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Synthesis of Chirally Pure 1-Deoxy-D-Xylulose-5-Phosphate: A Substrate for Ispc Assay to Determine MTP inhibitor

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Abstract

1-Deoxy-D-xylulsose-5-phosphate (DXP) is a key intermediate in the non-mevalonateor methyl erythritol phosphate (MEP) pathway for the biosynthesis of isoprenoid, which are essential building blocks involved in the construction of pathogens growth. Since the homologous enzymes of this pathway are not present in vertebrates, including humans, the MEP pathway presents a viable source for antimicrobial drug targets. However, an insight into the features of the enzymes involved in this pathway has been plagued by lack of chirally pure substrates. Here in, we report an efficient synthesis of enantiomerically pure 1-deoxy-D-xylulose-5-phosphatefrom commercially available 1, 2-O-isopropylidene-α-D-xylofuranose through Weinreb amide formation in shorter route.

Introduction:

Isoprenoids are important building blocks in the formation of cell wall, electron transfer process intermediates and many other necessary metabolites for the survival of bacteria [1]. Isoprenoids are also one of the most diverse classes of natural products with over 30,000 different compounds ranging from essential primary metabolites, secondary metabolites and intermediates [2]. Although, the diversity of structure and function, all isoprenoids are made from the five carbon precursors, isopentenyldiphosphate (IPP) and its isomer, dimethylallyldiphosphate (DMAPP), through polymerization or repetitive condensation. To date, two distinct pathways have been identified for the biosynthesis of IPP and DMAPP: the mevalonate pathway found in animals and the non-mevalonate or MEP pathway found in many bacteria, protozoa and plants [3]. Generally, in the MEP pathway, DXP is produced through DXS catalyzed condensation of pyruvate, 1 and glyceraldehyde-3-phosphate, 2. The DXP, 3 is then converted to 2-C-methyl-D-erythritol-4-phosphate, 4 (MEP), where IspC catalyzed reducto-isomerization takes place. Subsequently MEP is coupled with cytidine triphosphate (CTP) using IspD to produce 4-diphosphocytidyl-2-C-methyl-D-erythritol, 5 (CDPME), which is concurrently phosphorylated at tertiary hydroxyl group by IspE to synthesize cytidine diphosphate methyl erythritol-2- phosphate, 6 (CDPME2P). In order CDPME2P undergoes cyclization using IspF to give 2-C-methyl-D-erythritol 2,4-cyclodiphosphate, 7 (ME-CPP).

All reactions were performed under a dry argon atmosphere unless otherwise noted. Reagents were obtained from commercial sources and used directly. Flash chromatography was performed using flash silica gel (32-63 μ) from Dynamic Adsorbents Inc. Reactions were followed by TLC on precoated silica plates (250 μm, F-254 from SiliCycle Inc.). The compounds were visualized by UV fluorescence or by staining with anisaldehyde or KMnO4 stains. NMR spectra were recorded on a Varian INOVA 500 spectrometer. Proton NMR data is reported in ppm downfield from TMS as an internal standard. Mass spectra were recorded using ESI.

Conclusion:

In summary, in continuation with the synthesis of chirally pure MEP pathway intermediates, we have demonstrated an effective method for the preparation of enantiomerically pure DXP, 3 from commercially available 1, 2-O-isopropylidene-α-D-xylofuranose, 11. The terminal carboxylic acid group was converted into methyl ketone on the final step via the Weinreb amide methodology in good yield, even without protection of the free hydroxyl group. Radiolabelled compounds can be also prepared on reduction step. However, studies on the kinetic properties of Mycobacterium tuberculosis DXS enzyme using compound 3and determination of IspC inhibitors against Mycobacterium tuberculosis will be reported in due course.

Keywords: mycobacterium tuberculosis, chirality, inhibitor