Terpenoid Cyclization by SAM-Dependent *C*-Methyl Transferase

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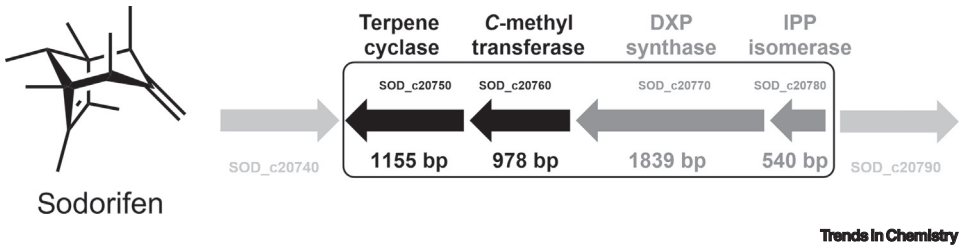
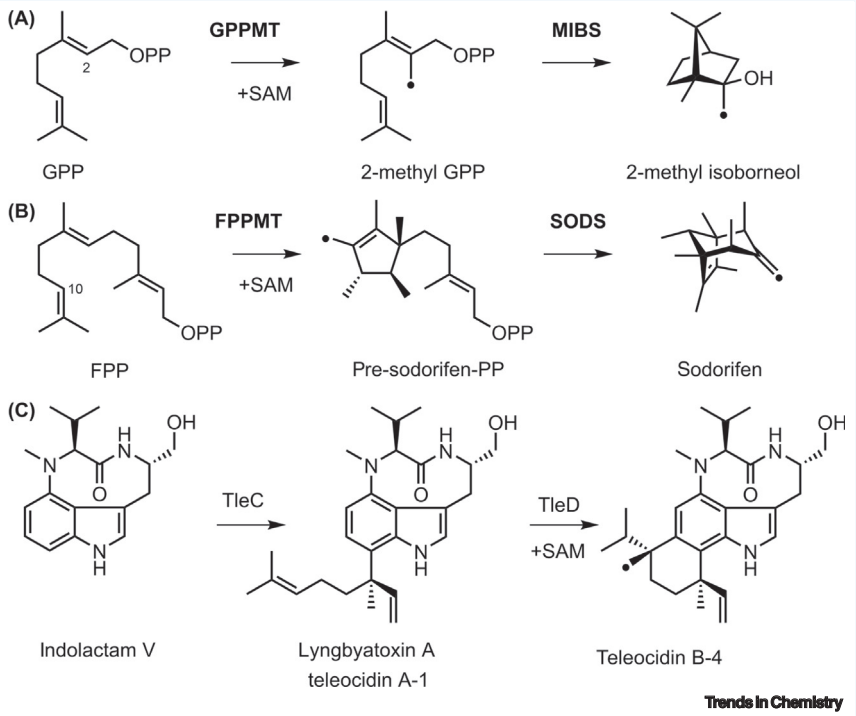


ORIGIN

Serratia plymuthica 4Rx13 emits the unique hydrocarbon sodorifen ($C_{16}H_{26}$) in which every carbon of the bicyclo[3.2.1]octane skeleton carries a methyl unit. Biosynthesis of this homosesquiterpene depends on a gene cluster comprising four genes, an isopentenyl pyrophosphate (PP) isomerase, a deoxyxylulose-5-phosphate synthase, a methyltransferase (MT), and a terpene synthase. The latter two enzymes are required and sufficient for the noncanonical biosynthesis of sodorifen.

REACTION MECHANISM

Canonical terpenoid biosynthesis is based on the successive attachment of isoprene units, generating the canonical substrates GPP, FPP, and GGPP that serve as precursors for cyclization and rearrangement reactions catalyzed by specific terpene synthases to afford a plethora of acyclic and cyclic structures. Previously, the *S*-adenosyl methionine (SAM)-dependent *C*-methylation of the canonical substrate GPP was shown to result in 2-methyl GPP that serves as a noncanonical substrate for methyl isoborneol synthase (MIBS) in *Streptomyces* (**A**), further expanding the structural space of terpenoids. Using a combination of *in vivo* and *in vitro* experiments, we recently demonstrated that sodorifen biosynthesis in *S. plymuthica* involves a novel pathway in which the SAM-dependent *C*-methyl transferase not only methylates the substrate FPP but also catalyzes its subsequent cyclization and rearrangement to furnish the monocyclic pre-sodorifen-PP (**B**). The latter represents a unique noncanonical substrate for the sodorifen synthase (SODS), a specialized terpene synthase that exclusively cyclizes pre-sodorifen-PP to sodorifen but does not react with FPP. During the SODS-catalyzed cyclization, the monocyclic pre-sodorifen-PP undergoes extensive rearrangements to generate the polymethylated sodorifen. Thus, the sodorifen biosynthesis includes two sequential cyclization reactions catalyzed by the *C*-methyl transferase and terpene synthase, thereby increasing the terpenoid structural space to include nonclassical compounds such as sodorifen. Cyclization by *C*-methyl transferases represents an unprecedented mechanism that was so far only once observed in teleocidin biosynthesis by *Streptomyces mediocidicus*, where methylation and cyclization of lyngbyatoxin to teleocidin is catalyzed by the SAM-dependent *TleD* methyl transferase (**C**).



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IMPORTANCE

The coupling of *C*-methylation and cyclization by the *S. plymuthica* FPP MT represents an unprecedented reaction mechanism that illustrates alternative avenues to enlarge terpene diversity. Substrate specificity of SODS for the noncanonical, monocyclic pre-sodorifen PP implies the coevolution of the two enzymes. Furthermore, *C*-methylations of prenyl PPs have been exclusively found in bacteria, scrutinizing the origin of respective biosynthetic pathways.

Literature

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