ACYCLIC-SUGAR NUCLEOSIDE ANALOGS. THYMINE DERIVATIVES FROM ACYCLIC D-GALACTOSE AND D-GLUCOSE PRECURSORS*†

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ABSTRACT

Fusion of 2,3,4,5,6-penta-*O*-acetyl-1-bromo-1-deoxy-1-*S*-ethyl-1-thio-*aldehydo*-D-galactose aldehydrol (**1**) with bis(trimethylsilyl)thymine (**2**) gave a 1-epimeric pair of acyclic-sugar nucleoside derivatives (**3a** and **3b**), which were saponified to their *O*-deacetylated analogs **4a** and **4b**. Similarly, the 1-methoxy (**5**) and 1-benzyloxy (**8**) analogs of the bromide **1** were converted into the corresponding protected nucleoside analogs **6** and **9**, respectively; subsequent saponification gave the corresponding *O*-deacetylated derivatives **7** and **10**. In the same way, 2,3,4,5,6-penta-*O*-acetyl-1-bromo-1-deoxy-1-*S*-ethyl-1-thio-*aldehydo*-D-glucose aldehydrol (**11**) was converted into the acyclic-sugar thymine nucleoside analog **13** by way of the pentaacetate **12**. Exposure of 1-deoxy-1-*S*-ethyl-1-thio-1-(thymin-1-yl)-*aldehydo*-D-galactose aldehydrol (**4**) to conditions of acetolysis led to the pentaacetate **3**, whereas similar treatment of the 1-(adenin-9-yl) analog (**14**) of **3** caused scission of the 1-substituents to give hepta-*O*-acetyl-*aldehydo*-D-galactose aldehydrol (**15**).

INTRODUCTION

Work in this laboratory has been concerned with (*a*) the synthesis of nucleoside analogs in which the sugar chain is acyclic, and (*b*) the quest for methods whereby the sugar chain can be cyclized, preferably into the furanoid form, without loss of the nucleoside base. In this paper is described the synthesis of acyclic-sugar nucleoside analogs containing the thymine residue and sugar chains derived from D-glucose and D-galactose. It is shown that, under conditions of acetolysis, one of these acyclic pyrimidine nucleoside analogs merely suffers acetylation of the sugar chain, whereas similar treatment of a purine analog[2] leads to cleavage of the nucleoside base.

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RESULTS AND DISCUSSION

The objective of this work was to obtain nucleoside analogs having thymine as the base, and the ethylthio, methoxy, or benzyloxy substituent at C-1 in the acyclic D-galactose structure; the well-known propensity of D-galactose derivatives to undergo conversion into furanoid systems under demercaptalation and other ring-closure conditions provided the incentive for choosing the D-galactose system for detailed evaluation.

In the earlier work[1,2], the method of Davoll and Lowy[3], involving reaction of 6-acetamido-9-(chloromercuri)purine with the appropriate glycosyl halide, was employed to prepare acyclic-sugar purine nucleoside analogs, by use of an appropriate acyclic 1-halogeno sugar derivative. Extension of the Davoll–Lowy method for synthesis of thymine analogs, by use of dithyminylmercury under the conditions of Fox and co-workers[4], had been used successfully in the preparation of 1-deoxy-1-*O*-methyl-1-(thymin-1-yl)-*aldehydo*-D-galactose aldehydrol[1] (**7**). However, difficulties were encountered in attempts to extend the method; condensation of 2,4,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α-D-glucopyranosyl bromide with dithyminylmercury yielded only the *O*-glycosyl derivative[5], and repeated attempts to condense 2,3,4,5,6-penta-*O*-acetyl-1-bromo-1-deoxy-1-*S*-ethyl-1-thio-*aldehydo*-D-galactose aldehydrol (**1**) with dithyminylmercury were unsatisfactory. More-satisfactory results were obtained in this work by application of the fusion method[6].

