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An Improved Synthesis of Phosphonomethyl Analogues of Glyceraldehyde-3-Phosphate and Dihydroxy-acetone Phosphate

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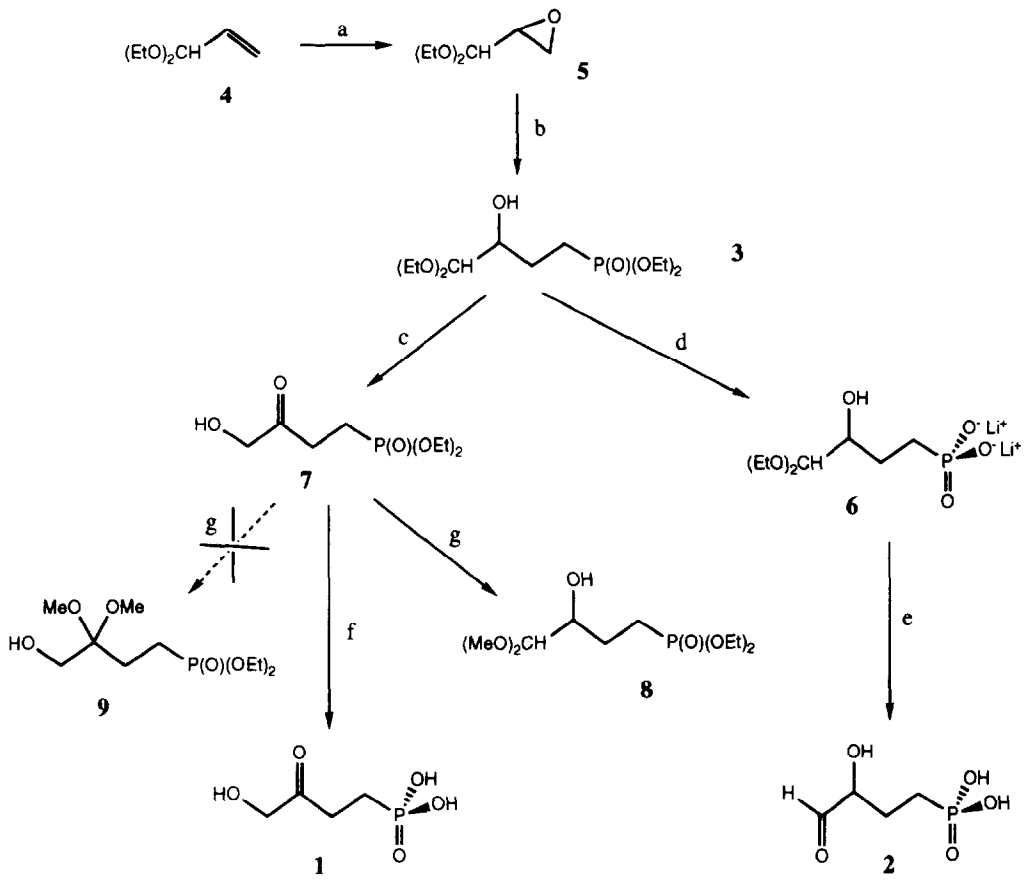
Abstract : Compounds **1** and **2**, phosphonate analogues of dihydroxy-acetone phosphate (DHAP) and glyceraldehyde-3-phosphate (GAP) respectively, are easily and quantitatively obtained from diethyl-4,4-diethoxy-3-hydroxybutyl-1-phosphonate **3**. Depending upon the acidic conditions utilised for the deprotection of the phosphonate and carbonyl groups, the aldol/ketol rearrangement allows the synthesis of either compound.

Phosphonate isosteres of biologically important phosphates are of high interest in biological chemistry and medicine, owing to the stability of the phosphorus-carbon bond towards phosphatases compared to the phosphorus-oxygen bond.[1,2] This feature allows us to look at the behaviour of these relatively long lived compounds in physiological conditions. Among these analogues, those corresponding to glycolysis intermediates[3] are of interest since this metabolism is the only source of energy for parasites such as the trypanosome (bloodstream form).[4] Thus, for example, the synthesis of 3-hydroxy-4-oxobutyl-1-phosphonate **2** and 4-hydroxy-3-oxobutyl-1-phosphonate **1**, isosteres of GAP and DHAP respectively, has been reported.[5,6] Besides their specific interest for the study of glycolysis, these compounds can also be used as substrates for enzymes such as aldolases[7], hence leading, in addition, to other analogues. In the previously described procedures, the synthesis of these compounds required separate strategies, with low yields in some steps.

