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Synthesis of 2-*C*-Methyl-D-Erythritol 2,4-Cyclopyrophosphate

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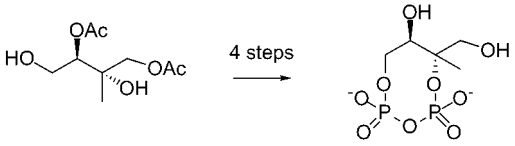
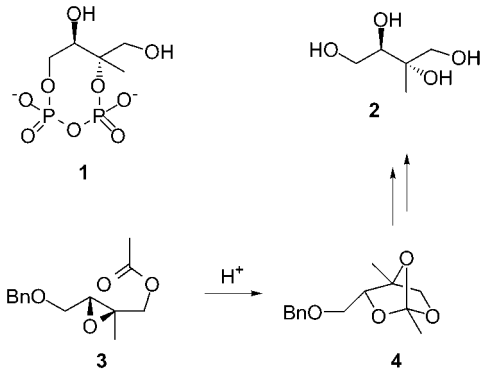
ABSTRACT



The synthesis of 2-*C*-methyl-D-erythritol 2,4-cyclopyrophosphate, a biochemical intermediate in the deoxyxylulose pathway of isoprenoid biosynthesis, was accomplished in four steps. Bisphosphorylation of 2-*C*-methyl-D-erythritol 1,3-diacetate, followed by carbodiimide cyclization and deprotection, led to the title compound in 42% overall yield.

2-*C*-Methyl-D-erythritol 2,4-cyclopyrophosphate (**1**) was first isolated from *Desulfovibrio desulfuricans* and *Corynebacterium ammoniagenes* bacteria.[1] Its structure was elucidated by NMR spectroscopy, and its absolute stereochemical configuration was determined by hydrolysis to the known 2-*C*-methyl-D-erythritol (**2**).[2] Due to its accumulation in bacteria under conditions of oxidative stress, its role in the bacteria was interpreted in terms of a protective function.[3] More recently, **1** was shown to be an intermediate in the newly discovered deoxyxylulose pathway of isoprenoid biosynthesis.[4] This pathway coexists with the mevalonate pathway in plants and replaces it altogether in many bacteria.[5] We have previously reported the syntheses of 1-D-deoxyxylulose and **2**.[6,7] In this communication we report the chemical synthesis of **1**.



Our synthesis of **2** via biomimetic epoxy ester−ortho ester rearrangement (**3** to **4**) also resulted in the preparation of 2-*C*-methyl-D-erythritol 1,3-diacetate (**5**, 58% yield from **3**).[7] This compound was used as the starting material for the synthesis of **1** (Scheme 1). Double phosphorylation of **5** by the phosphoramidite method led to the benzyl-protected

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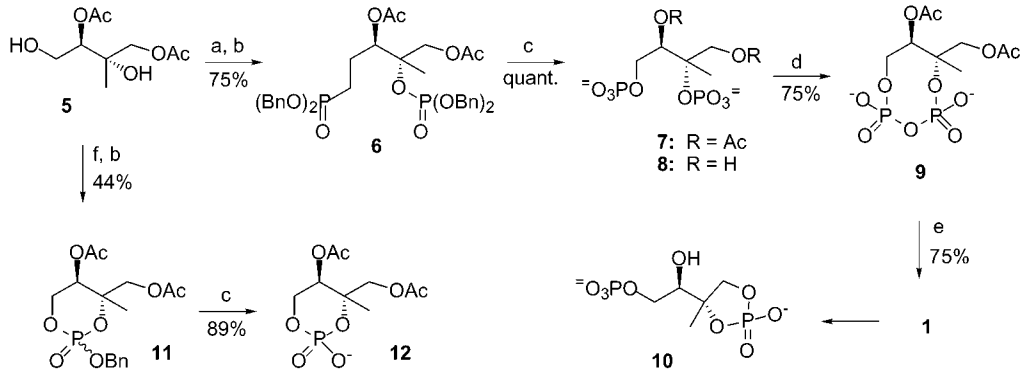
Scheme 1. Synthesis of 2-*C*-Methyl-D-erythritol 2,4-Cyclopyrophosphate (**1**)[a]



[a] (a) 3 equiv of $(BnO)_2PN$*i*-Pr_2, tetrazole, CH_2Cl_2, rt, 50 min; (b) *m*-CPBA, rt, 45 min; (c) H_2, 10% Pd/C, MeOH/1% NH_4HCO_3 4:1, rt, 3 h; (d) excess EDC, H_2O, rt, 3 d; (e) 1.36 M NH_4OH, 30 °C, 4 h; (f) 1.1 equiv of $(BnO)_2PN$*i*-Pr_2, tetrazole, CH_2Cl_2, rt, 50 min.

diphosphate **6**,[8] which upon hydrogenolysis gave 2-*C*-methyl-D-erythritol 1,3-diacetate 2,4-diphosphate (**7**). This compound could be converted into 2-*C*-methyl-D-erythritol 2,4-diphosphate (**8**) in 75% yield by saponification of the acetate esters with 0.6 M ammonium hydroxide.

An attempt to form **1** by carbodiimide cyclization of **8** failed as could be expected. However, carbodiimide coupling of **7** smoothly led to the formation of the protected cyclic pyrophosphate **9**. In these reactions, the carbodiimide used was not dicyclohexylcarbodiimide as in the synthesis of the cyclic pyrophosphate methanophosphagen,[9] but rather a large excess of the water-soluble carbodiimide EDC.[10] The substituted urea byproduct of the reaction was removed by cation exchange chromatography (DOWEX 50WX8-200). The product (**9**) thus obtained was mixed with ammonium chloride and could be further purified by silica gel chromatography (2-propanol/acetonitrile/1% aqueous ammonium acetate 4:1:1), or used directly for the next step. Deprotection of **9** by saponification with 1.36 M NH_4OH led to **1** in good yield. Careful control of the saponification reaction was necessary because **1** rearranges under basic conditions.[11] The product of rearrangement (**10**) could easily be separated from the desired cyclic pyrophosphate **1** by silica gel chromatography (2-propanol/acetonitrile/1% aqueous ammonium acetate 1:1:1). A similar isomer of **10** has been isolated together with **1** as an enzymatic product from the malaria parasite.[4c] Although a biochemical synthesis of **1** involving up to 15 enzymes has previously been published,[12] this represents the first chemical synthesis of **1**.

In an attempt to prepare 2-C-methyl-D-erythritol 4-phosphate, another intermediate in the deoxyxylulose pathway, diol **5** was treated with 1.1 equiv of dibenzyl diisopropyl phosphoramidite. This did not lead to the desired product; however, a monobenzylated product was isolated in moderate yield. A doubling of signals in the NMR spectra suggested that the product was a 1:1 diastereomeric mixture of cyclic monophosphates with a chiral center at phosphorus (**11**). Hydrogenolysis of the mixture led to a single product interpreted as being 2-*C*-methyl-D-erythritol 2,4-cyclophosphate 1,3-diacetate (**12**).

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Supporting Information Available: Experimental procedures and ^1H, ^{13}C, and ^{31}P NMR spectral data for compounds **6**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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