Synthesis of TP-2758

Significance: TP-2758 is in development for the treatment of complicated urinary tract infections caused by Gram-negative pathogens. The closing stage of the synthesis depicted features the installation of the chiral pyrrolidine moiety in fragment G using Ellman’s chiral sulfinamine auxiliary B (99% ee). The conjunction of complex fragments G and H using chemistry developed by Myers and co-workers (J. Am. Chem. Soc. 2008, 130, 17913) delivered the advanced intermediate I in 89% yield.

Comment: Enantioselective deprotonation of N-Boc pyrrolidine using s-BuLi and (-)-sparteine afforded the lithium reagent ((S)-K that participated in a palladium-catalyzed Negishi coupling with bromoarene J to give enantioenriched pyrrolidine (R)-L in 63% yield (>90% ee). By using diamine (S,S)-M as a (+)-sparteine surrogate, the corresponding Negishi reaction delivered (S)-L in 50% yield (93% ee). Neither of these alternatives was robust, and the yields could not be improved.