Z. PENG,* J. W. WONG, E. C. HANSEN, A. L. A. PUCHLOPEK-DERMENICI, H. J. CLARKE
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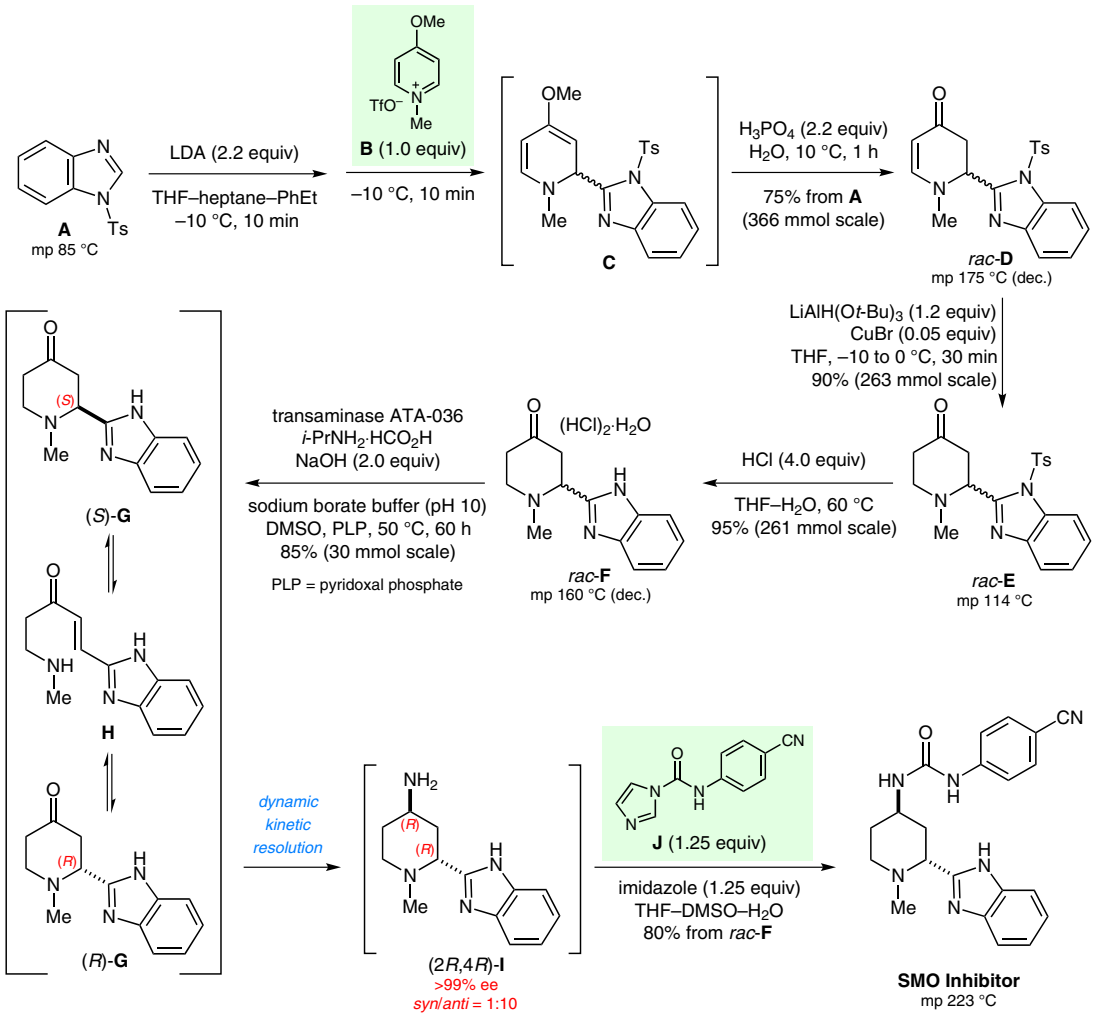
Development of a Concise, Asymmetric Synthesis of a Smoothened Receptor (SMO) Inhibitor: Enzymatic Transamination of a 4-Piperidone with Dynamic Kinetic Resolution
Org. Lett. **2014**, *16*, 860–863.

Synthesis of SMO Inhibitor PF-04449913



Significance: PF-04449913 is an antagonist of the smoothened receptor (SMO), a component of the hedgehog signalling pathway. It is currently undergoing human trials for the treatment of various blood-related cancers. The key steps in the synthesis depicted are (1) the addition of a lithiated benzimidazole to the pyridinium salt **B** and (2) the asymmetric construction of two stereogenic centers by an enzymatic transamination accompanied by a dynamic kinetic resolution.

Comment: Complete racemization of the single enantiomer (*S*)-**G** occurred in less than eight hours at 40 °C in a mixture of DMSO and aqueous pH 10 buffer, the medium for the enzymatic transamination. A retro-aza-Michael/aza-Michael mechanism for the racemization was proposed though no direct evidence of the ring-opened intermediate **H** could be adduced. For the discovery synthesis of PF-04449913, see: M. J. Munchhof et al. *ACS Med. Chem. Lett.* **2012**, *3*, 106.

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Synfacts 2014, 10(5), 0449 Published online: 17.04.2014
DOI: 10.1055/s-0033-1341076; **Reg-No.:** K01614SF

Category
Synthesis of Natural Products and Potential Drugs

Key words
PF-04449913
smoothened receptor antagonist
enzymatic transamination
dynamic kinetic resolution