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Short and efficient synthesis of a stock material of dihydroxyacetone phosphate from glycidol

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Abstract—As enzymatic syntheses are expensive for a large-scale preparation of DHAP, a precursor leading to DHAP was synthesized in three steps starting from (±) glycidol; the stable benzylated stock material afforded by hydrogenolysis DHAP in high purity, which may be used directly without purification in enzymatic aldol synthesis.

1. Introduction

The stereoselective formation of C–C bonds is one of the main goals in organic synthesis. Among many methods, the aldolization reaction with a chiral auxilliary allows to form diastereoselective and even enantioselective C–C bonds.[1] Aldolases are known as useful biocatalysts to form these bonds and the enzymatic reaction takes place with high enantio- and diastereoselectivity.[1] Of more than 20 known aldolases, D-fructose 1,6-biphosphate aldolase (EC 4.1.2.13), D-tagatose 1,6-biphosphate aldolase (EC 4.1.2.-), L-fucose 1-phosphate aldolase (EC 4.1.2.17) and L-rhamnulose 1-phosphate aldolase (EC 4.1.2.19) have demonstrated their synthetic utility: these enzymes catalyze the asymmetric addition of dihydroxyacetone phosphate (DHAP) as nucleophile (donor) on a variety of aldehydes as electrophilic substrate.[2] Each enzyme leads to only one of the four possible stereoisomers (Scheme 1).[3] Commercially available DHAP remains too expensive to be used in organic synthesis and therefore improvement of its preparation is still a subject of interest.

Currently, several enzymatic and chemical syntheses of DHAP have been reported in the literature.[4–13] The easiest method is the in situ formation of DHAP from fructose-1,6-biphosphate.[4] The fructose 1,6-biphosphate aldolase catalyzes the reversible condensation of two molecules of triose phosphate, the glyceraldehyde 3-phosphate and the DHAP. Two other enzymatic methods have been developed. One proceeds via phosphorylation of free dihydroxyacetone using glycerol kinase and ATP,[5] and the other is the oxidation of the L-glycerol 1-phosphate by oxygen in the presence of the glycerophosphate oxidase coupled with a catalase allowing the decomposition of hydrogen peroxide.[6] Enzymatic syntheses are however too expensive to be used for large-scale preparation of DHAP, and chemical methods are preferentially used.

The first chemical precursor of DHAP was the dihydroxyacetone phosphate dimethyl ketal **1a** (Scheme 2) synthesized by Ballou and Fischer.[7] Their synthesis led to DHAP in eight steps with an overall yield of 13%. Other chemical approaches based on ketal precursors (**1b–d**) of DHAP have been developed.[8] These methods were allowed to obtain DHAP in five or six steps with an overall yield of 48% starting from acetone[8a] and 56% starting from the expensive 1,3-dibromoacetone.[8b]

The most common syntheses of DHAP are targeted towards the preparation of the phosphorylated DHAP dimer **2**, a stock material, which was first described by Colbran et al.[9] This original method has been optimized by modifications of the phosphorylation step of the protected DHAP dimer. In the conditions reported by Effenberger and Straub,[10] DHAP was obtained in only three steps with an overall yield of 34%. Two improved procedures have been developed by Wong and co-workers and led to DHAP in four steps with 55%[11] and 61% yield, respectively.[12] Recently, labelled DHAP was

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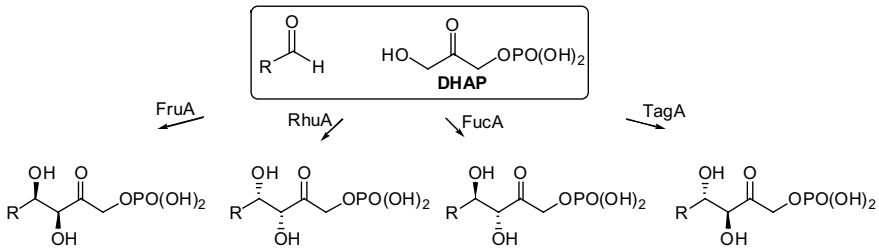
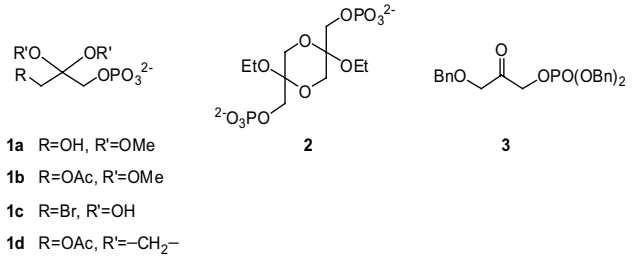


Scheme 1. Enzymatic asymmetric aldolization using D-fructose 1,6-biphosphate aldolase = FruA, L-rhamnulose 1-phosphate aldolase = RhuA, L-fucose 1-phosphate aldolase = FucA, D-tagatose 1,6-biphosphate aldolase = TagA.



