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Asymmetric Synthesis of Letermovir Using a Novel Phase-Transfer-Catalyzed Aza-Michael Reaction
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Synthesis of Letermovir by an Asymmetric Aza-Michael Reaction

Significance: Letermovir is a DNA terminase inhibitor that has entered phase III clinical trials for the treatment of cytomegalovirus infections. The seven-step synthesis depicted delivered over one ton of the target molecule in 60% overall yield without recourse to chromatography. The key step is the phase-transfer-catalyzed aza-Michael reaction (**G** → **I**) that installs the single stereogenic center. The stability of the carbodiimide **E** and the nucleophilicity of the piperazine **F** underpinned the success of this approach and the use of toluene as solvent prevented premature cyclization of **G**.

Comment: The aza-Michael cyclization revealed a number of features that suggest an atypical PTC-type mechanism. Both reaction rate and enantioselectivity were sensitive to (i) agitation rate; (ii) the concentration and equivalents of aqueous base, where superstoichiometric amounts of K_3PO_4 proved optimal; and (iii) PTC/base counterions, where deviation from Br^- or PO_4^{3-} respectively were detrimental.

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