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The first synthesis of a cyclic dihydroxyacetone phosphate, a new molecule of biological importance

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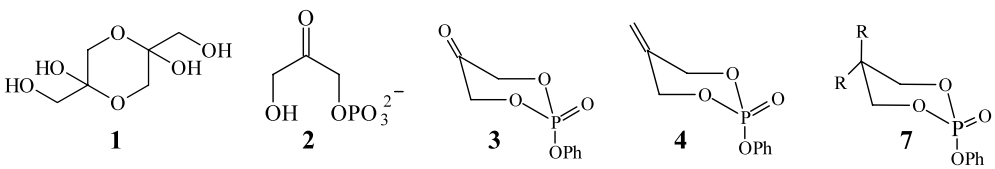
Abstract—A six-membered cyclic dihydroxyacetone phosphate (CDHAP) **3** (2-oxo-2-phenoxy-2λ^5-[1,2,3]-dioxaphosphinane-5-one) which is a new and interesting molecule of biological interest has been synthesised for the first time. Though dihydroxyacetone phosphate (DHAP) **2** is very well known and is the precursor for enzymatic synthesis of sugars, the six-membered cyclic dihydroxyacetone phosphate and its synthesis have not been reported to our knowledge.

Dihydroxyacetone (DHA) exists as a dimer **1**. Normally, dihydroxyacetone phosphate (DHAP) **2** is synthesised enzymatically as well as chemically. DHAP has been used extensively in organic synthesis for enzymatic aldol reactions in the synthesis of sugars.[1] Six-membered cyclic phosphates are important constituents present in a number of biologically important molecules, e.g. cyclic adenosine phosphate[2] and Form Z (a precursor) of molybdenum cofactor.[3,4] Rajagopalan and co-workers[5,6] have shown that the substrate of Form Z is an α-phosphorylated ketone where the phosphate is a part of the six-membered ring. In our synthetic studies[7] on the molybdenum cofactor, we were interested to have an efficient synthesis of CDHAP **3**. We report here the synthesis of the six-membered cyclic phosphate **3** and also the *exo*-methylene analogue **4**. We utilised a low temperature ozonolysis reaction for the synthesis of **3** from a stable phosphate triester 5-methylene-2-oxo-2-phenoxy-[1,2,3]-dioxaphosphorinane **4**. The β-hydroxyl group of Form Z, may be generated by $NaBH_4$ reduction of the keto group of CDHAP.

The DHA dimer **1** has been chemically phosphorylated to **2** via $POCl_3$,[8] $(PhO)_2P(O)Cl$[9] and also by Wong's improved method.[1] We reacted **1** with (*p*-NO_2–PhO)P(O)Cl_2 in various solvents containing Et_3N such as CH_2Cl_2, dioxan, CH_3CN and also in pyridine, but the yield was very poor (5–10%) in all the cases due to the notorious insolubility of **1** in the solvent used. We reasoned that **5** could be used as a more suitable starting material for making CDHAP **3** via conventional methods. The *exo*-methylene function could easily be converted into a keto group by ozonolysis at low temperature and under neutral conditions in which the cyclic phosphate moiety should survive.

We thus report here our successful approach to prepare **3** by this new and efficient method (Scheme 1) in good yield. High dilution coupling of **5** and (PhO)P(O)Cl_2 in dry CH_2Cl_2 and Et_3N afforded a thick, light yellow liquid **4**, which on ozonolysis gave the pale brown semi-solid **3** in 70% overall yield. Compound **4** was also made via the formation of intermediate **6** by the reaction of **5** with $POCl_3$ or PCl_5. Intermediate **6** was not



1 **2** **3** **4** **7**

Keywords: dihydroxyacetone dimer; cyclic phosphate; molybdenum cofactor; cyclic keto phosphate; ozonolysis.