Scheme 2. Known precursors of DHAP.

synthesized via precursor **3** having the alcohol function and the phosphate ester protected by benzyl groups.[13] After a hydrogenation, DHAP was obtained in five steps with an overall yield of 62%[13a] or 50%.[13b]

Many chemical procedures are quite low yielding and complicated by multistep purification procedures. In some cases, they involve unstable intermediates and/or expensive or toxic reagents. We report here a practical and efficient procedure suitable for a gram-scale synthesis of DHAP from the precursor **3**.

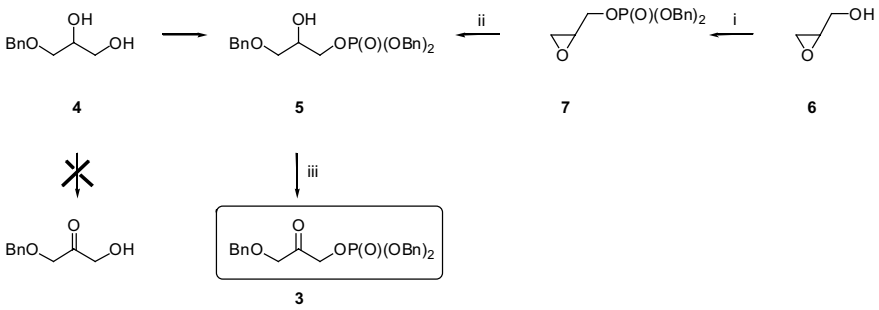
2. Results and discussion

Our approach to efficiently synthesize the benzylated DHAP precursor **3** was based on the chemical modifications of commercially available starting materials, the (±)-1-*O*-benzylglycerol **4** and (±)-glycidol **6**, with the same C_3 skeleton as DHAP.

Our first attempt was to synthesize the precursor **3** in two steps starting from the (±)-1-*O*-benzylglycerol **4**, a commercial protected glycerol. Two methods were investigated: a selective oxidation of the secondary alcohol followed by a phosphorylation of the primary hydroxyl group, or alternatively a selective phosphorylation of the primary alcohol followed by the oxidation of the secondary hydroxyl group (Scheme 3).

In order to selectively oxidize the secondary hydroxyl group, several oxidation conditions were tested like NBS/acetone or $CuBr_2/H_2O_2$, but the desired product was not isolated with satisfactory yields. Consequently, the selective phosphorylation of the primary hydroxyl group was investigated. The use of dibenzyl chlorophosphate as phosphorylating agent in presence of pyridine gave the desired phosphate **5**. With this method, no diphosphorylated compound was obtained, but migration of the phosphate from primary to secondary hydroxyl group was observed, which complicated the isolation of the desired product. Other phosphorylation methods like $P(OBn)_3/I_2$/pyridine in CH_2Cl_2 or $HPO(OBn)_2/NEt_3/CCl_4$/ultrasounds in toluene were tested. These conditions were not satisfactory and yielded a mixture of phosphates on the primary or the secondary hydroxyl group in both cases. By oxidizing this mixture with TPAP/NMO, the desired product **3** was easily obtained after flash chromatography with a 24% global yield.

In order to optimize the synthesis of precursor **3**, we decided to start from the commercially available (±)-glycidol **6**. The hydroxyl group was phosphorylated,



Scheme 3. Chemical synthesis of precursor **3**. (i) $(BnO)_2P\text{-}NEt_2$, tetrazole, *m*-CPBA, CH_2Cl_2 (85%), (ii) BnOH, BF_3/Et_2O, 4 Å molecular sieves, CH_2Cl_2 (88%), (iii) TPAP, NMO, 3 Å molecular sieves, CH_2Cl_2 (82%).

the epoxy ring selectively opened with benzyl alcohol following a methodology developed for the synthesis of phospholipids.[14] Finally the secondary alcohol was oxidized to give the DHAP precursor **3** (Scheme 2).

By using dibenzylchlorophosphate in the presence of pyridine, the desired phosphate was not obtained. Decomposition of the starting material and formation of many by-products were observed. The phosphoramidate method was therefore used. The epoxy alcohol **6** was treated with dibenzyl-*N*,*N*-diethyl phosphoramidite in the presence of tetrazole to give the corresponding phosphite, which was readily oxidized with *m*-CPBA into phosphate **7**.[15] The following selective oxirane ring opening was carried out in CH_2Cl_2 with boron trifluoride etherate as catalyst and benzyl alcohol as nucleophile.[16] Only alcohol **5**, resulting from reaction of the benzyl alcohol on the less hindered side, was obtained. The next step leading to the protected DHAP was the oxidation of this compound. The mild oxidation of **5** with TPAP/NMO gave rapidly after silica gel chromatography the precursor **3**.[17] Using this short synthesis, the DHAP precursor **3** was obtained with an overall yield of 61% and was stored for months without noticeable decomposition. The last step was the deprotection of all benzyl groups by catalytic hydrogenation. This was realized at atmospheric pressure in methanol/water (9/1) with palladium over charcoal (11%). After 1 h, DHAP was obtained in quantitative yield without side-products. This step required no purification. The catalyst was simply eliminated by filtration on Celite, and the filtrate was concentrated under vacuum. The residue was dissolved in water and the solution was neutralized by addition of 1 M sodium hydroxide. DHAP thus prepared was coupled with butanal using the same conditions than Schoevaart et al.,[18] and the same aldol, 1,3,4-tri-*O*-acetyl-5-deoxy-5-ethyl-D-xylulose was obtained.

