The Discovery of Polo-Like Kinase 4 Inhibitors: Identification of (1R,2S)-2-((E)-4-(((cis)-2,6-Dimethylmorpholino)methyl)styryl)-1H-indazol-6-yl)-5′-methoxyspirocyclopropane-1,3′-indolin]-2′-one (CFI-400945) as a Potent, Orally Active Antitumor Agent


Synthesis of PLK4 Inhibitor CFI-400945

Significance: CFI-400945 is an inhibitor of Polo-like kinase 4 (PLK4) that is a lead for the treatment of various cancers. The synthesis depicted features a diastereoselective one-pot double SN2 displacement reaction ([E] → [H]) for the creation of the cyclopropane ring. The authors propose that the stereoselectivity of the cyclopropanation is a consequence of π-π interactions that stabilize conformer G.

Comment: Attempted hydrogenolysis of the benzyl protecting groups from a close relative of H was accompanied by partial ring opening of the cyclopropane. However, the benzyl groups were removed cleanly using potassium tert-butoxide in an oxygen-saturated solution in THF and DMSO (R. M. Williams, E. Kwast Tetrahedron Lett. 1989, 30, 451).