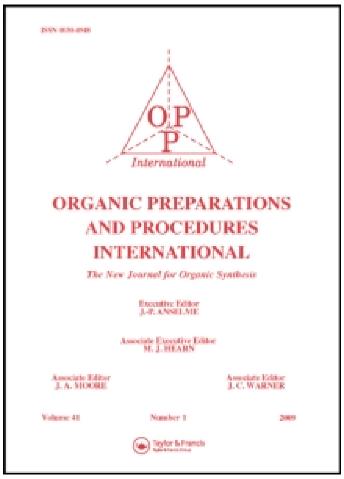

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IMPROVED PREPARATION OF DI-O-ISOPROPYLIDENE-1,2;5,6-D-MANNITOL

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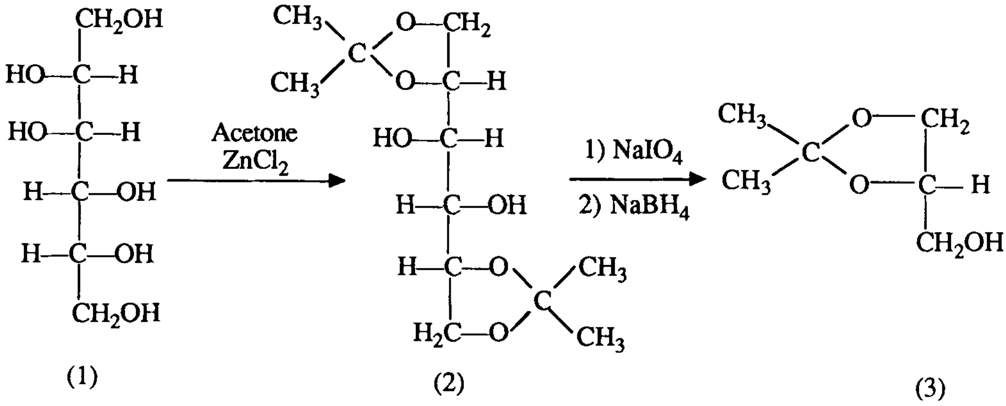
The O-isopropylidene-1,2-ns-glycerol (3) prepared via di-O-isopropylidene-1,2;5,6-D-mannitol (2) is an intermediate in the chemical synthesis of various optically active molecules of biological and/or pharmaceutical interest.[1] Its main and historical application has been in the preparation of glycerides and synthetic phospholipids,[2] and current interest involves the synthesis of fluorescent and/or photoactivable phospholipids, used largely as a probe of the dynamics of biological cell membranes and phospholipid-protein interactions.[3] O-Isopropylidene-1,2-ns-glycerol (3) is also a precursor of (R)- and (S)-epichlorohydrin, which is an intermediate in the preparation of several useful compounds.[4] Other applications of (R) and (S)-acetone glycerols are the preparations of biologically active molecules such as prostaglandin E_1, brefeldine A, and pharmacological β-blockers.[5] Finally, O-isopropylidene-1,2-ns-glycerol is a key intermediate in the synthesis of PAF acether (platelet activating factor) and its related analogs.[6]

There basically are two procedures to prepare di-O-isopropylidene-1,2;5,6-D-mannitol from D-mannitol, one by reaction with 2-methoxypropene in N,N-dimethylformamide (trace of p-toluenesulfonic acid)[7] or two by acetonation (Lewis acids) as shown in the Scheme.[8] Both methods have advantages and disadvantages. The first gives good yield, (83% vs 50-55%), but the product is of questionable purity.[7] Under similar conditions, mixtures of di-O-isopropylidene-D-mannitol isomers (1,2;5,6)-(1,2;4,6)-(1,2;3,4) and of monoisopropylidene-D-mannitol were obtained, thus requiring further separation by column chromatography.[7] In addition, this expensive technique is difficult to adapt on a large scale. The second route, although more tedious and longer, is cheaper, taking into account the cost



Scheme 1

of the reagents and solvents; in addition production on a large scale can be easily carried out. For several years,[9] we have been preparing 2 by the method of Baer.[10] Due to the increased interest of this intermediate, it was important to devise a procedure which was both simple and inexpensive which is now described below.

