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 (EC50 = 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 KHMS 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.