Asymmetric Synthesis of Letermovir Using a Novel Phase-Transfer-Catalyzed 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 K₃PO₄ proved optimal; and (iii) PTC/base counterions, where deviation from Br⁻ or PO₄³⁻ respectively were detrimental.