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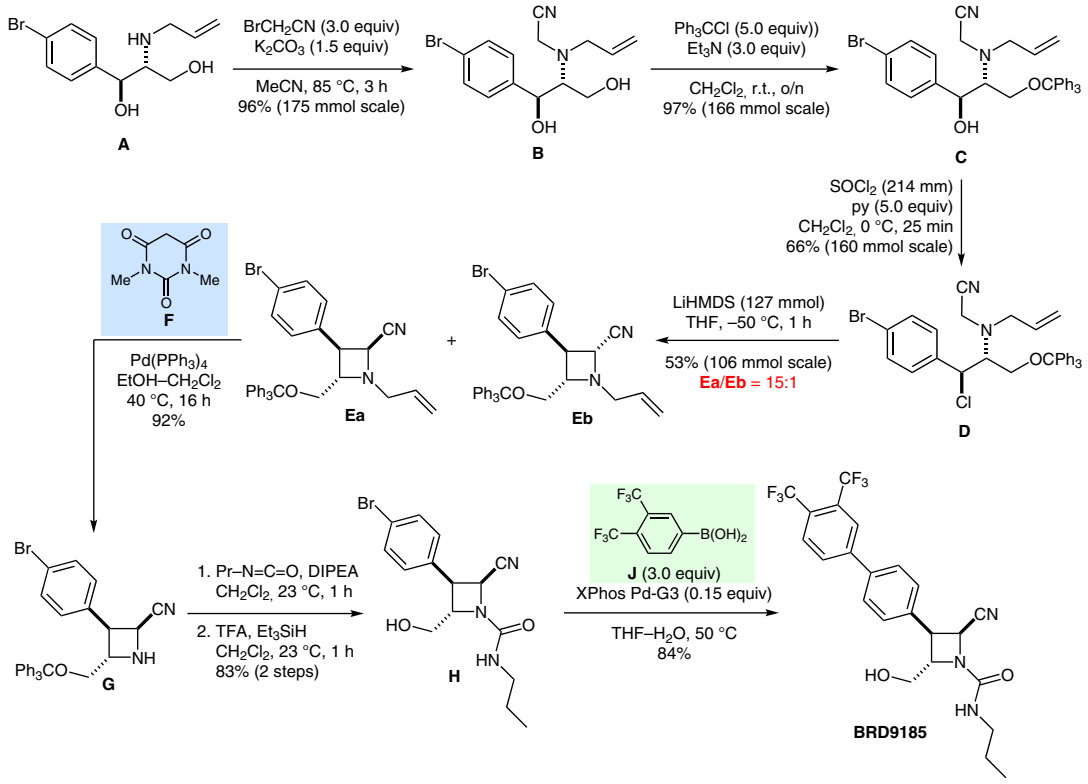
Discovery of Antimalarial Azetidine-2-carbonitriles that Inhibit *P. falciparum* Dihydroorotate Dehydrogenase
ACS Med. Chem. Lett. **2017**, *8*, 438–442.

Synthesis of Dihydroorotate Dehydrogenase Inhibitor BRD9185



Significance: Dihydroorotate dehydrogenase (DHODH) is necessary for pyrimidine biosynthesis in protozoan parasites of the genus *Plasmodium,* the causative agents of malaria. BRD9185 is a DHODH inhibitor that has in vitro activity against multidrug-resistant blood-stage parasites (EC_{50} = 0.016 μM) and is curative after just three doses in a *P. berghei* mouse model. BRD9185 has a long half-life (15 h) and low clearance in mice.

Comment: The key step in the synthesis depicted was the construction of the azetidine-2-carbonitrile core by a 4-*exo*-tet cyclization of the anion derived from **D**. The stereochemistry of the cyclization depended on the base. Treatment of **D** with LiHMDS at –50 °C provided the products **Ea** and **Eb** in a ratio of approximately 15:1 as a separable mixture. Alternatively, exposure of **D** to KHMDS at –78 °C gave nearly exclusively **Eb** (**Ea**/**Eb** ≈ 1:20). The conversion of **A** into **E** is described in a preceding paper: J. T. Lowe et al. *J. Org. Chem.* **2012**, *77*, 7187.

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Category

Synthesis of Natural Products and Potential Drugs

Key words

BRD9185

dihydroorotate dehydrogenase

azetidine-2-carbonitriles

4-*exo*-tet cyclization