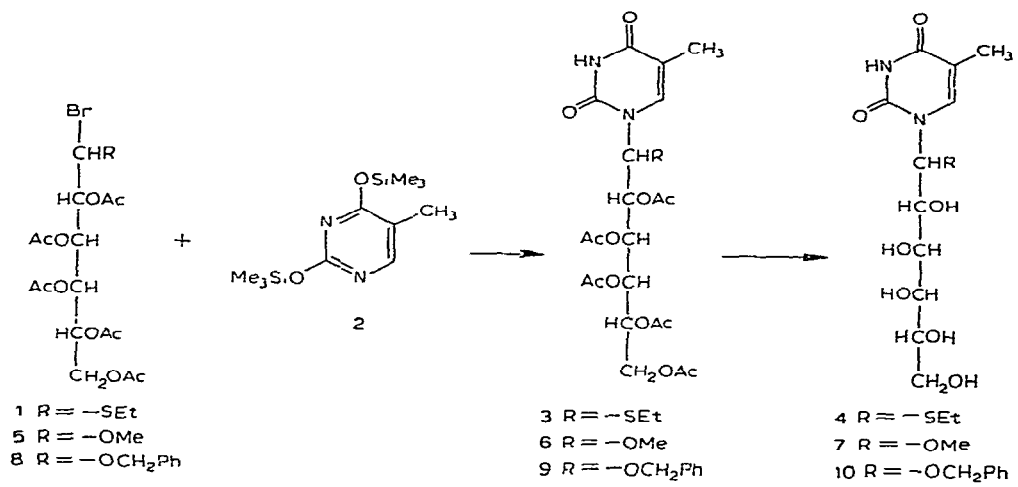
The bromide **1** was fused with bis(trimethylsilyl)thymine[7] (**2**), and the resultant product was treated with water to hydrolyze *O*-trimethylsilyl groups. There was obtained a separable mixture of 1-epimeric, acetylated derivatives **3a** and **3b**, both crystalline; a dextrorotatory epimer was obtained in 7% yield and a levorotatory epimer in 43% yield. *O*-Deacetylation with a boiling solution of butylamine[8] in methanol under reflux gave the corresponding pentols **4a** and **4b**, that from the dextrorotatory pentaacetate being crystalline. The configuration at C-1 of these products was not determined.

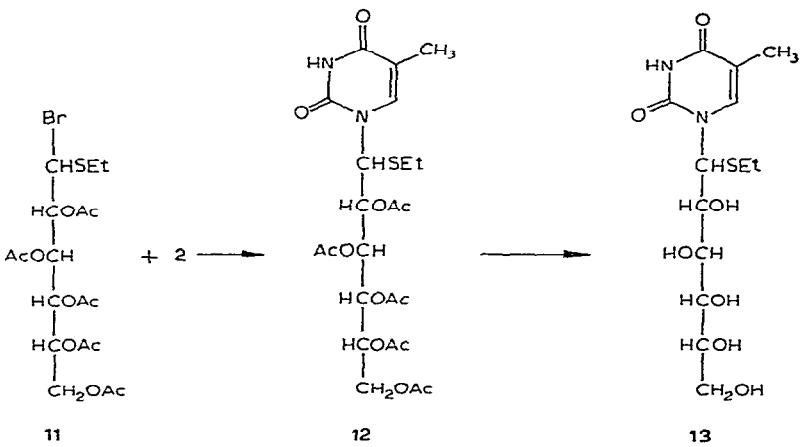
Fusion of the D-*gluco* analog[9] (**11**) of the bromide **1** with bis(trimethylsilyl)-thymine (**2**), and hydrolysis of the *O*-trimethylsilyl groups, gave the syrupy, protected nucleoside **12** which, on saponification with methanolic ammonia, gave a crystalline 1-deoxy-1-*S*-ethyl-1-thio-1-(thymin-1-yl)-*aldehydo*-D-glucose aldehydrol (**13**) in 51% yield; only a single form was encountered.

Fusion of 2,3,4,5,6-penta-*O*-acetyl-1-bromo-1-deoxy-1-*O*-methyl-*aldehydo*-D-galactose aldehydrol (**5**) with bis(trimethylsilyl)thymine (**2**), followed by hydrolysis of the *O*-trimethylsilyl groups, led to a crystalline, acetylated nucleoside derivative **6**, isolated in 50% yield; on *O*-deacetylation with methanolic ammonia, it gave crystalline 1-deoxy-1-*O*-methyl-1-(thymin-1-yl)-*aldehydo*-D-galactose aldehydrol (**7**), identical with a sample earlier prepared[1] by the Davoll–Lowy method.