Considering that DHAP and GAP are isomeric, we investigated the possibility of preparing their phosphonate analogues from the same precursor by taking advantage of the α-ketol rearrangement.[8] Indeed, **1** and **2** can be easily obtained from the common intermediate diethyl-4,4-diethoxy-3-hydroxybutyl-2-phosphonate **3**, as indicated on scheme.[9] The starting material is the commercially available diethylacetal **4** which furnishes glycidaldehyde diethylacetal **5** by reaction with hydrogen peroxide and benzonitrile.[10] Ring opening of epoxide **5** by the carbanion of diethylmethyl phosphonate, catalyzed by $BF_3.Et_2O$[2,11], quantitatively leads to the intermediate γ-hydroxyphosphonate **3** in 80% yield. Deprotection of the phosphonate group of



Preparation of phosphonic acids **1** and **2** from diethyl-3-hydroxy-4,4-diethoxybutyl-1-phosphonate **3**. (a) H_2O_2, Benzonitrile, $KHCO_3$ (70%); (b) $CH_3P(O)(OEt)_2$, BuLi, $Et_2O.BF_3$, -80°C (76%); (c) HCl 0.1 M (70%); (d) LiOH, 120°C, 2 Bar (86%); (e) Dowex 50WX8 (H^+), H_2O, 45°C (96%); (f) Me_3SiBr, -20°C, H_2O (91%); (g) MeOH, $(EtO)_3CH$, NH_4NO_3 (86.5%).

compound **3** in basic conditions[5] yields 4,4-diethoxy-3-hydroxybutyl-1-phosphonate **6** as the lithium salt. The GAP phosphonate isostere **2** is then obtained by acid treatment of **6** in mild conditions (Dowex 50WX8 resin, H^+ form) with an overall yield of 92% from **3**.

In contrast, the deprotection of the carbonyl group of **3**, in more acidic conditions gives quantitatively the diethyl-4-hydroxy-3-oxobutyl-1-phosphonate **7**.[12] Reaction of the latter with trimethylsilylbromide[13] furnishes the analogue phosphonate **1** of DHAP with 63% yield from **3**. The reversibility of the reaction between compounds **3** and **7** is evidenced by the reaction of **7** in methanol which leads to **8** and not to the acetal of the keto group **9** that would be *a priori*, expected.

These results can be rationalized in terms of the α-ketol rearrangement conditions : in mild acidic conditions (Dowex resin) compound **6** undergoes the acetal group deprotection without further rearrangement. Contrarily, in more severely acidic conditions (pH = 1), deprotection of the acetal group leads to the

thermodynamically more stable, rearranged ketone. The formation of the acetal **8** from **7** indicates that all steps in this rearrangement are reversible, the acetal formation proceeding on the more reactive aldol form. The significance of this synthesis of compounds **1** and **2** is upheld by the fact that the enzyme triosephosphate isomerase does not catalyse the interconversion of these two phosphonates.[6b]

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9. **Dilithium 3-oxo-4-hydroxybutyl-1 phosphonate 1**: ^{31}P NMR (81MHz,D_2O) δ 23.3; ^{1}H NMR (200MHz,D_2O) δ 1.7-2.0(m,2H,CH_2-P), 2.55-2.65(m,2H,$CH_2C(O)$), 4.32(s,2H,CH_2O); ^{13}C NMR (50MHz,D_2O) δ 25.1(d,CH_2P, $^{1}J_{CP}$ = 132.6Hz), 35.7(s,CH_2), 69.0(s,CH_2OH), 210.7(d,C=O, $^{3}J_{CP}$ = 12Hz); IR(KBr) ν(P=O)cm^{-1}: 1236, ν(C=O)cm^{-1}: 1710; Anal.Calcd for $C_4H_7O_5PLi_2$: C,26.7; H,3.9; O,44.4. Found: C,26.9; H,3.85; O,44.6. **Disodium 3-hydroxy-4-oxobutyl-1 phosphonate 2**: ^{31}P NMR (81MHz,D_2O) δ 23.75; ^{1}H NMR (200MHz,D_2O) δ 1.4-1.9(m,4H,CH_2CH_2-P), 3.75-3.85(m,1H,CH-O), 4.92(d,1H, $^{3}J_{HH}$ = 5.1Hz,O-CH-O); ^{13}C NMR (50MHz,D_2O) δ 25.74(d,CH_2P, $^{1}J_{CP}$ = 135.2Hz), 27.65(s,CH_2), 76.5(d,CH-O, $^{3}J_{CP}$ = 16.9Hz), 94.2(s,O-CH-O); Anal.Calcd. for $C_4H_9O_6PNa_2$: C,20.87; H,3.91; O,41.74. Found: C,21.62; H,4.09; O,42.26. **Diethyl 3-hydroxy-4,4-diethoxybutyl-1 phosphonate 3**: ^{31}P NMR (81 MHz,$CDCl_3$) δ 32.9; ^{1}H NMR (200MHz,$CDCl_3$) δ 1.15(t,3H,CH_3 acetal), 1.17(t,3H,CH_3 acetal), 1.27(t,6H,CH_3 ester), 1.4-1.9(m,4H,CH_2CH_2-P), 2.5(m,1H,OH), 3.3-3.8(m,5H,CH-O,OCH_2 acetal), 4.0-4.2(m,4H,CH_2O ester), 4.21(d,1H,CH acetal); ^{13}C NMR (50MHz,$CDCl_3$) δ 15.4(s,CH_3 acetal), 16.5(s,CH_3 ester), 21.8(d,CH_2P, $^{1}J_{CP}$ = 142Hz), 24.9(d,CH_2), 61.6(s,CH_2O ester), 63.6(s,CH_2O acetal),71.5(d,CH-O,$^{3}J_{CP}$ = 15.24Hz), 104.8(s,CH acetal); IR(film) ν(P=O)cm^{-1}: 1232; Anal.Calcd for $C_{12}H_{27}O_6P$: C,48.3; H,9.0; O,32.2. Found: C,47.9; H,9.1; O,31.6. **Dilithium 3-hydroxy-4,4-diethoxybutyl-1 phosphonate 6**: ^{31}P NMR (81 MHz,D_2O) δ 22.85; ^{1}H NMR (200MHz,D_2O) δ 1.22(t,6H,CH_3) 1.3-2.0(m,4H,CH_2CH_2-P), 3.5-3.9(m,5H,CH-O,OCH_2), 4.46(d,1H,$^{3}J_{HH}$= 4.5Hz,CH acetal); ^{13}C NMR (50MHz,D_2O) δ 17.07(s,CH_3), 27.9(d,CH_2P, $^{1}J_{CP}$ =

