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 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 could be adduced. For the discovery synthesis of PF-04449913, see: M. J. Munchhof et al. ACS Med. Chem. Lett. 2012, 3, 106.