**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 \( \text{A} \). The second-generation synthesis depicted also proceeded in ten steps, but in an improved 28% overall yield. Both routes share a common intermediate (\( \text{G} \)) 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 \( \text{M} \) and \( \text{N} \) displayed hindered rotation about the amide bond that permitted separation of the atropisomers. In ethanol, pure atropisomer \( \text{M} \) equilibrates to an 85:15 mixture of atropisomers after stirring for eight days at room temperature. The minor undesired atropisomer (\( \text{aR,4R} \)-\( \text{N} \)) displays less antiviral activity and had a markedly different pharmacokinetic profile from (\( \text{aR,4R} \)-\( \text{N} \)). The stereochemistry of the atropisomers was determined by calculation.