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Development and Scale-up of a Route to ATR Inhibitor AZD6738
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Synthesis of AZD6738

Significance: Workers at AstraZeneca recently reported a mol-scale synthesis of ATR inhibitor AZD6738 based on the use of chiral HPLC to access the chiral sulfoxide intermediate **G** (*J. Med. Chem.* **2018**, *61*, 9889). A plant scale synthesis of AZD6738 is now reported that features a biocatalytic asymmetric sulfoxidation reaction (**F** → **G**) and a cyclopropanation (**J** → **L**) in continuous stirred tank reactors.

Comment: The sulfoxidation reaction uses a Baeyer–Villiger monooxygenase in tandem with nicotinamide adenine dinucleotide phosphate (NADPH), which is oxidized to NADP⁺. NADPH is then regenerated through reduction of NADP⁺ by a ketoreductase (KRED) enzyme, which in turn oxidizes the co-solvent isopropanol to acetone. Efficient gas–liquid mass transfer of oxygen is key to obtaining a high yield.

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