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Synthesis of [5,5-$^2H_2$]-1-Deoxy-D-xylulose-5-phosphate

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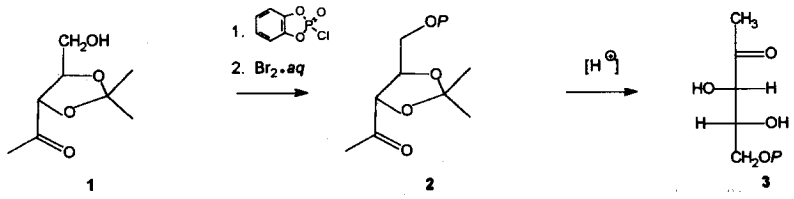
Abstract

[5,5-$^2H_2$]-1-Deoxy-D-xylulose-5-phosphate was synthetically prepared.

Key words: 1-Deoxy-D-xylulose-5-phosphate, deuterium labelling, methylerythritol phosphate (MEP) pathway

1-Deoxy-D-xylulose-5-phospate (**3**) is an intermediate of the methylerythritol phosphate (MEP) pathway of isopentenyl diphosphate (IPP) biosynthesis. Recently, the formation of IPP from **3** has received much attention as it has been shown to be an important route in terpenoid biosynthesis in bacteria and plants.[1] In plants, this mevalonate-independent MEP pathway is generally responsible for the build-up of plastid-derived terpenoids such as isoprene, monoterpenes, diterpenes, and carotenoids.[1] However, it could be shown that in some cases, the formation of the generally mevalonic acid derived sesquiterpenes and sterols also proceeds via the MEP pathway.[2] The involvement of 1-deoxy-D-xylulose (phosphate) has been demonstrated by its specific incorporation in terpenoids of bacteria and plants.[3] Intramolecular rearrangement of **3** to 2-*C*-methyl-D-erythritol-4-phosphate[4] and several subsequent, unknown steps, finally lead to IPP. In order to study this rearrangement reaction the substrate **3** was synthetically prepared with deuterium label in position 5. This paper describes an effective synthetic alternative to the previously reported synthetic and enzymatic syntheses of **3**.[5]

Scheme 1



The alcohol **1** (**1a**) can be synthesized via different routes.[6] We introduced the deuterium label in the corresponding step[6a] through reduction with Li[Al$^2H_4$] to obtain **1a**. Phosphorylation of **1** (**1a**) with *o*-phenylene phosphorochloridate[7] and subsequent oxidative deprotection with an excess of bromine water in neutral aqueous solution gave **2** or the corresponding deuterated compound.[8] After acidic cleavage of the isopropylidene group and desalting by size exclusion chromatography, **3** and [5,5-$^2H_2$]-1-deoxy-D-xylulose-5-phospate (**3a**) were obtained as sodium hydrogen salts in a yield of 83 % (3 steps) (scheme 2).[8]

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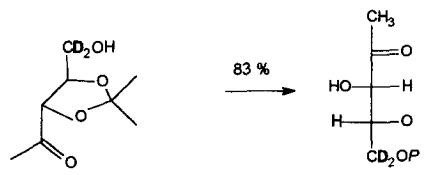
Scheme 2



1a **3a**

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8. *Phosphorylation of* ***1a*** *and deprotection.* A soln. of *o*-phenylene phosphorochloridate (229 mg, 1.2 mmol) (Fluka) in dry acetonitrile (5 ml) was added to a stirred soln. of alcohol **1a** (174 mg, 1 mmol) and 2,6-lutidine (0.462 ml, 4 mmol) in acetonitrile (5 ml) at r.t. After 3 h H_2O (3 ml) was added. 0.5 h later, the products were concentrated under reduced pressure (bath temp. < 40 °C). The solid residue was dissolved in 0.2 M triethylammonium bicarbonate (pH 7.5, 30 ml) and treated with 2% aqueous bromine soln (30 ml). After 10 min the mixture was extracted with diethyl ether (4x) and air was bubbled through the aqueous soln (10 min). The violet aqueous layer was passed over a column of activated carbon (2.5 x 2 cm) and acidified by passing over a cation exchange column (AMBERLITE IR 120, H^+-form). The acidic eluate was stirred at r.t. (48 h) and after adjusting the pH of the solution to 4.5 (NaOH) the crude product was lyophilized. The resulting solid was dissolved in a small amount of methanol/H_2O (1:1) and chromatographed on Sephadex LH-20 (2.5 x 180 cm, methanol/H_2O (1:1)). The **3a** containing fractions (R_f = 0.32; TLC (silica gel, *n*-propyl alcohol/ethyl acetate/H_2O (6:1:3), visualized with *p*-anisaldehyde/sulfuric acid, 110°C) were concentrated under reduced pressure (bath temp. < 40°C) to remove methanol. After lyophilization of the resulting aqueous solution 198 mg of the sodium hydrogen salt of **3a** were obtained (83 %).

   3a: $[\alpha]_D^{20}$ +24.0 (c 1.1, H_2O); ^1H NMR (500 MHz, D_2O) δ: 4.32 (*d*, *J* = 2.0 Hz, 1H), 4.19 (*d*, *J* = 2.0 Hz, 1H), 2.14 (*s*, 3H); ^{13}C NMR (125 MHz, D_2O) δ: 212.17, 76.01, 69.32 (*d*, *J* = 7.4 Hz), 64-65 (*m*), 25.03.