

Synthetic Development and Pilot Plant Scale-up of a Heterocyclic Pharmaceutical Intermediate

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A scalable, asymmetric synthesis of (3a*S*,6a*S*)-6a-(5-bromo-2-fluorophenyl)-1-((*R*)-1-phenylpropyl)tetrahydro-1*H*,3*H*-furo[3,4-*c*]isoxazole (**1**), a key intermediate in the synthesis of **LY2886721** is reported. Highlights of the synthesis include: (1) The development of an asymmetric [3+2] intramolecular cycloaddition through a combined kinetic modeling and experimental approach; (2) The development of a new synthesis of (*R*)-*N*-(1-phenylpropyl)hydroxylamine tosylate (**2**) which proceeds through a *p*-anisaldehyde imine and avoids the formation of toxic hydrogen cyanide gas as a by-product. Results of a synthesis executed on the multi-100 kg scale (which proceeded in 36% overall yield) will be discussed.