Several parameters can be adjusted in this preparation: 1) the ratio D-mannitol/$ZnCl_2$acetone, 2) the reaction time, 3) the temperature, 4) the procedure used to stop the reaction and to neutralize the zinc chloride (this is determinant for the final yield) and 5) the recrystallization solvent. Most of these parameters were tested and the results show that the optimal conditions involve the use of a ratio of 1:2:8 of D-mannitol-zinc chloride-acetone for 18 hrs at 25°; this procedure provides the best yield (61%), avoids the filtration step and permits work on large scale. Since 2 is poorly soluble in hot hexane under reflux (1 g for 100-150 ml), this solvent is inadequate. Crystallization from a mixture of chloroform-hexane is possible, but the residual acidity can promote the reverse reaction. A mixture of toluene-hexane is to be preferred to benzene-hexane since toluene is less toxic than benzene and is a better solvent at its boiling point for 2. A small amount of tri-O-isopropylidene-1,2;3,4;5,6-D-mannitol was isolated.

EXPERIMENTAL SECTION

D-mannitol, zinc chloride, anhydrous potassium carbonate from Aldrich are purum grade (98%). ACS grade reagents give slightly better results. Zinc chloride is melted before use. Acetone (purum grade) is dried over anhydrous potassium carbonate (200 g of K_2CO_3 for 2.5 L of acetone). Toluene, hexane (or petroleum ether 40-60°) are purum grade. Mps. are measured on a Kofler hot bench. Optical rotations were measured with a ROUSSEL micropolarimeter; NMR spectra were recorded at 60 MHz (^1H) on a VARIAN 60 and at 200 MHz (^1H) and (^{13}C) on a BRUKER AC 200 spectrometer (solvent $CDCl_3$ with TMS as internal reference).

Di-O-Isopropylidene-1,2;5,6-D-mannitol (Diacetone-D-mannitol).- Melted zinc chloride (182 g, 1.34 mole) was dissolved in 750 ml of anhydrous acetone in a 2 L flask equipped with a mechanical stirrer. The dissolution which was slightly exothermic, was complete within 0.5 hr. Then, D-mannitol (91 g, 0.5 mole) was added to the solution at room temperature; the mixture became slightly turbid. It was stirred for 18 hrs at 750 RPM and a clear, slightly colored solution was formed. At this time, 460 g of previously pulverized and sieved anhydrous potassium carbonate was added. After 1 hr stirring, 10 ml of water was added every 0.5 hr in order to bring the pH to 8-9 (60 to 120 ml total); stirring was continued 1 hr more. The insoluble material was allowed to settle and the supernatant solution was filtered using a sintered glass funnel (porosity 3). Then 400 ml of acetone was added to the insoluble material in the reaction flask, stirred for 0.5 hr and the process was repeated twice more. The combined filtrates (~ 2 L of solution) were concentrated under vacuum and the resulting solid mass was dried in a vacuum desiccator, either for 1 hr at 50° or for several hours at room temperature, before recrystallization (mp. 100-106°). The resulting product was dissolved in 200 ml of hot toluene under reflux. In case of turbidity or the presence of insoluble material, the solution was filtered using sintered glass funnel. While the solution was cooling, 200 ml hexane or petroleum ether was added. The solution was left standing for 12 to 18 hrs at room temperature, after which the precipitate was collected and washed twice with 100 ml of hexane. The average yield of several preparations was 80 g (60%), mp. 119-121°, lit.[8] mp. 118-119°, $[\alpha]_D$ = +7.5-8.3° ($CHCl_3$); if the mp. is unsatisfactory, the material should be recrystallized again.

^1H NMR ($CDCl_3$): δ 1.36 (s, 6H) and 1.4 (s, 6H $2Me_2C$), 2.85 (d, 2H, J = 7 Hz, 2 OH), 3.75 (dd, 2H, J = 6 and 7 Hz, $\underline{H}$-C_3-OH and $\underline{H}$-C_4-OH), 4.05 (ddd, 2H, J = 4.5,6 and 7 Hz, $\underline{H}$-C_2-O and $\underline{H}$-C_5-O) and 4.17 (m, 4 H, $\underline{H_2}C_1$-O and $\underline{H_2}C_6$-O).

The filtrate obtained after separation of the di-O-isopropylidene-1,2;5,6-D-mannitol was concentrated under vacuum to give an oily residue which was extracted twice with 100 ml of hexane under stirring for 0.5 hr. The extracts were concentrated to dryness and diluted with 20 ml of ethanol and 20 ml of water. After 24 hrs the precipitate was collected and washed with a little volume of a mixture ethanol-water (1/1) to give 2-3 g tri-acetone D-mannitol, mp. 69°, $[\alpha]_D$ = +13.8° ($CHCl_3$), lit. mp. 70° and $[\alpha]_D$ = +13.8° ($CHCl_3$);[9] mp. 69°, $[\alpha]_D$ = +13.6° (CH_2Cl_2).[9] The amount of triacetone D-mannitol is low and does not increase with reaction time as one might expect.

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