Synthesis of an Atropisomeric HIV Integrase Inhibitor

Significance: The first-generation synthesis of HIV-1 integrase inhibitor 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 M equilibrates to an 85:15 mixture of atropisomers after stirring for eight days at room temperature. The minor undesired atropisomer (aR,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.

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