Note

An evaluation of methods for the preparation of 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose. Oxidation of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose with lead tetraacetate–pyridine

D. J. WARD, W. A. SZAREK, AND J. K. N. JONES
Department of Chemistry, Queen's University, Kingston, Ontario (Canada)
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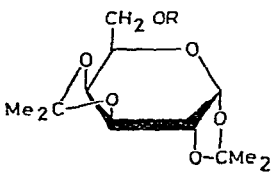
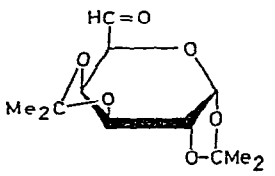
A key intermediate in two syntheses[1,2] of the antibiotic lincomycin is 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose (**2**). Several chain-extension reactions have been performed with this aldehyde, namely, those involving treatment with ethynylmagnesium bromide[3], benzylamine and hydrogen cyanide[4], vinylmagnesium bromide[5,7], nitroethane[5], ethylidenetriphenylphosphorane[6,7], or sodium cyanide[2]. Although a number of procedures have been described for the preparation of compound **2**, by oxidation of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**1**), technical difficulties, as regards the isolation of a pure product aldehyde, have frequently been encountered. The continued synthetic utility of compound **2** has prompted us, therefore, to undertake an evaluation of methods for its preparation; a new procedure is described, namely, oxidation of **1** with lead tetraacetate–pyridine.



1 R = H
3 R = CH_2SMe
4 R = Ac



2

All of the published methods for the conversion of **1** into **2** have involved oxidations in methyl sulfoxide; a variety of activating electrophiles has been used. Thus, Horton *et al.*[8], using the Pfitzner–Moffatt reagent[9] (methyl sulfoxide–*N,N'*-dicyclohexylcarbodiimide–pyridinium phosphate), obtained the crude 6-*aldehydo* derivative **2** in 80% yield, and a highly purified product in 46% yield after two fractional distillations. In this laboratory, with pyridine hydrochloride as the proton source, the preparation of **2** in a chromatographically homogeneous state in 83% yield was reported[5] originally; however, subsequent experimentalists have frequently experienced difficulty in the separation of the product aldehyde from the dicyclohexyl-

urea byproduct. Saeki *et al.*[4] prepared **2** by treatment of **1** with *N,N'*-dicyclohexylcarbodiimide in methyl sulfoxide in the presence of phosphoric acid; in our hands, by this method after 18 h, compound **2** was obtained in 73% yield together with about 10% of the 6-(methylthio)methyl ether[10] (**3**) of **1**. A separation of these two components is conveniently achieved by partitioning between petroleum ether (b.p. 100–120°)–water, as a consequence of the ready solubility of **3** in the organic solvent. It has been reported[2] that the use of 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate in place of *N,N'*-dicyclohexylcarbodiimide in an oxidation in methyl sulfoxide gave a good result without contamination by a urea derivative. In the present work, when this modified procedure* was applied to **1**, even after 36 h, only the presence of starting material could be detected by t.l.c. Godman and Horton[10] have shown that treatment of **1** with methyl sulfoxide–acetic anhydride gave only a small proportion of the aldehyde **2**. Instead, the principal product was the 6-(methylthio)methyl ether (**3**); a small amount of the 6-acetate (**4**) was also formed. The final published method for the preparation of **2** from **1** is that of Cree *et al.*[11], who used a modified oxidant, developed by Parikh and Doering[12], consisting of methyl sulfoxide, sulfur trioxide, pyridine, and triethylamine. In our hands†, after only 45 min, compound **2** was obtained in 71% yield together with about 12% of the derivative **3**. The application of the procedure employed by Onodera *et al.*[13] (methyl sulfoxide–phosphorus pentaoxide) for the oxidation of hydroxyl groups in sugar derivatives was also investigated in the present work. It was found that, even after 95 h, only a 63% yield of compound **2** was obtained; compound **3** was also formed in about 10% yield. Finally, a new procedure for the preparation of compound **2** was developed, namely, oxidation of **1** with the lead tetraacetate–pyridine reagent introduced by Partch[14].

