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Asymmetric Synthesis of a Potent HIV-1 Integrase Inhibitor
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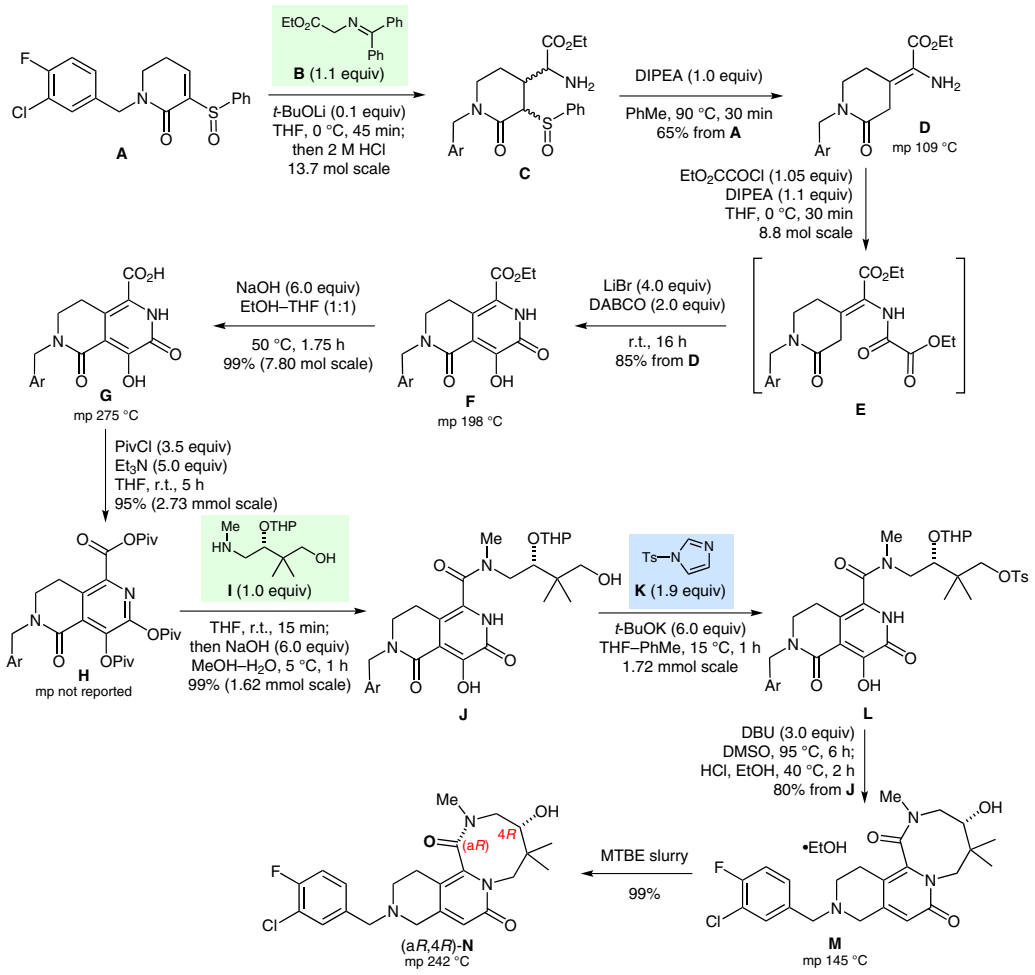
Synthesis of an Atropisomeric HIV Integrase Inhibitor



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 (a*S*,4*R*)-**N** displays less antiviral activity and had a markedly different pharmacokinetic profile from (a*R*,4*R*)-**N**. The stereochemistry of the atropisomers was determined by calculation.

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atropisomer