Similarly, fusion of 2,3,4,5,6-penta-*O*-acetyl-1-*O*-benzyl-1-bromo-1-deoxy-*aldehydo*-D-galactose aldehydrol[1] (**8**) with bis(trimethylsilyl)thymine (**2**) gave, in 55%

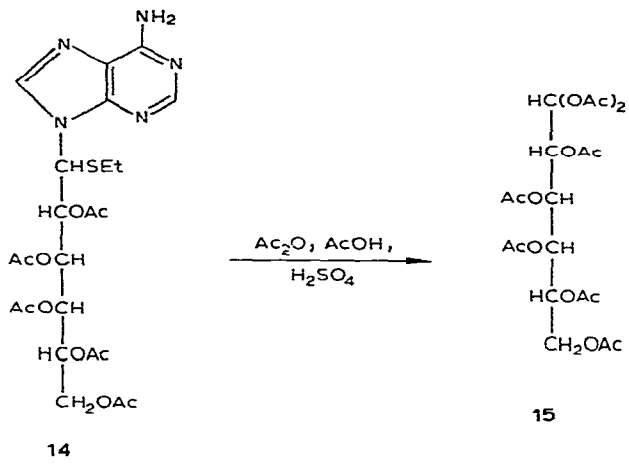
yield, a crystalline, acetylated nucleoside derivative **9** which, with methanolic ammonia, gave the crystalline, *O*-deacetylated analog **10**.





Treatment of the acylic-sugar nucleoside derivative **4** with 1:1 acetic acid–acetic anhydride containing sulfuric acid (acetolysis conditions) gave, in low yield, the acetylated, acyclic-sugar nucleoside derivative **3** as the only product isolated. Similar treatment of 2,3,4,5,6-penta-*O*-acetyl-1-(adenin-9-yl)-1-deoxy-1-*S*-ethyl-1-thio-*aldehydo*-D-galactose aldehydrol[2] (**14**), but with a lower concentration of acid, led to scission of the purine moiety and the recovery, in 25% yield, of hepta-*O*-acetyl-*aldehydo*-D-galactose aldehydrol[10] (**15**).

Further work on the cyclization reactions of these nucleosides is in progress.



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EXPERIMENTAL

General methods. — I.r. spectra were recorded with a Perkin–Elmer Infracord spectrophotometer, and u.v. spectra with a Bausch & Lomb Spectronic 505 spectrophotometer. X-Ray powder diffraction data give interplanar spacings in Å for CuKα radiation (camera diameter = 114.59 mm). Relative intensities were estimated visually: m, moderate; s, strong; v, very; w, weak. The stronger lines are numbered in order (1, strongest). Polarimetric readings were obtained in a 2-dm tube. Microanalyses were performed by W. N. Rond of this laboratory.

2,3,4,5,6-Penta-O-acetyl-1-deoxy-1-S-ethyl-1-thio-1-(thymin-1-yl)-aldehydo-D-*galactose aldehydrol* (**3**). — 2,3,4,5,6-Penta-*O*-acetyl-1-bromo-1-deoxy-1-*S*-ethyl-1-thio-*aldehydo*-D-galactose aldehydrol[9] (**1**, 20 g) was intimately mixed with bis(trimethylsilyl)thymine[7] (**2**, 13.6 g), and the mixture was placed in a 250-ml flask. The flask was then closed, and evacuated with a water aspirator. The mixture was gradually heated to 150° in an oil bath, and the flask was intermittently re-evacuated. After 20 min, the flask and contents were cooled, the pale-yellow residue was mixed with aqueous sodium acetate and ethanol, and the mixture was warmed and then evaporated to dryness. The residue was extracted with chloroform, the extract was filtered, and the filtrate was washed, dried, and evaporated. The syrup thus obtained was crystallized from methanol, to give a dextrorotatory product (**3a**); yield 1.5 g (7%), m.p. 211°, $[\alpha]_D^{21}$ +53.5° (*c* 2.4, chloroform); λ_{max}^{EtOH} 212 (ε 8,150), 268 nm (9,520); λ_{max}^{KBr} 2.95 (OH), 3.1 (NH), 5.7 (OAc), 5.9 (thymine), 6.85, 7.3, 8.1–8.3 (ester), 9.7, 10.5, and 11.7 μm; X-ray powder diffraction data: 3.85 w, 7.08 vs (1), 6.11 vs (2), 5.44 m, 4.96 s, 4.53 m, 4.04 m, 3.69 m, 3.55 s, 3.41 m, 3.27 m, 2.96 m, 2.19 w, and 2.09 s.

