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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


**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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