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Practical One Pot Synthesis of 2,3-O-Isopropylidene-D-Glyceraldehyde: High Atom Economy, Yield and Recycling of the Starting Materials and Solvents

KEYWORDS: 2,3-O-isopropylidene-D-glyceraldehyde, Gemcitabine, Atom Economy, Green Chemistry, Recycling

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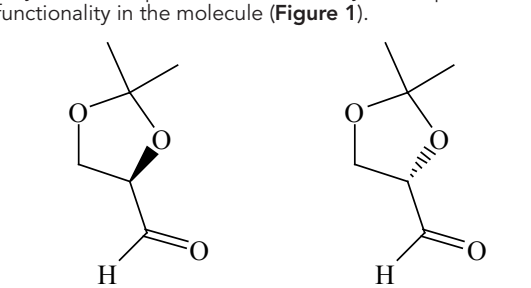
ABSTRACT *A practical and efficient protocol is developed for the synthesis of 2,3-O-isopropylidene-D-glyceraldehyde as a key raw material for the synthesis of gemcitabine hydrochloride. Our observations on differences in solubility based on the structure of the molecules lead us to recycling of the byproducts making the process highly atom efficient. Simple work up enables telescoping of the steps that makes the procedure high yielding and readily adaptable at industrial scale.*

Introduction

Contemporary asymmetric synthesis is a widely used method for stereocontrolled creation of C-C bonds in organic molecules (1). During recent years, this approach to organic synthesis has greatly contributed to progress in the directed introduction of various functionalities, and in the highly controlled formation of new centres of chirality. Preparation of the desired optical isomers by application of chiral starting materials is very advantageous, enabling precise planning and efficient realization of synthesis pathways (Chiron approach) (2).

Many monosaccharides and their readily available derivatives are versatile substrates for the synthesis of optically active target molecules. 2,3-O-isopropylideneglyceraldehyde is one of them; it is characterized by ready availability of both enantiomers from natural sources, and by pronounced versatility due to the presence of the aldehyde and protected diol functionality in the molecule (**Figure 1**).

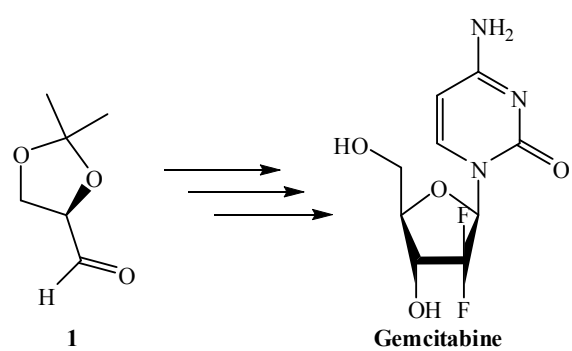


2,3-O-isopropylidene-D-glyceraldehyde **(1)** 2,3-O-isopropylidene-L-glyceraldehyde **(1a)**

Figure 1. Enantiomers of 2,3-O-isopropylideneglyceraldehyde

On account of the increasing interest of chemists in 2,3-O-isopropylidene-D-glyceraldehyde (**1**), reflected by the numerous number of relevant publications (3), and in view of our belief that its further potential applications may be very important. It has wide applications in stereocontrolled organic syntheses such as the reactions using the carbonyl group of aldehyde (**1**) to form a new centre of chirality (nucleophilic additions, aldol condensations and cycloadditions), chiral C_3-synthons, Wittig reactions and stereocontrolled functionalization of the resulting double bonds. As a very important member of chiral pool, it is widely used in natural product synthesis.

2,3-O-Isopropylidene-D-glyceraldehyde (**1**) is a key raw material for the synthesis of gemcitabine hydrochloride (**Figure 2**) (4,5). As were in the development of this anticancer agent we required an expedient, practical synthesis for 2,3-O-isopropylidene-D-glyceraldehyde (**1**) that would be readily adaptable to a multi-kilogram scale.



1 **Gemcitabine**

Figure 2: Synthesis of Gemcitabine

The number of reported procedures, for obtaining this material bears witness to the generally unsatisfactory nature of existing technologies for its synthesis. Our involvement with this compound as a key raw material required development of a robust, environmentally friendly process that should be adaptable on industrial scale.

We report here our findings, which represent improvements on existing literature procedures and provide access to 2,3-O-Isopropylidene-D-glyceraldehyde (**1**) of high quality, in an efficient, greener and reliable manner.

