Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# Preparation and Storage of (R)-2,3-O-Isopropylideneglyceraldehyde (D-Glyceraldehyde Acetonide)

L. W. Hertel [a], C. S. Grossman [a] & J. S. Kroin [a]
[a] Lilly Research Laboratories, Eli Lilly and Company Lilly Corporate Center Indianapolis, Indiana, 46285
Version of record first published: 23 Sep 2006.

To cite this article: L. W. Hertel , C. S. Grossman & J. S. Kroin (1991): Preparation and Storage of (R)-2,3-O-Isopropylideneglyceraldehyde (D-Glyceraldehyde Acetonide), Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 21:2, 151-154

To link to this article: http://dx.doi.org/10.1080/00397919108020805

SYNTHETIC COMMUNICATIONS, 21(2), 151-154 (1991)

# PREPARATION AND STORAGE OF (R)-2,3-O-ISOPROPYLIDENEGLYCERALDEHYDE (D-GLYCERALDEHYDE ACETONIDE)

L. W. Hertel*, C. S. Grossman, J. S. Kroin

Lilly Research Laboratories, Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285



ABSTRACT: This is a report on the synthesis and on the storage of D-glyceraldehyde acetonide for as long as three years after initial preparation while retaining its enantiomeric purity.

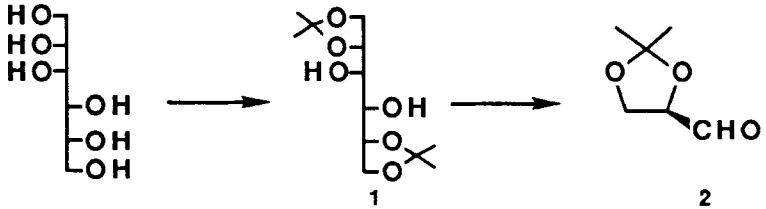
D-Glyceraldehyde acetonide is known to be a useful and inexpensive chiral synthon for a number of biologically active compounds such as prostaglandins, brefeldin A, ipsdienol, prestalotine and leukotriene $A_4$.[1] Although its preparation has been described many times previously, its ultimate utility is somewhat limited by the reported need to prepare fresh material prior to use.[2] We report here our observations involving the storage and reuse of large quantities of this chiral building block, which has allowed us to utilize it as a convenient, large scale starting material.

There are three references for the synthesis of the R-enantiomer of glyceraldehyde, that we feel are the most pertinent.[3,4,5] The first paper is the historical reference always quoted for the synthesis of D-glyceraldehyde published

* To whom correspondence should be addressed

by Baer and Fisher in 1939[3] (Scheme 1). The second reference is by Baer published in 1945 in which he reports improvements on the first step of the synthesis, where he makes diacetone mannitol. In this paper, which contains experimental details of his improvements, he says "Several of the changes proved distinctly advantageous and their combination led to a procedure which is less time consuming, cheaper and which can be carried out easily on a larger scale".[4] The third reference is by Horton[5] and deals with an improvement of the second step in the synthesis i. e. the oxidative cleavage of diacetone mannitol with lead tetraacetate, to yield two moles of D-glyceraldehyde. These improvements involve a work up which makes elimination of acetic acid from the final product easier. Horton also reports the NMR spectrum of the final product which obviously was not included in the original Baer paper.

**Scheme 1**



1 2

In addition to combining the published modifications to the originally reported synthesis, the storage of D-glyceraldhyde acetonide, for as long a three years with eventual synthetic use, has been achieved. Even if stored cold, the freshly prepared 2 does polymerize, though polymerization is much slower at reduced temperature. This is evident by the change in viscosity and the gradual disapperance of the aldehyde proton in the $H^1$ NMR spectrum. However, recovery of the D-glyceraldhyde acetonide from the polymerized material may be acomplished through a simple cracking procedure that involves distillation of the material *in vacuo* with a pot temperature of 60°-80° C. The integrity of the stereogentic center is evidenced by the optical rotation of the cracked material after reduction to the glycerol[6] ( $[\alpha]_D$ = + 10.0328°)[7]. Additional proof was obtained from the synthetic results, which were identical to those obtained using freshly prepared material.[8]

## Experimental:

D-mannitol (27 g) is added to a solution of zinc chloride ( 42 g) in dry acetone (210 ml) and the mixture is stirred at 20° C for three hours. Unreacted D-Mannitol is removed by filtration and the filtrate is added quickly to an aqueous solution of potassium carbonate (53 g / 53 ml ) containing diethyl ether (210 ml). After vigorous stirring for one hour at about 25° C, the mixture is filtered. The filtrate is concentrated to precipitate 1 as a thick slurry. To facilitate the collection of the crystalline product, acetone may be added to aid the filtration of the slurry. The product may be rinsed with acetone and then vacuum dried. (18g of 1, 50 - 55% of theory based on the amount of mannitol that dissolved in the reaction mixture).

A solution of 1 (18 g) in ethyl acetate (130 ml) is cooled to 5°C and lead tetraacetate (26 g) is added portionwise until starch iodide paper shows that a slight excess of lead tetracetate is present. After the completion of the addition, the reaction mixture is warmed to about 25° C and the stirring is continued for 2.5 hours. The reaction mixture is filtered and the filtrate is concentrated to give compound 2 as a clear syrup. To the syrup was added carbon tetrachloride and this was evaporated under reduced pressure. This operation was carried out three more times. This azeotropic coevaporation of the crude product with carbon tetrachloride was employed to remove all acetic acid before vacuum distillation of the product. The resulting clear syrup was then distilled in a vacuum. The main fraction was collected, yield 8.0 g (45%) of 2 : bp 50° C (8-10 torr) Lit.[3] bp 35°- 42° C @ 8-11 torr. IR (neat) 1740 $cm^{-1}$ (C=O), $^1H$ NMR (90mz, neat) $\partial$ 1.19 & 1.25 (two s, 3H each, $CMe_2$), 3.86 (m, 2H, 3-H), 4.12 (m, 1H, 2-H), 9.43 ( bs, 1H, 1-H).

## References

1. T. Kametani, Heterocycles, 19, 205 (1982) and references therein.

2. J. Jurczak, S. Pikul and T. Bauer, Tetrahedron, 42, 447, (1986).

3. E. Baer, H. O. L. Fischer, J. Biol. Chem., 128, 463 (1939).

4. E. Baer, J. Am. Chem. Soc., 67, 338 (1945).

5. D. Horton, J. B. Thomson, J. Org. Chem., 33, 728 (1968).

6. S. Takano, H. Numata, K. Ogasawara, Heterocycles, 19, 327, (1982).

7. Reference 3, [alpha]$_D$ = + 10.7°

8. L. W. Hertel, J. S. Kroin, J. W. Misner, J. M. Tustin, J. Org. Chem. 53, 2406 (1988).

(Received in USA 29 October, 1990)