Anal. Calc. for $C_{23}H_{32}N_2O_{12}S$: C, 49.28; H, 5.72; N, 5.00; S, 5.72. Found: C, 49.52; H, 5.92; N, 5.33; S, 5.56.

The mother liquor was evaporated, the material was treated with ether, and the resultant crystals of levorotatory product (**3b**) were filtered off; yield 9.0 g (43%), m.p. 152°, $[\alpha]_D^{21}$ −88.5° (*c* 2.9, ethanol); λ_{max}^{EtOH} 212 (ε 8,350), 268 nm (8,890); λ_{max}^{KBr} 2.9 (OH), 3.1 (NH), 5.7 (OAc), 5.9 (thymine), 6.9, 7.3, 8.1–8.3 (ester), 9.7, 10.5, 11.7, and 12.3 μm; X-ray powder diffraction data: 9.83 s, 7.9 vs (1), 7.63 s, 6.97 m, 6.28 m, 5.87 vs (3), 4.87 w, 4.72 m, 4.37 s, 3.99 vs (2), 3.79 m, 3.38 m, and 3.22 m.

Anal. Calc. for $C_{23}H_{32}N_2O_{12}S$: C, 49.28; H, 5.72; N, 5.00; S, 5.72. Found: C, 49.34; H, 5.43; N, 5.30; S, 5.95.

1-Deoxy-1-S-ethyl-1-thio-1-(thymin-1-yl)-aldehydo-D-*galactose aldehydrol.* — *Dextrorotatory epimer* (**4a**). The pentaacetate **3a** having m.p. 211° (0.5 g) was treated with boiling methanol (15 ml) and butylamine (0.15 ml) for 6 h under reflux. The mixture was evaporated to dryness, and the residual syrup chromatographed on two silica-gel plates by using 4:1 (v/v) ethyl acetate–methanol as the developer. The band having R_F 0.5 was isolated, and obtained from acetone–ethanol as a solid; yield 0.2 g (65%), m.p. 145–150°, $[\alpha]_D^{20}$ +98° (*c* 3.2, methanol); λ_{max}^{EtOH} 215 (ε 7,950), 273 nm (9,175); λ_{max}^{KBr} 2.9–3.1 (OH), 5.95 (thymine), 6.8, 7.3, 8.0, 8.2, 9.1, and 9.7 μm.

Anal. Calc. for $C_{13}H_{22}N_2O_7S$: C, 44.57; H, 6.29; N, 8.00; S, 9.15. Found: C, 44.36; H, 6.03; N, 8.23; S, 8.71.

Levorotatory epimer (**4b**). The pentaacetate **3b** having m.p. 152° (1.0 g) was *O*-deacetylated by treatment with boiling methanol (25 ml) and butylamine (0.3 ml) for 6 h under reflux. The product was purified by chromatography as for **4a**, to give **4b** as a glass; yield 520 mg (83%), $[\alpha]_D^{20}$ −95° (*c* 3.1, methanol); λ_{max}^{EtOH} 215 (ε 7,200), 273 nm (8,200); λ_{max}^{KBr} 2.9–3.1 (OH), 6.0 (thymine), 6.8, 7.5, 8.0, 8.2, 9.1, and 9.7 μm.

Anal. Calc. for $C_{13}H_{22}N_2O_7S$: C, 44.57; H, 6.29; N, 8.00; S, 9.15. Found: C, 44.25; H, 6.51; N, 8.08; S, 8.74.

2,3,4,5,6-Penta-O-acetyl-1-deoxy-1-O-methyl-1-(thymin-1-yl)-aldehydo-D-*galactose aldehydrol* (**6**). — 2,3,4,5,6-Penta-*O*-acetyl-1-bromo-1-deoxy-1-*O*-methyl-*aldehydo*-D-galactose aldehydrol[9] (**5**, 7.2 g) was intimately mixed with bis(trimethylsilyl)thymine (**2**, 6.0 g), and the mixture was heated in an evacuated flask. At 125–130°, a clear melt was formed with frothing. After 20 min, the flask was cooled under evacuation and opened, and the contents were triturated with 95% methanol. The mixture was evaporated to dryness, and the residue extracted with chloroform. The extract was filtered, dried, and evaporated, and the residual syrup was crystallized from ethanol; yield 4.0 g (50%), m.p. 164°, $[\alpha]_D^{21}$ +17.0° (*c* 3.4, chloroform); λ_{max}^{EtOH} 210 (ε 7,500), 263 nm (8,800); λ_{max}^{KBr} 2.9 (OH), 3.1 (NH), 5.7 (OAc), 5.9 (thymine), 6.8, 7.3, 8.1–8.3 (ester), 9.0, 9.6, 10.4, 11.8, and 12.9 μm; X-ray powder diffraction data: 12.28 s, 8.85 vs (3), 6.66 vs (1), 6.28 m, 5.68 s, 4.93 vs (2), 4.48 m, 4.25 s, 3.97 s, 3.72 s, 3.53 s, 3.38 m, 3.21 s, and 3.06 s.