This new synthesis of DHAP occurs in four steps and with an overall yield of 61% from the (±)-glycidol **6**. This yield ranges among those of the most recent syntheses (56% in Bolte's synthesis and 62% or 50% in the Raap's syntheses). However, our method offers the major advantage of preparing DHAP from inexpensive racemic glycidol and non-toxic reagents in a short and facile manner. Indeed, Raap's methods for preparation of the DHAP precursor **3** require the use of hazardous diazomethane. DHAP is generated by hydrogenation of **3** in dioxane/propan-2-ol/water (4:2:1) overnight at atmospheric pressure with 42% of Pd/C catalyst, whereas we obtained DHAP without the formation side-products after 1 h using only 11% of catalyst in methanol/water (9/1) at the same pressure. The latter method was designed to obtain labelled DHAP and intermediate **3** was firstly obtained with a yield of 66%. However, two years later Raap reported a modified procedure for the synthesis of **3** with a yield of 52%. This method was realized in order to bring out less side reactions than in the previous experiments.[13]

The short and efficient procedure reported here represents a completely new route for the preparation of the DHAP precursor **3**, a stable stock material, which can be can be stored for several months at −18 °C and hydrogenolyzed into DHAP just before its use in enzyme-catalyzed synthesis. This compound represents thus a convenient stock material for DHAP.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.08.148.

References and notes

1. Gijsen, H. J. M.; Qiao, L.; Fitz, W.; Wong, C.-H. *Chem. Rev.* **1996**, *96*, 443–473, and references cited therein.
2. (a) Lees, W. J.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 1887–1894; (b) Toone, E. J.; Simon, E. S.; Bednarski, M. D.; Whitesides, G. M. *Tetrahedron* **1989**, *45*, 5365–5422.
3. Henderson, I.; Sharpless, K. B.; Wong, C.-H. *J. Am. Chem. Soc.* **1994**, *116*, 558–561.
4. Wong, C.-H.; Whitesides, G. M. *J. Org. Chem.* **1983**, *48*, 3199–3205.
5. Simon, E. S.; Grabowski, S.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989**, *111*, 8920–8921.
6. Fessner, W.-D.; Sinerius, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 209–212.
7. Ballou, C. E. L.; Fischer, H. O. *J. Am. Chem. Soc.* **1956**, *78*, 1659–1661.
8. (a) Valentin, M.-L.; Bolte, J. *Bull. Soc. Chim. Fr.* **1995**, *132*, 1167–1171; (b) Gefflaut, T.; Lemaire, M.; Valentin, M.-L.; Bolte, J. *J. Org. Chem.* **1997**, *62*, 5920–5922.
9. Colbran, R. L.; Jones, J. K. N.; Matheson, N. K.; Rozema, I. *Carbohydr. Res.* **1967**, *4*, 355–358.
10. Effenberger, F.; Straub, A. *Tetrahedron Lett.* **1987**, *28*, 1641–1644.
11. Pederson, R. L.; Esker, J.; Wong, C.-H. *Tetrahedron* **1991**, *47*, 2643–2648.
12. Jung, S.-H.; Jeong, J.-H.; Miller, P.; Wong, C.-H. *J. Org. Chem.* **1994**, *59*, 7182–7184.
13. (a) Ouwerkerk, N.; van Boom, J. H.; Lugtenburg, J.; Raap, J. *Eur. J. Org. Chem.* **2000**, 861–866; (b) Ouwerkerk, N.; Steenweg, M.; de Ruijter, M.; van Boom, J. H.; Lugtenburg, J.; Raap, J. *J. Org. Chem.* **2002**, *67*, 1480–1489.
14. Lindberg, J.; Ekeroth, J.; Konradsson, P. *J. Org. Chem.* **2002**, *67*, 194–199.
15. de Viguerie, N. L.; Willson, M.; Périé, J. *New J. Chem.* **1994**, *18*, 1183–1195.
16. Byun, H.-S.; Bittman, R. *Tetrahedron Lett.* **1989**, *30*, 2751–2754.
17. Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13–19.
18. Schoevaart, R.; van Rantwijk, F.; Sheldon, R. A. *Tetrahedron: Asymmetry* **1999**, *10*, 705–711.