121Hz), 29.2(s,CH_2), 66.7(s,CH_2O), 67.2(s,CH_2O), 75.3(d,CH-O, $^3J_{CP}$ = 14.0Hz), 107.3(s,CH, acetal); IR(KBr) ν(P=O)cm^{-1}: 1253, ν(OH)cm^{-1}: 3382; Anal.Calcd. for $C_8H_{17}O_6PLi_2$: C,37.8; H,6.7; O,37.8.Found: C,37.65; H,6.9; O,38.07. **Diethyl 3-oxo-4-hydroxybutyl-1 phosphonate 7**: To a 100-ml round-bottomed flask containing **3** (1.5g, 5.03 mmol) in 10ml of demineralized water were added 100ml of HCl concentrated(35%). The mixture was warmed to 45°C and monitored by TLC(CH_2Cl_2/MeOH 9:1) ; the solution was freeze-dried. The oil was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH 9:1 to yield **7** (0.79g, 3.53 mmol, -70%) ^{31}P NMR (81 MHz,$CDCl_3$) δ 30.7; ^1H NMR (200MHz,$CDCl_3$) δ 1.26(t,3H,CH_3), 1.8-2.2(m,2H,CH_2-P), 2.6-2.8(m,2H,$CH_2C(O)$), 4.04(m,4H, CH_2O), 4.2(s,2H,CH_2O); ^{13}C NMR (50MHz,$CDCl_3$) δ 16.4(s,CH_3),19.1(d,CH_2P, $^1J_{CP}$ = 145Hz), 31.3(s,CH_2), 61.8(s,CH_2O ester), 66.0(s,CH_2O), 208.1 (d,C=O, $^3J_{CP}$ = 13.4Hz); IR(film) ν(P=O)cm^{-1}: 1220, ν(C=O)cm^{-1}: 1724; Anal.Calcd for $C_8H_{17}O_5P$: C,42.8; H,7.6; O,35.7. Found: C,43.1; H,7.7; O,35.4. **Diethyl 3-hydroxy-4,4-dimethoxybutyl-1 phosphonate 8**: ^{31}P NMR (81 MHz,$CDCl_3$) δ 33.0; ^1H NMR (200MHz,$CDCl_3$) δ 1.28(t,6H,CH_3 ester), 1.4-1.9(m,4H,CH_2CH_2-P), 2.8(m,1H,OH), 3.37 (s,3H,CH_3O), 3.41(s,3H,CH_3O), 3.7-3.75(m,1H,CH-O), 4.0-4.10(m,4H,CH_2O ester), 4.12(d,1H,CH acetal); ^{13}C NMR (50MHz,$CDCl_3$) δ 16.5(s,CH_3 ester), 21.7(d,CH_2P, $^1J_{CP}$ = 141Hz), 24.9(d,CH_2), 55.0(s,CH_3O acetal), 55.3(s,CH_3O acetal), 61.6(s,CH_2O ester), 71.1(d,CH-O,$^3J_{CP}$ = 14.7Hz), 106.7(s,CH acetal); IR(film) ν(P=O)cm^{-1}: 1236.

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