Non-mevalonate Pathway: Synthesis of MEP Pathway Intermediates and Their Derivatives

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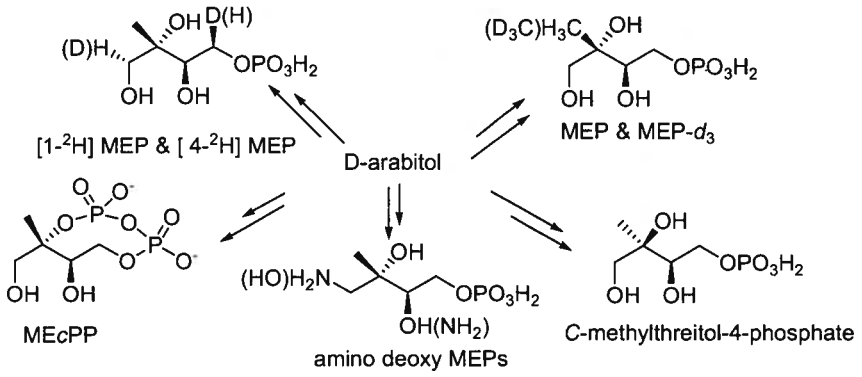
Recently, the non-mevalonte (methylerythritol phosphate, MEP) pathway was discovered in bacteria and plant chloroplasts for biosynthesis of isoprenoids. The genes, enzymes, and intermediates of this pathway have been established over the past few years. Experiments with ^{13}C- and/or ^{2}H-labeled precursors were crucial in the elucidation of this route. The chemical synthesis of MEP pathway intermediates and labeled derivatives is also very important in the investigation of the biosynthesis of isoprenoids in bacteria and plants. Here, the synthesis of methylerythritol phosphate, its cyclodiphosphate, and deuterium-labeled and amino analogues of MEP pathway intermediates is discussed.



Synthesis of Sulfur and Fluorine-Containing Fatty Acid Substrate Analogs

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Prostaglandin H synthases (PGHS) and lipoxygenases (LOX) are two classes of enzymes that play key roles in a number of biological processes. In humans, these enzymes convert the polyunsaturated fatty acid arachidonic acid to compounds known as eicosanoids, which are important mediators of pain, fever and inflammation, as well as modulators of cardiovascular, gastrointestinal, renal, and reproductive function. However, the mechanism of these enzymatic transformations still possesses many unanswered questions.

In our laboratory, we are working on the synthesis of linoleic and arachidonic acid substrate analogs containing fluorine and sulfur. The goal of these syntheses is two-fold: (a) to characterize radical intermediates and to provide insight into the mechanism of oxygen incorporation into fatty acids by PGHS and (b) to obtain competitive inhibitors that may be used to generate crystal structures of lipoxygenases with a substrate analog bound in a productive conformation.