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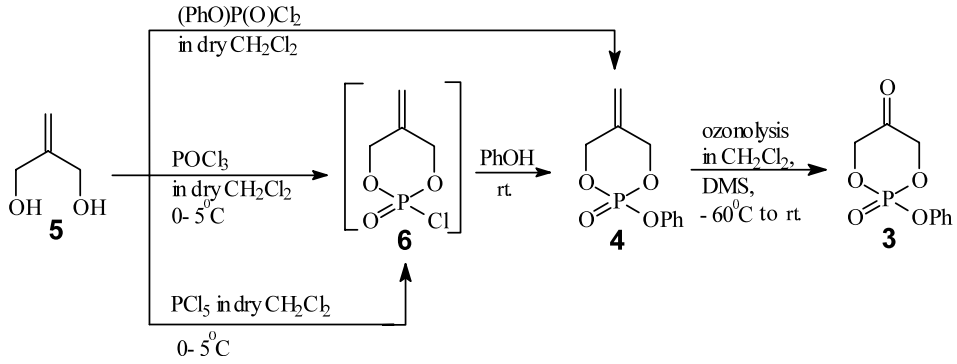

Scheme 1.

isolated, but directly converted to compound **4** by reaction with phenol in dry CH_2Cl_2 at room temperature. However, the $(PhO)P(O)Cl_2$ route was found to be more efficient for the synthesis of **4**. Compounds **3** and **4** were well characterised[10] by spectroscopic means including ^{31}P NMR.

A solid state X-ray study[11] of 2-oxo-2-phenoxy-1,2,3-dioxaphosphorinane **7** (R = H) revealed that the phenoxy substituent favours an axial orientation in the chair conformation. In **3** and **4**, the phosphorus is more strongly coupled to the equatorial protons ($^3J_{P-H\ (eq.)}$ = 18.73 Hz for **3** and 18.91 Hz for **4**) compared to the axial protons ($^3J_{P-H\ (ax.)}$<4.5 Hz both for **3** and **4**) (Fig. 1 and Fig. 2). These findings are consistent with the $^3J_{P-H}$ coupling constants for axial and equatorial protons in **7** ($R = CH_3$)[12] and those found in other dioxaphosphorinane ring systems[13] and thus, it is likely that **3** and **4** exist as a single conformer at room temperature.

In conclusion, we have developed a new route for the synthesis of a cyclic dihydroxyacetone phosphate. The new compounds, e.g. 5-methylene-2-oxo-2-phenoxy-[1,2,3]-dioxaphosphorinane and CDHAP are promising synthons for the synthesis of keto sugars or analogues attached to different groups having biological importance.

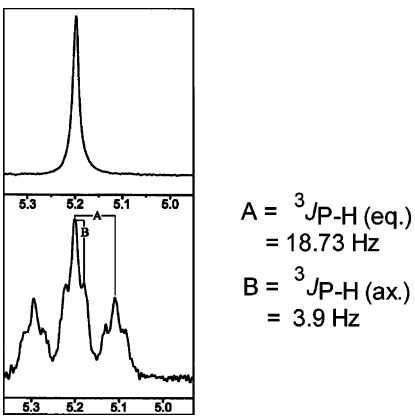

Figure 1. ^1H decoupled ^{31}P NMR (top) and ^1H undecoupled ^{31}P NMR (bottom) of **3** at 22°C.

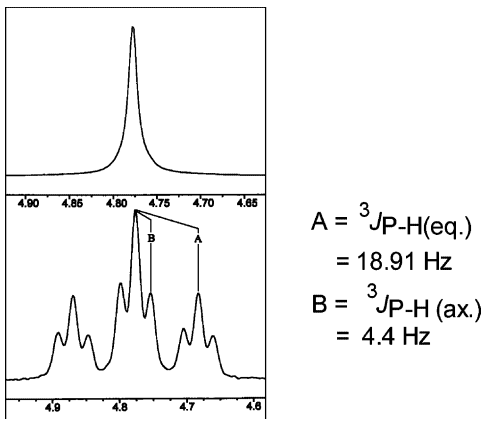

Figure 2. ^1H decoupled ^{31}P NMR (top) and ^1H undecoupled ^{31}P NMR (bottom) of **4** at 22°C.

Acknowledgements

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