Attempted oxidations of "isolated" hydroxyl groups in sugar derivatives with lead tetraacetate in pyridine have been reported previously. It has been shown[15] that lead tetraacetate in pyridine had no detectable effect on 1,6-anhydro-2,3-*O*-isopropylidene-*β*-D-mannopyranose under anhydrous conditions, and that addition of a trace of water gave partially the 4-acetate of this substrate as the sole new product. Furthermore, no oxidation of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose was observed with lead tetraacetate–anhydrous pyridine, but addition of a trace of water in this case afforded partially the 1-acetate and 2,3:5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone. In the present work, treatment of compound **1** with lead tetraacetate in pyridine gave in 18 h a 74% yield of the desired aldehyde **2**; the only byproducts were the 6-acetate **4** (10%) and unreacted alcohol **1** (12%). Similar results have been obtained by Partch[14] with several primary and secondary alcohols. Compounds **1** and **4** could easily be separated from the aldehyde by crystallization and chromatography on silica gel. A particular virtue of this method for the preparation of **2** is the fact that the starting material (**1**) can be easily regenerated from the

*1-Cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate was purchased from Aldrich Chemical Co., Inc., Milwaukee, Wisc.

†Pyridine–sulfur trioxide (practical grade) was purchased from Eastman Organic Chemicals, Rochester, N.Y.

acetate byproduct, and then treated again with the oxidation reagent. It is important that freshly prepared lead tetraacetate be used, since low yields of the aldehyde were obtained with lead tetraacetate that had been stored in a desiccator or under glacial acetic acid for only 4 days.

Although the oxidation of **1** by lead tetraacetate–pyridine is an effective and convenient method for the preparation of compound **2**, the scope of this reagent for the oxidation of "isolated" hydroxyl groups in sugar derivatives may be quite limited. Thus, in addition to the lack of any significant oxidation of the two mannose derivatives cited above[15], it has been shown, in the present work, that 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose was essentially unaffected by treatment with lead tetraacetate in pyridine for 36 h at room temperature; only a trace of the 1-acetate of the fructose derivative was formed.

EXPERIMENTAL

*Oxidation of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose* (**1**) *with lead tetraacetate in pyridine.* — A solution of **1** (Ref. 16) (1.75 g) in pyridine (10 ml) was added to a stirred solution of freshly prepared lead tetraacetate[17] (3.83 g) in pyridine (20 ml). After 18 h at room temperature, the deep red solution had become pale yellow. The solution was diluted then with chloroform (100 ml), and washed successively with water, M sulfuric acid, saturated sodium hydrogen carbonate solution, and water again; the dried (sodium sulfate) organic solution was evaporated to a syrup. T.l.c. on Silica Gel G, with 1:1 (*v/v*) ethyl acetate–petroleum ether (b.p. 60–80°) as the developing solvent and indication with sulfuric acid, showed the presence of a major component, R_F 0.5, and two minor components having R_F 0.3 (starting material **1**) and 0.66 (acetate **4**). The fastest-moving component was isolated by crystallization from an ethanolic solution of the syrup, which had been seeded with a small crystal of authentic 6-*O*-acetyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[18], yield 0.2 g (10%). The mother liquor from the crystallization was concentrated to dryness, and the residue was fractionated on silica gel, with 1:4 (*v/v*) petroleum ether (b.p. 40–60°)–ethyl acetate as eluant, to give chromatographically homogeneous **2** (1.3 g, 74%) and starting material **1** (0.2 g, 12%).

The (*p*-nitrophenyl)hydrazone was prepared from a solution of the syrupy aldehyde **2** (0.1 g) in methanol (10 ml) by adding (*p*-nitrophenyl)hydrazine (0.1 g), heating for 20 min at reflux temperature, evaporating, and following the published procedure[8] to give yellow needles, m.p. 208–209°, $[\alpha]_D^{23}$ −90° (*c* 1.5, chloroform); lit.[8] m.p. 214–215°, $[\alpha]_D^{22}$ −83.5° (*c* 1.0, chloroform).

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