The Discovery of Polo-Like Kinase 4 Inhibitors: Identification of \((1R,2S)\)-2-(3-((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 \((E \rightarrow H)\) for the creation of the cyclopropane ring. The authors propose that the stereo-selectivity of the cyclopropanation is a consequence of \(\pi-\pi\) 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).