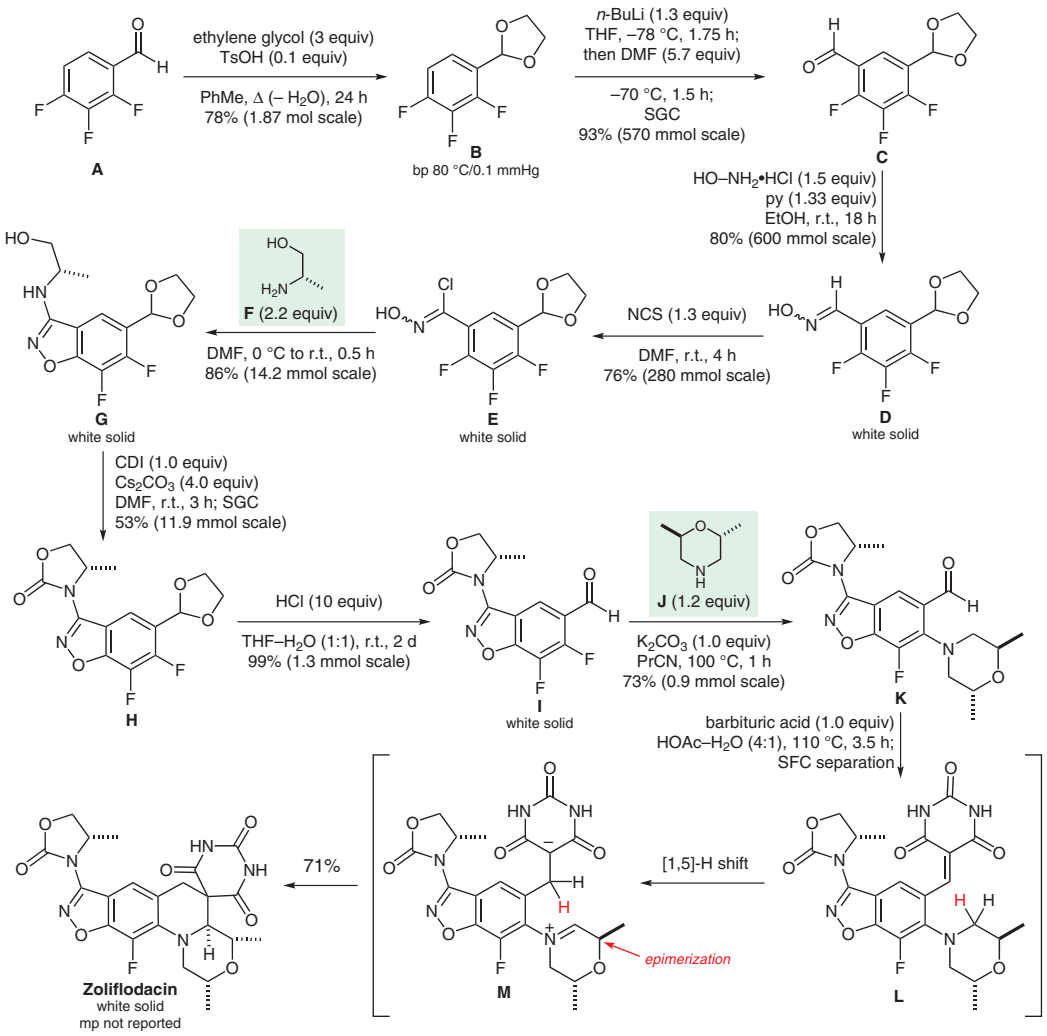
G. S. BASARAB* ET AL. (ASTRAZENECA R&D BOSTON, WALTHAM, USA)

Discovery of Novel DNA Gyrase Inhibiting Spiropyrimidinetriones: Benzisoxazole Fusion with N-Linked Oxazolidinone Substituents Leading to a Clinical Candidate (ETX0914)

J. Med. Chem. **2015**, *58*, 6264–6282.

Synthesis of Zoliflodacin



Significance: Zoliflodacin is an oral antibiotic with a unique mode of inhibition against type II topoisomerases with binding sites in bacterial gyrase. It has entered phase 3 clinical trials for the treatment of gonorrhea (P. A. Bradford, A. A. Miller, J. O'Donnell, J. P. Mueller *ACS Infect. Dis.* **2020**, *6*, 1332). Zoliflodacin also has activity against Gram-positive, Gram-negative, and atypical pathogens including multidrug-resistant strains.

Comment: In 2015, Basarab and co-workers reported the discovery of this DNA gyrase inhibiting spiropyrimidinetrione fused to a benzisoxazole scaffold. In the key spirocyclization reaction, intermediate (2*R*,6*R*)-morpholine **L** underwent a 1,5-hydrogen shift to generate intermediate **M** that epimerized before cyclization to the spiropyrimidinedione in zoliflodacin (dr = 9:1).

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