Synthesis of an Atropisomeric HIV Integrase Inhibitor

Significance: The first-generation synthesis of HIV-1 integrase inhibitor \( \text{N} \) proceeded in ten steps and 14% overall yield on a multikilogram scale from unsaturated sulfoxide \( A \). The second-generation synthesis depicted also proceeded in ten steps, but in an improved 28% overall yield. Both routes share a common intermediate \( G \) and feature the construction of the challenging eight-membered ring via an intramolecular N-alkylation that does not require isolation of any intermediates.

Comment: Compounds \( M \) and \( N \) displayed hindered rotation about the amide bond that permitted separation of the atropisomers. In ethanol, pure atropisomer \( (aR,4R)-N \) equilibrates to an 85:15 mixture of atropisomers after stirring for eight days at room temperature. The minor undesired atropisomer \( (aS,4R)-N \) displays less antiviral activity and had a markedly different pharmacokinetic profile from \( (aR,4R)-N \). The stereochemistry of the atropisomers was determined by calculation.