Anal. Calc. for $C_{22}H_{30}N_2O_{13}$: C, 49.80; H, 5.65; N, 5.27. Found: C, 49.53; H, 5.82; N, 5.41.

1-Deoxy-1-O-methyl-1-(thymin-1-yl)-aldehydo-D-*galactose aldehydrol*[1] (**7**). — A solution of compound **6** (310 mg) in methanol (10 ml) was saturated at 0° with ammonia. After 16 h at room temperature, the solution was concentrated until crystalliza-

tion commenced. Recrystallization from 90% methanol gave **7**; yield 160 mg (90%), m.p. 202–203°. The mixed m.p. with a sample prepared by a different route was undepressed, and the X-ray powder patterns of the two products were identical.

*2,3,4,5,6-Penta-*O*-acetyl-1-deoxy-1-*O*-benzyl-1-(thymin-1-yl)*-aldehydo-D-*galactose aldehydrol* (**9**). — A mixture of 2,3,4,5,6-penta-*O*-acetyl-1-*O*-benzyl-1-bromo-1-deoxy-*aldehydo*-D-galactose aldehydrol[1] (**8**, 2.4 g) and bis(trimethylsilyl)-thymine (**2**, 2.0 g) was treated for 20 min under vacuum in an oil bath at 160°. The flask was cooled, and the mixture processed as for **3** and **6**, to give a colorless product that crystallized from aqueous methanol; yield 1.4 g (55%), m.p. 106°, $[\alpha]_D^{22}$ −27.5° (*c* 3.2, chloroform); λ_{max}^{EtOH} 210 (ε 13,200), 264 nm (8,700); λ_{max}^{KBr} 2.9 (OH), 3.1 (NH), 5.7 (OAc), 5.9 (thymine), 6.9, 7.3, 8.1–8.3 (ester), 9.2, 9.7, 13.2, and 14.2 μm; X-ray powder diffraction data: 14.03 m, 12.11 m, 10.40 s, 8.51 w, 6.86 vs (1), 611 m, 5.64 w, 5.13 vs (2), 4.93 m, 4.72 m, 4.27 m. 4.10 m, 3.93 w, 3.77 w, 3.56 vs (3), and 3.40 s.

Anal. Calc. for $C_{28}H_{34}N_2O_{13}$: C, 55.45; H, 5.61; N, 4.62. Found: C, 55.30; H, 5.91; N, 4.62.

*1-Deoxy-1-*O*-benzyl-1-(thymin-1-yl)*-aldehydo-D-*galactose aldehydrol* (**10**). — A solution of compound **9** (310 mg) in methanol (15 ml) was saturated with ammonia at 0°, and kept for 18 h at room temperature. The solution was concentrated until crystallization occurred, and the product (**10**) was recrystallized from methanol; yield 190 mg (95%), m.p. 243°, $[\alpha]_D^{22}$ −80° (*c* 0.7, 5:3 ethanol–water); $\lambda_{max}^{H_2O}$ 211 (ε 13,100), 268 nm (9,300); λ_{max}^{KBr} 2.9 (OH), 3.1 (NH), 5.8, 6.0 (thymine), 6.8, 8.0, 8.1, 9.1, 9.4, 10.8, 13.3, and 14.3 μm; X-ray powder diffraction data: 13.19 vs (1), 7.76 vs (2), 6.71 m, 6.15 m, 5.44 vs (3), 5.17 s, 4.72 s, 4.51 s, 4.37 s, 3.93 s, 3.79 m, 3.58 s, 3.35 s, 3.21 s, 2.99 s, and 2.76 s.

