Synthesis of an Inhibitor of Histone Lysine Demethylases KDM2/7

**Significance:** The target molecule M is a first-in-class highly selective cell-active inhibitor of the histone lysine demethylases KDM2/7 that are involved in epigenetic gene expression. In total 45 racemic N-acyl indoline derivatives were prepared, from which the enantiomers of M were selected for further evaluation.

**Comment:** Synthesis of the indoline (S,S)-H entails treatment of the N-aryl imine F with cesium hydroxide under phase-transfer conditions in the presence of the quinine-derived salt G (0.1 equiv). A delocalized 2-aza-pentadienyl anion is generated that undergoes 6π electrocyclization in 89% yield (dr = 10:1, er = 88:12). Preparative chiral HPLC then delivered H with dr > 20:1 and er > 99:1. For details on the asymmetric electrocyclization, see: E. E. Maciver, S. Thompson, M. D. Smith Angew. Chem. Int. Ed. 2009, 48, 9979.

SYNFACTS Contributors: Philip Kocienski

Synfacts 2018, 14(02), 0113 Published online: 18.01.2018
DOI: 10.1055/s-0037-1609195; Reg-No.: K06118SF

Category

Synthesis of Natural Products and Potential Drugs

Key words

histone lysine demethylases KDM2/7 inhibitor
6π electrocyclization
indolines
organocatalysis