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A Facile Synthesis of 1-Hydroxy-2-Phosphonocyclobutenedione

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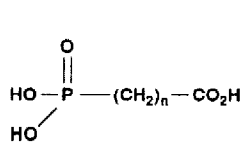
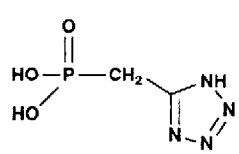
Abstract: A novel synthesis of 1-hydroxy-2-phosphonocyclobutenedione (**4**) is described.

Phosphonoformic acid (PFA, **1**) and phosphonoacetic acid (PAA, **2**) are selective inhibitors of RNA and DNA polymerases from several viruses.[1-3] As pyrophosphate analogues, these compounds appear to interfere with the polymerases at the pyrophosphate binding site.[3-4] Recently, PFA (also known as Forscarnet) has been approved for the treatment of cytomegalovirus retinitis in patients with AIDS.[5] Previously, 5-(phosphonomethyl)tetrazole (**3**) in which the tetrazole moiety was employed as a mimic of the carboxylic acid functionality of PAA has been prepared and showed a significant inhibitory activity against the RNA transcriptase of influenza.[1] As a part of the program to study the structure-activity relationship of this class of compounds, we undertook the synthesis of 1-hydroxy-2-phosphonocyclobutenedione (**4**). Analogous to the tetrazole derivative **3**, we hoped that the squaric acid moiety in **4** might function as an isoelectronic replacement of the carboxylic acid functionality of PAA in the biological system. Conceptually, compound **4** might be considered as a conformationally fixed analogue of PAA. Since squaric acid (**5**) is a very strong acid, pK_a = 2.2 (within 0.7 pK unit of sulfuric acid[6,7]) the hydroxyl group of **4** should be more acidic than the carboxyclic acid of PAA.



1 n = 0
2 n = 1



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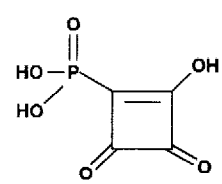
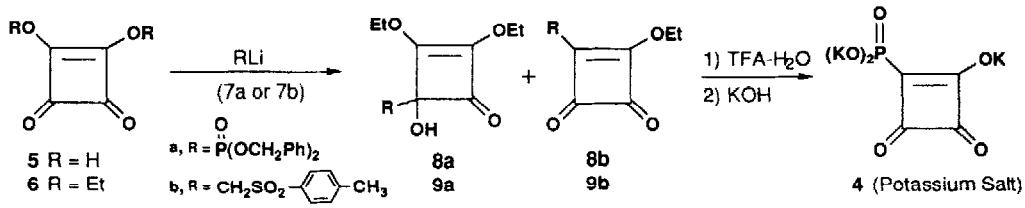


4

When diethyl squarate (**6**)[7] was treated with one equivalent of the lithium phosphonate (**7a**) in THF at -20°C, a mixture (approximately 1:1) of the 1,2- and the 1,4-addition products (**8a** and **8b**) was obtained in 50% yield. Interestingly, when the above anion reaction was carried out at -70°C, only the 1,2-addition product **8a** was obtained in 75% yield. Thus, it appears that the regioselectivity of the anion addition to the squarate **6** is completely dictated by kinetic factors at low temperature. This observation was further confirmed by the addition reaction of (p-toluenesulfonyl)methyl lithium (**7b**)

to **6**. The reaction of **7b** with **6** at -70°C gave cleanly the 1,2-addition product **9a** in 75% yield, but provided a mixture (approximately 1:1) of the 1,2-addition product **9a** and the 1,4-addition product **9b** at -20°C.[8] Treatment of **8a** with TFA-H_2O (2:1) at 23°C, followed by neutralization of the reaction mixture with KOH, afforded the tripotassium salt **4**. It should be noted that hydrolysis of the mixture **8a** and **8b** also gave the single product **4** The ^{13}C NMR of the potassium salt **4** showed that C-1 and C-3 are equivalent, indicating the extended delocalization of the anion charge.[9] In the influenza RNA polymerase inhibition test, **4** exhibited an almost equal inhibitory activity as PAA[10], strongly suggesting that this analogue binds the enzyme as effectively as PAA at the pyrophosphate binding site.



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9. Selected data for **4** (potassium salt): UVmax (H_2O) 230 nm (ε9510); IR (KBr) 1770, 1700, 1570 cm^{-1}; ^{13}C NMR (D_2O) δ 182.27 (d, J=157.6 Hz), 200.69, 213.54 (d, J=43.5 Hz). Anal. Calcd. for $C_4K_3O_6P \cdot 1.5\ H_2O$: C, 15.08; H, 0.94; P, 9.69. Found: C, 15.40; H, 1.01; P, 9.64.
10. We are indebted to the Virology Department of Bristol-Myers Squibb Company for this test. The full biological activity of **10** will be published elsewhere.

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