Anal. Calc. for $C_{18}H_{24}N_2O_8$: C, 54.54; H, 6.06; N, 7.05. Found: C, 54.47; H, 6.45; N, 7.25.

*1-Deoxy-1-*S*-ethyl-1-thio-1-(thymin-1-yl)*-aldehydo-D-*glucose aldehydrol* (**13**). — Syrupy 2,3,4,5,6-penta-*O*-acetyl-1-bromo-1-deoxy-1-*S*-ethyl-1-thio-*aldehydo*-D-glucose aldehydrol[9] (3.0 g), prepared by the method of Weygand *et al.*[9], was mixed with bis(trimethylsilyl)thymine (3.0 g), and the mixture was heated to 140° under diminished pressure. After complete fusion had occurred, the flask was cooled under evacuation, and opened. Aqueous ethanol was added, and the mixture was heated to boiling, and then cooled and evaporated to dryness. The residue was extracted with chloroform, and the extract filtered. The filtrate was washed with water, dried, and evaporated, to give the acetate **12** as a glass (2.2 g). This product (1.24 g) was dissolved in methanol (30 ml), and the solution saturated with ammonia at 0°. After 24 h at 0°, evaporation gave a syrup that crystallized from aqueous ethanol to give **13**; yield 360 mg (51%), m.p. 166–167°, $[\alpha]_D^{23}$ −135° (*c* 2.0, water); $\lambda_{max}^{H_2O}$ 272 nm (ε 13,700); λ_{max}^{KBr} 2.90 (OH), 5.90 (thymine), 6.85, 7.90, 9.18, 9.30, and 9.75 μm; X-ray powder diffraction data: 7.79 vs (1), 7.10 vw, 6.30 vw, 5.57 s (2), 5.16 w, 4.77 m, 4.54 m, 4.34 m, 3.97 m, 3.76 s (3), 3.58 vw, 3.44 m, 3.25 w, 3.13 m, 3.03 vw, and 2.91 vw.

Anal. Calc. for $C_{13}H_{22}N_2O_7S$: C, 44.57; H, 6.29; N, 8.00; S, 9.15. Found: C, 44.82; H, 6.50; N, 8.15; S, 8.86.

Acetolysis of 1-deoxy-1-S-ethyl-1-thio-1-(thymin-1-yl)-aldehydo-D-*galactose aldehydrol* (**4b**). — 2,3,4,5,6-Penta-*O*-acetyl-1-deoxy-1-*S*-ethyl-1-thio-1-(thymin-1-yl)-*aldehydo*-D-galactose aldehydrol having m.p. 152° (**3b**, 1.0 g) was dissolved in abs. methanol (25 ml), and a small piece of sodium metal was added. After 3 h, the solution was evaporated to dryness. The residue (0.5 g) was dissolved in a mixture of acetic acid (5 ml) and acetic anhydride (5 ml). The solution was cooled to 0°, and concentrated sulfuric acid (5 ml) was added at 0°. After 1 h at 0°, the mixture was treated with an excess of aqueous sodium hydrogen carbonate, the slurry was diluted with chloroform, and shaken, and the chloroform layer was separated, successively washed with cold, aqueous sodium hydrogen carbonate and water, dried, and evaporated. The residual syrup crystallized on trituration with ether; yield 180 mg (18%), m.p. 151–152°; X-ray powder diffraction pattern identical with that of compound **3b**.

*Acetolysis of 2,3,4,5,6-penta-*O*-acetyl-1-(adenin-9-yl)-1-deoxy-1-S-ethyl-1-thio-*aldehydo-D-*galactose*[2] (**14**). — A solution of compound **14** (2.0 g) in acetic acid (10 ml) and acetic anhydride (10 ml) was treated at 0° with concentrated sulfuric acid (1 ml). After 1 h at room temperature, the solution was treated with an excess of sodium hydrogen carbonate. The suspension was extracted with chloroform, and the extract filtered, washed, dried, and evaporated, to give a syrup (1.49 g) that crystallized from isopropyl alcohol; yield 400 mg (25%), m.p. 100–104°, $[\alpha]_D^{22}$ +12° (*c* 0.7, chloroform). The product was identical with hepta-*O*-acetyl-*aldehydo*-D-galactose aldehydrol[10] (**15**); lit.[10] m.p. 106°, $[\alpha]_D$ +4° (in chloroform).

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