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A convenient synthesis of (*E*)-4-hydroxy-3-methyl-2-butenyl pyrophosphate and its [4-^{13}C]-labeled form

José-Luis Giner

Department of Chemistry, State University of New York-ESF, Syracuse, NY 13210, USA

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Abstract—The synthesis of (*E*)-4-hydroxy-3-methyl-2-butenyl pyrophosphate, an intermediate in the deoxyxylulose pathway of isoprenoid biosynthesis, was accomplished by pyrophosphorylation of (*E*)-4-chloro-2-methyl-2-buten-1-ol. This route enables convenient access to isotopically labeled products, as demonstrated through the preparation of [4-^{13}C]-(*E*)-4-hydroxy-3-methyl-2-butenyl pyrophosphate in 28% overall yield from [1-^{13}C]-2-bromopropionic acid.

(*E*)-4-Hydroxy-3-methyl-2-butenyl pyrophosphate (**1**) has recently been shown to lead to the universal isoprenoid precursors IPP (**2**) and DMAPP (**3**) in *E. coli* (Scheme 1).[1] As such, it represents the substrate for the final step in the deoxyxylulose pathway of isoprenoid biosynthesis, a newly discovered pathway that co-exists with the mevalonate pathway in plants and replaces it altogether in many bacteria and protists.[2] Other recent work has shown that **1** is a potent activator of γδ T cells in the human immune system.[3] In this communication we report the simple and convenient synthesis of **1**.

In our previous syntheses of intermediates in the new isoprenoid pathway, 1-D-deoxyxylulose (**4**),[4] 2-methyl-D-erythritol (**5**),[5] and 2-*C*-methyl-D-erythritol 2,4-cyclopyrophosphate (**6**),[6] the C_5 frameworks were conveniently assembled through Wittig reactions of commercially available starting materials (Scheme 2). This approach has permitted the preparation of a variety of isotopically labeled intermediates for investigations of the biosynthetic pathway.[7] Similarly, our present synthesis of **1** proceeds via the intermediacy of (*E*)-4-chloro-2-methyl-2-buten-1-ol (**7**), available through the modification of a Wittig route outlined by Stotter and Hill.[8]

The formation of the Wittig reagent **8** was best accomplished through the reaction of triphenylphosphine and the 2-iodopropionic ester **9**[8] in the presence of triethylamine (Scheme 3).[9] Treatment of the intermediate phosphonium salt with aqueous base yielded **8** as a pale yellow precipitate. The reaction of **8** with chloroacetaldehyde in CH_2Cl_2 proceeded rapidly and exothermically to give the *t*-butyl ester of **10** in a 9:1 ratio of the *E* and *Z* isomers, and it was found unnecessary to dry the aqueous 40% chloroacetaldehyde prior to the reaction.[8] The crude ester thus obtained, upon treatment with trifluoroacetic acid, gave γ-chlorotiglic acid (**10**),[10] which could be conveniently separated from the neutral reaction products by extraction with 5% NaOH, followed by acidification of the aqueous layer and extraction into dichloromethane. This treatment also serves to remove the undesired *Z*-isomer by lactonization.[8] Treatment of the triethylammonium salt of **10** with methyl chloroformate, removal of the precipitated salts by filtration, and reduction of the mixed carbonic anhydride with $NaBH_4$ and methanol, provided the desired chloroalcohol (**7**) in excellent yield.[8,11]

To complete the synthesis, the chloroalcohol (**7**) was treated with tris(tetrabutylammonium) pyrophosphate in acetonitrile (Scheme 3).[12] Initially, the product

1 2 3

Scheme 1.

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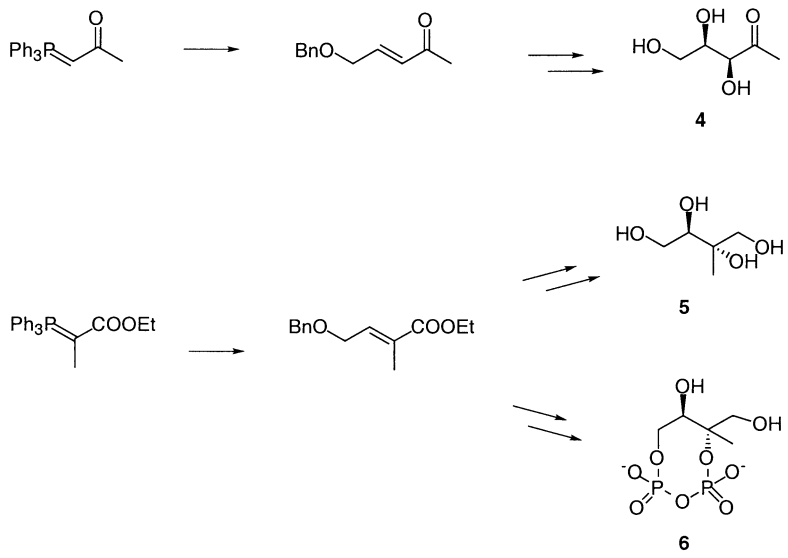
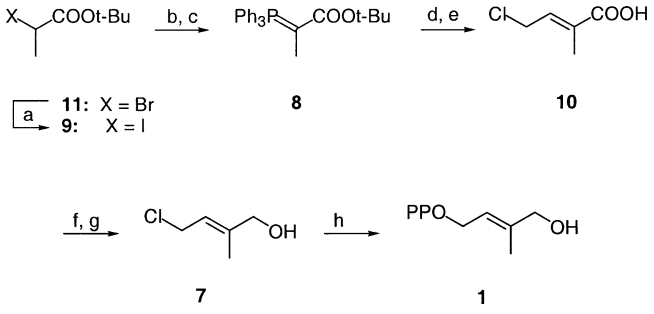


Scheme 2. Synthetic approaches to intermediates in the deoxyxylulose pathway.



