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Discovery of an unprecedented use of thiamine diphosphate in natural product biosynthesis
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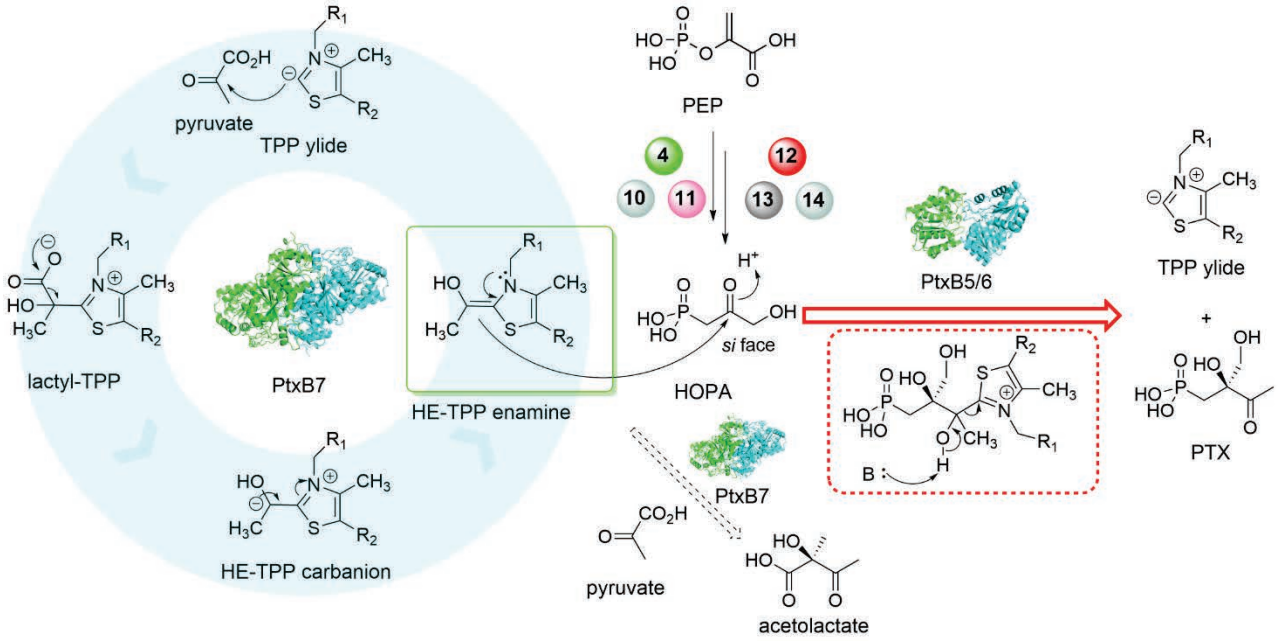
Phosphonates often exhibit biological activities by mimicking the phosphates and carboxylates of biological molecules. The phosphonate phosphonothrixin (PTX), produced by the soil-dwelling bacterium *Saccharothrix* sp. ST-888, exhibits herbicidal activity. In this study, we propose a complete biosynthetic pathway for PTX by reconstituting its biosynthesis in vitro. Our analysis demonstrated that two dehydrogenases together reduce phosphonopyruvate (PnPy) to 2-hydroxy-3-phosphonopropanoic acid (HPPA) to accelerate the thermodynamically unfavorable rearrangement of phosphoenolpyruvate (PEP) to PnPy. The next four enzymes convert HPPA to (3-hydroxy-2-oxopropyl)phosphonic acid (HOPA). In the final stage of PTX biosynthesis, the 'split-gene' transketolase homolog, PtxB5/6, catalyzes the transfer of a two-carbon unit attached to the thiamine diphosphate (TPP) cofactor (provided by the acetohydroxyacid synthase homolog, PtxB7) to HOPA to produce PTX. This study reveals a unique C–C bond formation in which two distinct TPP-dependent enzymes PtxB5/6 and PtxB7 divide the work to transfer an acetyl group, highlighting an unprecedented biosynthetic strategy for natural products.



biosynthesis, reaction mechanism, thiamine diphosphate

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