P. D. O'SHEA,* C. CHEN,* W. CHEN, P. DAGNEAU, L. F. FREY, E. J. J. GRABOWSKI, K. M. MARCANTONIO, R. A. REAMER, L. TAN, R. D. TILLYER, A. ROY, X. WANG, D. ZHAO (MERCK FROSST CENTRE FOR THERAPEUTIC RESEARCH, QUEBEC, CANADA; MERCK RESEARCH LABORATORIES, RAHWAY, USA)

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

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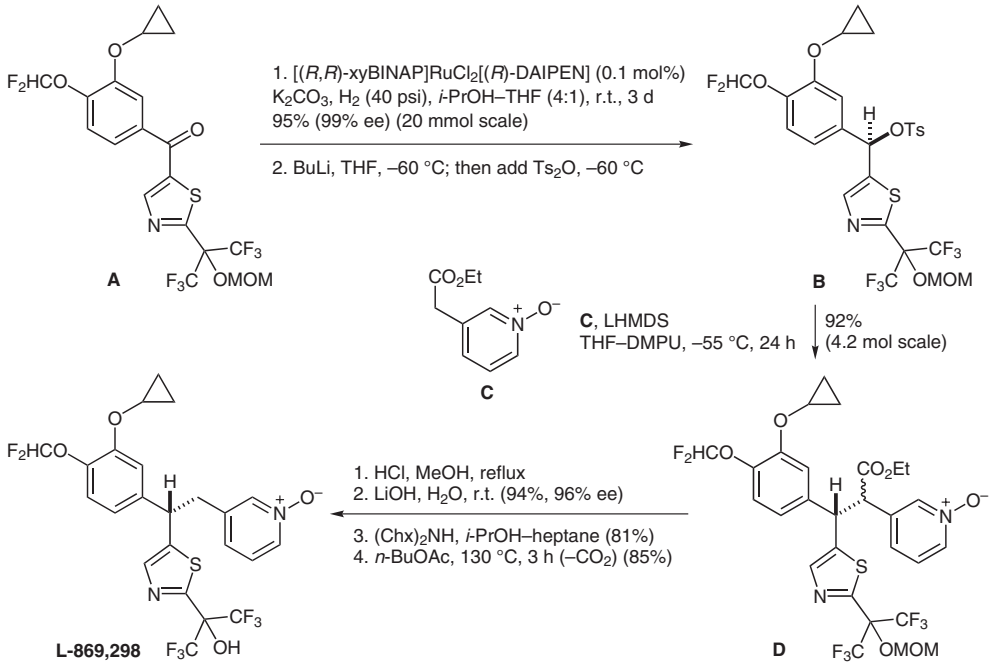
Category

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.

SYNFACTS Contributors: Philip Kocienski
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