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Development of a Biocatalytic Process as an Alternative to the (–)-DIP-Cl-Mediated Asymmetric Reduction of a Key
Intermediate of Montelukast
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Synthesis of Montelukast

Significance: Montelukast sodium (Singulair®) is a leukotriene receptor antagonist prescribed for the treatment of asthma and allergies. Workers at Codexis used directed evolution and high-throughput screening to engineer a robust and efficient ketoreductase enzyme (CDX-026) that accomplished the asymmetric reduction of ketone **A**, which is essentially water insoluble, at a loading of 100 g/L in the presence of ca. 70% organic solvents at 45 °C. The (S)-alcohol **B** was obtained in >95% yield in >99.9% ee and in >98.5% purity on a >500 mol scale.

Comment: The enzymatic reduction entails the reversible transfer of a hydride from isopropanol to the ketone **A** with concomitant formation of acetone. The reaction is driven to completion by the fortuitous crystallization of the monohydrate **B**. The four-step conversion of **B** into montelukast sodium is described in the Merck process patent (M. Bhupathy, D. R. Sidler, J. M. McNamara, R. P. Volante, J. J. Bergan US 6320052, **2001**). This biocatalytic reduction is superior to the reduction of **A** with (–)-DIPCl previously used in the manufacture of montelukast.

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