Scale Up of Azaindole Compound VRT-200: A Story of Synthetic Evolution

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Azaindole compound **VRT-200** is a potent inhibitor of influenza PB2, and has complex structure which is a challenge for scale up. We use enzymatic desymmetrization of 1,3-bisester-cyclohexane to generate the two chiral centers with high yield (99%) and high ee (99%). The first generation of synthesis employs the displacement of chiral mono-Boc-diaminocyclohexane with sulfoxide, followed by urea formation (10 steps); The second generation of synthesis is racemic and need SFC separation (6 steps); The third generation of synthesis employs a Curtius rearrangement of acid to install morpholin urea in one step (7 total steps with 33% overall yield). All steps from last route are high yielding and easy to scale up