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Practical Asymmetric Synthesis of a Potent PDE4 Inhibitor via Stereoselective Enolate Alkylation of a Chiral Aryl-Heteroaryl Secondary Tosylate

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Category

Synthesis of
Natural Products
and Drugs

Key Words

asymmetric
hydrogenation

Asymmetric Synthesis of L-869,298, a Potent PDE4 Inhibitor

Significance: The target molecule inhibits phosphodiesterase-4 (PDE4), an enzyme that hydrolyzes cAMP. It is a potential drug for the treatment of asthma and chronic obstructive pulmonary disease.

Comment: Noyori asymmetric hydrogenation gave the most efficient reduction of **A**. The unstable tosylate **B** underwent substitution with the lithium enolate of pyridine *N*-oxide **C** to give **D** in 92% yield with no loss of enantiopurity. The cyclopropyl ether was synthesized on a 21.5 mol scale by reaction of a phenolic vinyl ether with Et_2Zn and CH_2I_2 .

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