Scheme 3. Synthesis of **1**. *Reagents and conditions*: (a) NaI (1.5 equiv.), acetone, rt, 12 h; (b) Ph_3P (1.2 equiv.), TEA (1.05 equiv.), EtOAc, reflux, 12 h; (c) dil. NaOH, 50% aq. MeOH, 85% from **11**; (d) $ClCH_2CHO$ (1.2 equiv.), DCM; (e) 25% TFA/DCM, 40°C, 4 h, 77% from **8**; (f) TEA (1.0 equiv.), MeOCOCl (1.1 equiv.), THF, 0°C, 10 min; (g) 15% $NaBH_4$/MeOH, THF, 0°C, 5 min, 91% from **10**; (h) $(Bu_4N^+)_3$ pyrophosphate (1.35 equiv.), MeCN, rt, 20 min, 80%.

obtained was contaminated with another organic pyrophosphate as shown by ^{31}P NMR. This contaminant could be traced to the commercial tris(tetrabutylammonium) pyrophosphate which was found to contain *n*-butyl pyrophosphate (20 mol%). The use of freshly prepared tris(tetrabutylammonium) pyrophosphate obviated this problem.[12] Purification of **1** was accomplished by absorption on Dowex 1X4 anion-exchange resin (HCO_3^- form) and elution with 0.3 M ammonium bicarbonate, followed by cellulose chromatography (Whatman CF11).[12,13] An overall yield of 48% starting from *t*-butyl 2-bromopropionate **11** was obtained.

This simple synthesis allows the facile introduction of isotopic label into various positions. It was of interest to synthesize a sample of **1** with ^{13}C at the 4-position, since this position undergoes the greatest change in ^{13}C NMR chemical shift upon biochemical conversion into **2** and **3**. Thus, preparation of [1-^{13}C]-**11** from commercially available [1-^{13}C]-2-bromopropionic acid using EDC as the esterification reagent, led to the synthesis of [4-^{13}C]-**1** in 28% overall yield.[13]

Acknowledgements

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10. Compound **10**: ^{1}H NMR (300 MHz, $CDCl_3$): 6.97 (1H, t, $J=7.8$ Hz, C-3), 4.18 (2H, d, $J=7.8$ Hz, C-4), 1.93 (3H, s, Me); ^{13}C NMR (75 MHz, $CDCl_3$): 172.8 (C-1), 137.7 (C-3), 130.9 (C-2), 38.9 (C-4), 12.1 (Me). [1-^{13}C]-**10**: ^{1}H NMR (300 MHz, $CDCl_3$): 6.97 (1H, q, $J=7.3$ Hz, C-3), 4.17 (2H, d, $J=7.7$ Hz, C-4), 1.91 (3H, d, $J=4.4$ Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$): 173.1 (C-1), 137.7 (d, $J=2.4$ Hz, C-3), 131.0 (d, $J=69$ Hz, C-2), 39.0 (d, $J=6.7$ Hz, C-4), 12.0 (d, $J=3.0$ Hz, Me).
11. Compound **7**: ^{1}H NMR (300 MHz, $CDCl_3$): 5.73 (1H, t, $J=8.0$ Hz, C-3), 4.13 (2H, d, $J=8.0$ Hz, C-4), 4.07 (2H, s, C-1), 1.74 (3H, s, Me); ^{13}C NMR (75 MHz, $CDCl_3$): 141.2 (C-2), 120.3 (C-3), 67.5 (C-1), 40.2 (C-4), 13.5 (Me). [1-^{13}C]-**7**: ^{1}H NMR (600 MHz, $CDCl_3$): 5.69 (1H, q, $J=7.6$ Hz, C-3), 4.11 (2H, d, $J=8.0$ Hz, C-4), 4.02 (2H, d, $J=142$ Hz, C-1), 1.74 (3H, d, $J=4.5$ Hz, Me); ^{13}C NMR (151 MHz, $CDCl_3$): 141.1 (d, $J=45$ Hz, C-2), 120.2 (d, $J=2.8$ Hz, C-3), 67.2 (C-1), 40.1 (d, $J=5.5$ Hz, C-4), 13.5 (m, Me).
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13. Compound **1**: ^{1}H NMR (600 MHz, D_2O): 5.44 (1H, br t, $J=6.8$ Hz, C-2), 4.13 (2H, t, $J=7.0$ Hz, C-1), 3.82 (2H, s, C-4), 1.50 (3H, s, Me); ^{13}C NMR (151 MHz, D_2O): 140.1 (C-3), 121.0 (d, $J=7.5$ Hz, C-2), 66.8 (C-4), 62.6 (br d, $J=5.0$ Hz, C-1), 13.6 (d, $J=6.5$ Hz, Me); ^{31}P NMR (D_2O, 243 MHz): −5.7 (d, $J=20.6$ Hz), −8.9 (d, $J=20.6$ Hz). [4-^{13}C]-**1**: ^{1}H NMR (600 MHz, $CDCl_3$): 5.63 (1H, q, $J=6.9$ Hz, C-2), 4.51 (2H, t, $J=7.2$ Hz, C-1), 3.99 (2H, d, $J=143$ Hz, C-4), 1.68 (3H, d, $J=4.3$ Hz, Me); ^{13}C NMR (151 MHz, D_2O): 140.3 (d, $J=45$ Hz, C-3), 121.3 (dd, $J=3$, 8 Hz, C-2), 67.1 (C-4), 62.6 (t, $J=6$ Hz, C-1), 13.7 (m, Me); ^{31}P NMR (D_2O, 243 MHz): −6.7 (d, $J=20.8$ Hz), −8.9 (d, $J=20.8$ Hz).