Regio- and Enantio-selective Chemo-Enzymatic C–H-Lactonization of Decanoic Acid to (S)-δ-Decalactone

Valorization of a Saturated Fatty Acid to Enantioenriched (S)-δ-Decalactone

**Significance:** Hydroxy fatty acids (HFAs) have a wide range of applications as fragrances, food supplements, and pharmaceuticals. The direct, regio- and enantioselective C–H hydroxylation of nonactivated fatty acids would provide an elegant and efficient approach toward HFAs. Flitsch and co-workers report the first example of a regio- and stereoselective C5 hydroxylation of decanoic acid (1) to give (S)-5-hydroxydecanoic acid (2), catalyzed by a wild-type cytochrome P450 monoxygenase (CYP116B46 from *Tepidiphilus thermophilus*). Acid-catalyzed cyclization of 2 gave access to the lactonization product (S)-δ-decalactone (3), a high-value fragrance compound.

**Comment:** Methodologies for the proximal α- and β-positions or the terminal ω-1, ω-2 and ω-3-hydroxy acids have been investigated in the past. The mid-chain γ- and δ-positions have previously been synthesized from functionalized materials. The authors explain the high enantioselectivity of the C–H oxyfunctionalization in terms of molecular docking of acid 1 with the active site of P450-TT. Accordingly, substrate 1 folds in a U-shaped conformation and is placed above the heme prosthetic group, permitting hydroxylation in the middle of the chain, giving access to the (S)-enantiomer at C5. It is noteworthy that further engineering of this protein family might enable utilization of a variety of nonactivated substrates.