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Experimental Section

Preparation of 2,3-O-isopropylidene-D-Glyceraldehyde (1)

Charged mixture of D-mannitol (250g, 1.37 mol), p-toluene sulfonic acid (1.25g, 9 mmol), and 2,2-dimethoxy propane (400 ml, 3 mol) in dimethyl sulfoxide (425 mL) and mixture was stirred at room temperature 25-35°C for 16 h. After completion of reaction, the reaction mixture was poured into 5% sodium bicarbonate (4.5 L). The aqueous layer was washed with petroleum ether then aqueous layer was extracted with dichloromethane and washed with 5% sodium bicarbonate solution. In dichloromethane extract added saturated aqueous sodium bicarbonate (80 mL) and sodium periodate (300g, 1.4 mol) under stirring at 20-25°C. Stirring continued for further 2h at same temperature for the completion of reaction. After completion of reaction, the reaction mixture was filtered and the dichloromethane solution was carefully concentrated to a constant weight to yield the titled compound **1** (180g).

Liquid: 180g; overall yield: 50.4%. (While based on recovery of D-Mannitol: 90%).

IR (neat, cm^{-1}): 2990, 2940, 2890, 2820, 1730, 1375, 1250, 1215, 1150, 1070, 840; ^1H NMR (300 MHz; $CDC1_3$) δ 9.55 (d, 1H, *J* = 1.8 Hz), 4.25-4.28 (m, 1H), 4.05-3.93 (m, 2H), 1.42 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75 MHz; $CDC1_3$) δ 201.38, 110.79, 79.49, 65.11, 25.84, 24.73; Exact mass found 131.0710, calculated for $C_6H_{10}O_3$ (M+H) 131.0708.

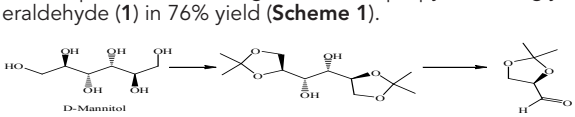
Conversion of tri- and mono-acetonide (4 and 5) to D-Mannitol

The petroleum ether solution after concentration afforded 131.3g (0.43 mol) triacetonide **4**. The DMSO solution after neutralization, concentration and water wash afforded 48.6g (0.22 mol) of monoacetonide **5.** Both the byproducts were mixed and taken up in acetonitrile:water (10:1) and trichloroacetic acid (5g, 0.03 mol) was added and the reaction mixture was refluxed for 2h and azeotropically distilled, after the complete removal of water further acetonitrile was added (solvent chasing), the reaction mixture was cooled and filtered to get the D-Mannitol (105g).

MP = 166-169°C.
Recovery of D-Mannitol = 89.79%

Results and Discussion

The first effective preparation of 2,3-O-isopropylidene-D-glyceraldehyde (**1**) was reported by Baer and Fischer in l939 (6,7). D-Mannitol, a naturally occurring inexpensive polyhydroxy compound was used as a starting material. Bis(acetonide) of D-mannitol (**3**) was prepared in 55% yield, and the resulting diol was cleaved with lead tetraacetate or sodium periodate (8,9) to give 2,3-O-isopropylidene-D-glyceraldehyde (**1**) in 76% yield (**Scheme 1**).



Scheme 1: Synthesis of 2,3-O-isopropylidene-D-glyceraldehyde (1)

In recent years, several modifications of this classical, but still most often applied method were reported. As concerns the first stage of preparation of compound **3** from D-Mannitol, modifications of Chittenden *et.al*. (10), Debost *et.al*. (11), and Kierstead *et.al*. (12) are noteworthy. The former modification involves the use of 2,2-dimethoxypropane (instead of acetone) in l,2-dimethoxyethane (Monoglyme), in the presence of tin(II) chloride.

The Difficulties with this modification are: (a) The yield of the process is only 40-45%; (b) Along with desired product 1,2-acetonide and 1,2:3,4:5,6-triacetonide are the impurities; (c) Huge amount of solvents dichloromethane and hexane were used for the recrystallization of diacetonoid (**3**).

The second one concerns the use of 2-methoxypropane in anhydrous dimethylformamide, in the presence of catalytic amounts of p-toluenesulfonic acid. The yield is comparable, only triacetonide was the impurity but the same difficulty for the recrystallization was encountered.

