]) in the systems $CHCl_3$–$CH_3COC_2H_5$ (98.5 : 1.5) (A) and $CHCl_3$–CH_3COCH_3 (95 : 5) (B). Paper chromatography was carried out in the system *n*-butanol–pyridine–water (6 : 4 : 3) (C), on Goznak paper. Solutions were evaporated in vacuum at 40–50°.

1,3,5,6-Tri-*O*-acetyl-1,2-*O*-methyl orthoacetyl-α-*D*-galactofuranose (I).

15.5 g (42.5 mmoles) of 2,3,5,6-tetra-*O*-acetyl-β-*D*-galactofuranosyl chloride, obtained by the method of Wolfrom and co-workers** ([7]), is dissolved in a mixture of 100 ml of absolute methanol and 28 ml of dry 2,6-dimethylpyridine. The solution is left at room temperature for 20 h, after which it is extracted several times with hexane, and the methanolic layer is diluted

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* The authors express their sincere gratitude to Prof. Lindberg (Sweden), who kindly provided us with a sample of natural 3-*O*-(β-*D*-galactofuranosyl)-*D*-mannitol.

** In reproducing this procedure, we observed an extremely rapid decomposition of the crystalline chloride, accompanied by conversion of the crystals into a syrup and evolution of HCl. The decomposition began immediately after separation of the crystals from the mother liquor.

50 ml of methanol and 75 ml of water are added, and the mixture is extracted with ether (4×75 ml); the ether solution is washed with water, combined with the hexane extract, and evaporated to dryness. The residue is recrystallized from a mixture of benzene and hexane. The crystals that separate are removed and discarded. The mother liquor is evaporated to dryness; the remaining syrup (13 g) is chromatographed on Al_2O_3 ($S = 11.2$ cm^2, $h = 24.5$ cm; gradient elution $CCl_4 \rightarrow CCl_4$–$CHCl_3$ (97 : 3); fraction control by thin-layer chromatography in system A). Fractions containing the ortho ester are combined and evaporated. The yield of chromatographically homogeneous syrupy 3,5,6-tri-*O*-acetyl-1,2-*O*-methyl orthoacetyl-α-*D*-galactofuranose is 5.36 g (35%)*, $[\alpha]_D + 24 \pm 1°$ (*C* 1.71; $CHCl_3$). The preparation is sufficiently pure for use in the next stage (the additional purification described below does not change the specific rotation).

The substance is completely hydrolyzed in 10 min at 20° in 0.01 N H_2SO_4 in 90% aqueous acetone (substance concentration 0.2%; control by chromatography in system A).

To remove traces of halogen-containing impurities, a sample of the preparation

is evaporated four times with methanol containing several drops of pyridine, dissolved in ether, and the ether solution is washed with water and evaporated to dryness. The resulting syrup is dried in vacuo over P_2O_5 at 61° for 12 h; n_D^{20} 1.4599.

$C_{15}H_{22}O_{10}$.	Found, %:	C 50.13; 50.22; H 5.94; 6.02
	Calculated, %:	C 49.71; H 6.15

2. 3-*O*-(2′,3′,5′,6′-tetra-*O*-acetyl-β-*D*-galactofuranosyl)-1,2,5,6-tetra-*O*-benzoyl-*D*-mannitol (II).

1.81 g (5.00 mmol) of I, 2.00 g (4.00 mmol) of 1,2,5,6-tetra-*O*-benzoyl-*D*-mannitol ([8]), and 20 ml of absolute nitromethane are boiled with a straight condenser, while absolute nitromethane is simultaneously added dropwise at such a rate that the volume of the reaction mixture remains approximately constant. After 5 ml has distilled off, 72 mg (0.2 mmol) of $HgBr_2$ is added; the reaction mixture is boiled under the same conditions for 2 h, the straight condenser is replaced by a reflux condenser, and boiling is continued for another 1 h 20 min. The mixture is cooled, 1 ml of pyridine is added, the small precipitate is filtered off, and the filtrate is evaporated to dryness. The resulting syrup is dissolved in 10 ml of chloroform; 90 ml of ether and 40 ml of petroleum ether are added, and the mixture is left overnight. The crystals of II that have separated are isolated, washed with ether and petroleum ether, and dried. Yield 1.05 g (28.3%), mp 159–162°. Chromatographically homogeneous. In the mother liquor, chromatography (system B) revealed the starting compounds (R_f 0.1 and 0.77) and traces of the reaction product (R_f 0.35). Repeated recrystallization of the preparation does not change the melting point; $[\alpha]_D - 36 \pm 1°$ (C 2.0; $CHCl_3$).

$C_{48}O_{48}O_{19}$.	Found, %:	C 62.26; 62.44; H 5.27; 5.39
	Calculated, %:	C 62.07; H 5.21

3. 3-*O*-(β-*D*-galactofuranosyl)-*D*-mannitol (III).

0.27 g of II is dissolved in 10 ml of $CHCl_3$, 30 ml of a 10% solution of triethylamine in absolute methanol is added, and the mixture is left at 37° for 5 h. The solution is evaporated to dryness; the residue is dissolved in 20 ml of a 10% solution of triethylamine in absolute methanol and left at 37° for 13 h. The solution is evaporated to dryness; the residue is dried for several hours at 50–60° and 1 mm, dissolved in 1 ml of alcohol, and 4 ml of acetone and 15 ml of ether are added. The white precipitate that separates is isolated, washed with ether, and dried. Yield 0.10 g (100%). The preparation is recrystallized again from alcohol, completing the crystallization by the addition of acetone and ether. The crystals obtained are isolated, washed with ether, and dried in vacuo over P_2O_5 at 61°. $[\alpha]_D - 60 \pm 1°$

* A partially decomposed chloride was used in the synthesis (see the preceding note). This apparently explains the relatively low yield of the ortho ester.

(C 1.86; H_2O); mp 158.5–159° (corr.); a mixed sample with an authentic specimen gives no depression of the melting point.

Literature data ([3]): mp 161–163°; $[\alpha]_D - 64^\circ$ (H_2O).

Found, %: C 41.66; 41.87; H 7.15; 7.27
$C_{12}H_{24}O_{11}$. Calculated, %: C 41.85; H 7.03

The preparation is chromatographically homogeneous (system B) and identical with an authentic specimen.

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Received
16 X 1964

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Note: Figure translations are in progress. See original paper for figures.