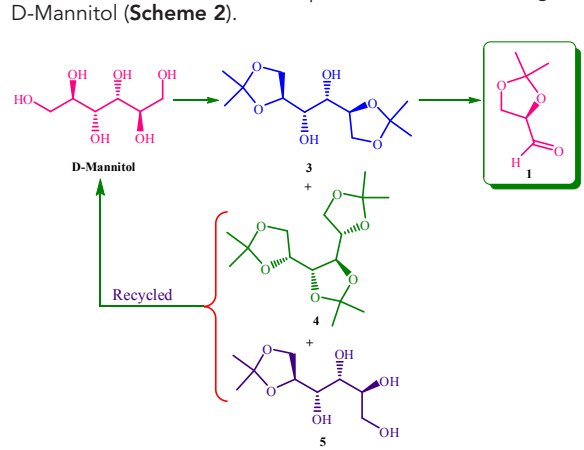
The latter modification consists of the action of 2,2-dimethoxypropane on D-mannitol in the presence of p-toluenesulfonic acid in dry dimethylsulfoxide as a solvent; this procedure affords only a slightly higher yield (62%).

Schmid et.al. (13) recently reported a large scale preparation method. In this process, they have used the first modification and avoided recrystallization and the reaction mass was directly used for the second step and distillation was carried out for the purification of bis acetonoid (**3**).

Tight control of reaction parameters is the limitation of this procedure, especially temperature control during distillation, since 2,3-O-isopropylidene-D-glyceraldehyde (**1**) is prone to undergo polymerization. Quite a significant amount of high boiling viscous material left as such after the distillation. The overall yield to the procedure is only 30%. The modification reported by Kierstead et.al. appeared to be promising for its combination of low catalyst load, reduction in solvent volume and simple work up that can enable telescoping of the steps.

Our initial examination of this procedure posed several problems for large scale one pot processing. Attempted recrystallizations of the crude bis acetonoid (**3**) from dichloromethane and hexane produce gelatinous material requiring large volumes of solvents. Use of other solvents gave similar results. Moreover the recrystallized material varied in quality and was eventually found to be contaminated with 5-10% of 1,2-monoacetonide (**5**) (**14**). Since the cleavage of bis acetonoid (**3**) would require 3 molar equivalent of oxidant to afford aldehyde (**1**), its presence was undesirable. The other major byproduct, triacetonide (**4**) was formed in 25% yield, it needs to be addressed.

Our improved process comprises of the following observations and modifications. D-Mannitol was directly converted to the desired 2,3-O-isopropylidene-D-glyceraldehyde (**1**). The reaction was carried out in bare minimum DMSO, after the completion of the reaction the reaction mixture was poured in 3% sodium carbonate solution, extracted with pet ether (60-80°C fraction). The aqueous layer was separated and extracted with dichloromethane. The dichloromethane layer is subjected to the vicinal diol cleavage reaction. While the pet ether extract contains selectively triacetonide **4** this on concentration and further aqueous acidic treatment gives D-Mannitol (**Scheme 2**).



Scheme 2: General scheme for the synthesis of aldehyde (1) with byproducts

Following are the salient features of our procedure: (a) In

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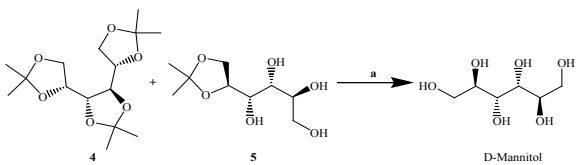
the first step along with the desired product two additional impurities **4** and **5** were also formed; (b) Impurity **4** that is triacetonide being non-polar could be extracted cleanly in petroleum ether; (c) While impurity **5** monoacetonide being more polar, prefers to remain in aqueous DMSO layer. So the work up was executed by pouring the reaction mass in 10 times water with respect to DMSO. The DMSO was chosen as a solvent because of its low emission and high boiling point that makes its recovery up to 95%. The monoacetonide (**5)** so obtained after distillation of DMSO could be cleaved to afford D-Mannitol (**Scheme 3**).



Scheme 3: Recycling of impurities 4 and 5 to D-Mannitol

The desired diacetonide **3** could be extracted in dichloromethane from aqueous DMSO layer. The dichloromethane layer as such could be taken up for the vicinal diol cleavage to yield the desired aldehyde (**1**) with excellent purity. This strategic work up ensures high yield, minimizes contaminations, handling losses and moreover circumvents cumbersome recystallization and high vaccum distillation.

Conclusions

This whole process ensures quality product with high yield, use of minimum amount of solvents with their recoveries, reduction in unit operations. The unavoidable impurities that are **4** and **5** are cleaved back to the starting material D-Mannitol. So it is evident that our process is atom economical on one hand and on the other green chemistry is demonstrated by literally nothing is drained out as an effluent. These results are more pronounced when producing the 2,3-O-isopropylidene-L-glyceraldehyde (**1a**) since it involves the precious unnatural L-Mannitol as the starting material.

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